Obstructive Sleep Apnea in WTC responders: Role of nasal Pathology

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1. **Purpose/Specific Aims**
Following the World Trade Center (WTC) disaster, responders who worked in rescue, recovery and debris removal were initially exposed to greater than 100,000 µm/m³ total particles\(^1\). 63% of these responders examined in 2004 reported at least one new or worsened upper airway respiratory symptom since 911, and in June 2007, 50% of responders continued to have symptoms of chronic rhino-sinusitis or upper airway disease (UAD). In addition, about 50% of those with UAD referred to our sleep center reported new onset snoring on their questionnaires immediately following their exposure and had unusually high prevalence of obstructive sleep apnea (OSA)\(^2\). Usual risk factors for OSA include a high body mass index (BMI) and increasing severity of OSA as determined by the apnea+hypopnea index (AHI) correlates with increasing BMI. Unique to the WTC population was the fact that there was no correlation between AHI and BMI and those with new onset snoring had a lower BMI compared to habitual snorers. This suggests that mechanisms other than obesity may be important in the pathogenesis of OSA in these subjects and given their chronic nasal symptoms, provides a unique opportunity to examine the relationship between nasal pathology and OSA. Our hypothesis is that the nasal symptoms reported by the subjects in the WTC medical monitoring and treatment program (WTCMMTP) now termed WTC Health Program (WTCHP) are an indicator of increased nasal resistance due to nasal inflammation resulting from exposure to the WTC dust. In particular reversible nasal resistance may play an important role. Alternatively inflammation of the posterior pharynx without influencing nasal resistance may predispose to OSA in this population. Continuous Positive Airway Pressure (CPAP) is the standard therapy for OSA but despite its efficacy has poor adherence. Subjects with high nasal resistance may experience additional pressure during expiration at the upper airway due to high nasal resistance. This may result in greater difficulty in tolerating this therapy than those who do not have high nasal resistance. Reduction of excess expiratory positive pressure by the modality known as Cflex™ during CPAP therapy (CPAP\(_{\text{Flex}}\)) has been suggested to improve comfort without compromising CPAP efficacy.

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**Principal Investigator:** Jag Sunderram

**Funding Source(s):** Centers for Disease Control/ NIOSH
SA3. Relate nasal resistance to CPAP adherence in patients with OSA and show that reduction of expiratory pressure using CPAP_{flex} will improve CPAP adherence. Patients with OSA will be randomized in a double blind cross over design to receive CPAP or CPAP_{flex} and adherence will be measured.

*In patients with OSA, we will test:*

*Hypothesis 3a:* Increased nasal resistance is associated with decreased adherence to CPAP.

*Hypothesis 3b:* Use of CPAP_{flex} will improve adherence with CPAP in subjects with high nasal resistance, but not in those with low nasal resistance.

*Hypothesis 3c:* The benefit of CPAP_{flex} on adherence will be greatest if it is offered at CPAP initiation rather than as a “rescue” therapy in subjects with high nasal resistance.

2. **Background and Significance**

From September 11, 2001 onward following the World Trade Center (WTC) disaster, an estimated 40,000 individuals were exposed to significant amounts of dust while working in rescue, recovery and debris removal. These workers included traditional first responders, such as firefighters and police, and a diverse population of construction, utility, and public sector workers. A medical screening program was developed to evaluate the health status of workers and volunteers who spent time at the WTC site and thus sustained exposure in the aftermath of September 11th. Standardized questionnaires were adapted for use in this unique population. These questionnaires underpin our exploration of the relationship between the new symptoms following the exposure and the presence of diseases such as OSA. The WTC Worker and Volunteer Medical Screening Program (MSP) and the follow up World Trade Center Medical Monitoring and Treatment program (WTCMMP) now called the World trade Center Health program (WTCHP) have successfully recruited more than 27,000 responders to assess and treat health effects from these exposures. About 1700 of these responders are followed at the Environmental and Occupational Health Sciences Institute (EOHSI) of Rutgers Biomedical Health Sciences in Piscataway, New Jersey, about 2100 in the NYU School of Medicine Clinical Center of Excellence (NYUSOM CCE) at Bellevue Hospital in New York City and about 22,000 are followed at Mt. Sinai School of Medicine (MSSM CCE).
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The collapse of the WTC towers resulted in a massive plume of building debris and particulates. Sources of associated pollutants varied over the months after the disaster,\textsuperscript{1,5} but included combustion products, evaporating gases, gaseous fine and supercoarse particles\textsuperscript{1}. These were from dust, rubble and debris from breakdown of WTC buildings, gases, dust, soot and smoke formed as a result of fires at the WTC site and motor vehicle emissions from vehicles at the WTC site. The dust was highly alkaline and corrosive, capable of causing chemical irritation to the upper respiratory tract.\textsuperscript{6} It contained high levels of calcium sulfate (gypsum) and calcium carbonate (calcite)\textsuperscript{7} known causes of irritation to mucus membranes (eyes, nose throat and large airways) as well as cough and sneezing and are likely to be among the major irritants of WTC dust.

OSA is a chronic condition with recurrent episodes of partial or complete upper airway collapse during sleep. The main risk factors for OSA are obesity and male gender and it is highly prevalent in the general population, with estimates ranging from 5-10\% to >25\%\textsuperscript{18,19}. Upper airway inflammation resulting in mucosal congestion could mimic these predisposing conditions and provide an alternate mechanism for development of compromised upper airway patency during sleep.
favoring suction forces (iv) increased mouth breathing in the presence of elevated nasal resistance
with forward shift of the tongue and mandible and increased resistance of oral breathing during sleep (v) activation of nasopulmonary reflexes (trigeminal nerve stimulation causing decreased respiratory effort) (v) Nasal–ventilator reflex: decreased nasal airflow results in decreased activation of nasal receptors with subsequent inhibition on muscle tone and ventilation. All these mechanisms assume inflammation resulting in increased nasal resistance is the key link of UAD to OSA but it is also possible that the same factors causing elevated nasal resistance may also directly affect the collapsible downstream UA segment. The resulting local swelling and edema could directly predispose to upper airway collapse independent of nasal resistance.

Previous studies of the relationship between WTC-related conditions and OSA have reached differing conclusions on the association between GERD and and/or chronic rhino–sinusitis and increased risk for OSA. In a pilot study of a small sample of WTC responders with aero–digestive symptoms, snoring and daytime symptoms of sleep deprivation, we found that out of 50 responders referred for sleep studies, 48 of them had OSA. In contrast to a comparison population who were referred to our sleep center for snoring and daytime symptoms where there was a strong association between body mass index (BMI) and AHI, there was no association between BMI and AHI in WTC responders, suggesting a possible role for an inflammatory etiology for OSA. Additionally, a subset of WTCHP responders who had developed habitual snoring after 911 had a significantly lower BMI than WTCHP responders who were habitual snorers prior to 911, despite having the same severity of OSA. The findings in our study differed significantly from a recent publication by de la Hoz et.al. Those authors found that OSA was associated with BMI and male gender in their sample of 100 WTCHP responders. De la Hoz et.al, also did not find an association between OSA and UAD. In contrast, our study findings are similar to the results of Webber et.al who, based on questionnaire data, found that in 11,701 responders, 16.9% of those not previously at high risk for OSA qualified as high risk for OSA following 911.

These contradictory findings call for a larger and more systematic study to examine risk factors that may play a role in the development of OSA in the WTC population. In specific aim 1 of this proposal we will examine the relationship between post-9/11 OSA and new or worsened upper airway disease.

Many patients with OSA have nasal symptoms and nasal pathology is associated with snoring. Studies creating nasal obstruction have induced OSA in normal subjects, but there are limited and conflicting data in the literature on a causal relationship between nasal resistance, nasal symptoms and OSA in the clinical population, because prior studies have not used objective measures of nasal resistance and many have not objectively documented OSA. In addition, some studies suggest that obesity may mask the independent effect of nasal obstruction in the pathophysiology of OSA. Despite this, two population studies suggest nasal symptoms contribute to risk of OSA. The Wisconsin Cohort study reported a 1.8 times higher AHI in subjects with allergic rhinitis compared to those without nasal symptoms. Other studies have reported an association between nasal congestion and OSA, and nasal decongestants may improve the AHI. However, to date there has been no large epidemiologic study relating objective nasal resistance and OSA, and a recent review summarizing the role of nasal obstruction in OSA by McNicholas emphasized the need for such data. The WTC cohort provides us with this opportunity to explore the relationship between upper airway inflammation and resultant upper airway disease, nasal resistance and OSA (See model). We hypothesize that WTC dust exposure...
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The health benefits of diagnosis and treatment of OSA are well recognized: untreated OSA is associated with daytime sleepiness, increase in motor vehicle accidents, increased hypertension, stroke, impaired glucose metabolism, and increase in all-cause mortality. CPAP is the primary treatment for OSA. CPAP use normalizes sleep architecture, reduces daytime sleepiness, and reduces automobile accidents and decreases blood hypertension and cardiovascular events. Despite its efficacy, 29-83% of patients are non-adherent to CPAP and no specific factors (demographic, disease specific) that predict CPAP adherence have been identified. In addition to problems with the mask and claustrophobia, pressure intolerance and “difficulty exhaling” are frequently cited by patients as limiting acceptance of CPAP therapy. Nasal symptoms and side effects are also common and may account for 30-50% of cases of CPAP intolerance. Small studies have shown that nasal resistance was significantly higher in OSA patients who did not tolerate CPAP and reduction of nasal resistance by surgery has been shown to increase CPAP use. CPAP adherence in WTC responders with UAD is unknown but in general has anecdotally been thought to be poor. High nasal resistance can play a potential role in their poor adherence.

CPAP keeps the UA open and nasal resistance becomes the primary determinant of total UA resistance. Thus, during CPAP use, high nasal resistance may continue to cause a patient to experience discomfort while exhaling despite adequate relief of OSA and could contribute to intolerance of CPAP. In preliminary data we have shown that, as expected, increased nasal resistance results in higher expiratory pressure. By decreasing this excess pressure during the expiratory cycle, CPAP Flex (Philips Respironics) may improve CPAP adherence. Although prospective, randomized studies have demonstrated that CPAP Flex is not inferior to conventional fixed CPAP, increased adherence has not been uniformly demonstrated. Some studies have shown CPAP Flex reduces discomfort and improves adherence, but larger randomized studies have shown no difference in adherence between CPAP and CPAP Flex. However none of these studies have attempted to target therapy to patients based on elevated nasal resistance as we propose to do. In specific aim 3 of this proposal we will relate nasal resistance to CPAP adherence in patients with OSA and show that reduction of expiratory pressure using CPAP Flex will improve CPAP adherence.
This potential increase in nightmares could reduce CPAP adherence, particularly in PTSD, as was demonstrated in a study by El-Solh et al.47. The present proposal should have broad impact on the diagnosis and management of OSA potentially caused by upper airway pathology resulting from toxic inhalation of WTC dust. Although the relationship between UAD and OSA appears to be strong in the WTC cohort, only a small numbers of subjects have had objective evaluation of sleep with nocturnal polysomnography (NPSG), in part due to the high cost and patient burden. We will use a validated portable monitor in Specific Aim 1 to evaluate large numbers of subjects specifically for the presence of OSA. Our first specific aim addresses the need to examine the relation of UAD to OSA in this population. Our second specific aim will examine the role of nasal pathology in the etiology of sleep apnea, important in the WTC population but these results also extends to the general population with UAD from allergies and other causes. In specific aim three, we will also address the important specific question of whether nasal pathology negatively impacts on the ability to use CPAP, with the potential that addressing this with modified CPAP will improve the therapeutic approach to OSA. The proposed research will be performed in collaboration with the NYUSOM CCE for Responders (PI Denise Harrison, MD) which follows 2100 subjects, MSSM CCE (PI Michael Crane, MD, MPH) for Responders which follows 22,000 responders, and EOHSI, RWJMS, Piscataway (PI Iris Udasin, MD) which follows 1700 responders. The present proposal is in keeping with the mission of NIOSH and will address several areas of current need listed in PAR-12-126. It will generate new knowledge about conditions common in WTC exposed individuals, including nasal pathology and OSA. By using a less costly but equally effective evaluation of sleep disordered breathing (limited channel portable monitoring) and automated CPAP initiation, it will improve access to care for individuals exposed to WTC dust. The objective measures of nasal inflammation and nasal resistance measurements will help answer whether the OSA is attributable to nasal consequences of WTC exposure. Adherence and efficacy of different therapies will be evaluated providing guidelines to physicians caring for these patients. The growing, but anecdotal, awareness of the large number of patients in the WTC population who present with OSA has prompted much internal discussion as to possible mechanisms and implications. A well-attended day-long symposium on this topic was organized by the WTC working group at the request of NIOSH in August 2009, and concluded that further investigation into the relationships between WTC exposure, nasal pathology and OSA was warranted. A particular strength of the WTC databases is the potential for future analyses. For OSA, there is particular interest in the evaluation of systemic markers of inflammation that may play a role in cardiovascular outcomes. As all the sleep data collected will be merged with the central database and blood has been banked on all subjects, multiple future research directions can be supported by the data we will collect.

This proposal capitalizes on the complimentary academic fields of the investigators including epidemiology, clinical pulmonary and sleep medicine, physiology, inflammation and biostatistics. The investigators have extensive experience in clinical medicine, and research in the epidemiology of diseases including OSA, in both laboratory and human physiology models of OSA, expertise in measuring nasal inflammation, nasal resistance and its effects on OSA, as well as longstanding experience in laboratory and portable sleep monitoring. Finally, they have been involved in the use, modification and monitoring of CPAP since its inception.
3. Research Design and Methods

Specific Aim 1: Examine the relationships between post-9/11 OSA and UA Disease.

Specific Aim 2: Determine the relationship between post-9/11 OSA, upper airway disease, nasal inflammation and nasal resistance.

Study Protocol: The first two specific aims will be addressed through a cross-sectional design. Study subjects will be evaluated for:

1) nasal signs and symptoms, 2) clinical interview to confirm onset of or worsening of symptoms post 9/11, 3) medication review including nasal steroids, use of Neti pots, and CPAP therapy, 4) review of symptoms of OSA and measures of sleepiness, 5) nasal resistance measurement (rhinomanometry) in the upright and supine positions, 6) nasal lavage and 7) home sleep study to determine presence or absence of OSA. Medical records will be reviewed for a history of snoring and development of nasal symptoms. Changes in weight will also be recorded.

Procedures for SA1 and SA2:

Medical Chart Review: As part of the WTCHP, participants are asked to complete several questionnaires during their monitoring visits. Data from Visit 1 questionnaires (Mail Home Snoring and Interview Administered Medical Questionnaire (IAMQ)) will be abstracted for the research. The abstracted data will focus on upper respiratory symptoms, snoring and sleepiness. The participant's height, weight, and blood pressure at Visit 1 will also be recorded. Within the WTC patient database, an aggregate exposure measurement (Exposure Ranking Index) has been calculated for each patient. The index is based on patient responses to an Exposure Assessment Questionnaire (EAQ) completed at Visit 1. Responses to individual questions will also be abstracted from the EAQ. The questions concern the following areas of their WTC work/volunteer experience: dates, hours, locations, and conditions as well as experience with respiratory protection. Additionally, diagnoses of GERD and PTSD will be abstracted from the periodic IAMQs which are completed at each monitoring visit in the WTCHP. In order to assess the severity of PTSD, the PCL score from the periodic WTCHP Mental Health Questionnaire from the most recent monitoring visit will be recorded.

Subjective Assessment of nasal symptoms: Participants will complete a nasal symptom questionnaire. Presence of at least 3 symptoms of rhinitis with onset or worsening after 9/11 will classify a subject as positive for nasal symptoms (UAD). The symptoms must have been present for >8 weeks and be unrelated to an infection, with or without associated symptoms of sinusitis, pharyngitis or laryngitis. This definition was used previously in evaluating UAD in the WTC population.

Current medication use for chronic symptoms including nasal steroid use or use of Neti pots etc. will be documented.

Subjective Assessment for sleep disorders: We will evaluate excessive daytime sleepiness with a sleep questionnaire to evaluate for sleep disorders (insomnia, RLS, circadian rhythm disorders) and the Epworth Sleep Scale (ESS), a well-validated questionnaire that asks the subject to rate the likelihood of falling asleep in 8 commonly encountered situations. Possible scores range from 0 (the least sleepy) to 24 (the most sleepy) with a score of ≥ 10 indicative of excessive daytime somnolence. ESS correlates with the severity of OSA and with objectively measured sleepiness in patients with OSA.

Current snoring will be ascertained using responses to the following questions, developed for use in the Sleep Heart Health study: "Have you ever snored?" and "How
Objective Assessment of nasal pathology:
Clinical Examination: An investigator (a study physician, a research assistant, or the research coordinator) will perform a visual inspection of the inside of the nose to identify redness, swelling, polyps or polypoid swelling, crusting, mucus, and or frank pus. An oral exam will also be done to evaluate characteristics of the mouth (including tongue position, tonsillar size, and uvula size and a score will be given for each Dr. Sunderram will train all study investigators to perform the visual exams.

Rhinomanometry: The study technician will perform rhinomanometry which is a measurement of airflow through the nose. We will assess nasal resistance using the 4-phase-rhinomanometer (RhinoLab GmbH, Rendsburg, Germany) following the detailed technical, practical methodology, and referenced normative data published in the literature. Briefly, during the rhinomanometry procedure, a small tube is held in place using tape over one nostril and a mask is placed on the subject’s nose. The subject will be asked to take a few breaths with his/her mouth closed. The procedure will be repeated with the other nostril. Initially, the subject will be seated during measurement and measurements will be performed twice, before and 10 minutes after decongestion with 0.05% Xylometazoline solution. The procedure will be repeated while the subject is lying down. We have previously collected data using active anterior rhinomanometry (RhinoStream, Rhinometrics A/S, Lyng, Denmark) and published supine and sitting nasal resistances in subjects in patients coming to NYU sleep laboratory. For the present study, we will change to the newer technology to bring it into accord with the more recent standardization recommendations.

Home monitoring for OSA: Subjects will be given an ARES™ Unicorder (pictured) or a similar device (such as Emblettta) and a separate wrist pulse oximeter (Nonin WristOx2 Model 3150) to take home and wear for 2 nights, with a pre-addressed mailer to return the devices to the sleep lab. The ARES Unicorder is routinely used in clinical practice for home monitoring of OSA. The ARES Unicorder is worn on the forehead and does not require additional wires to external devices. It measures oxygen saturation and pulse rate from reflectance oximetry, airflow from a nasal cannula/pressure transducer, snoring via acoustic microphone and head movement actigraphy and head position from accelerometers. The device also provides audible alerts during the study if poor quality airflow or SpO2 is detected so the subject can reposition the device. The wrist pulse oximeter
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will be used to correct for the drift in oxygen saturation found in previous studies with the ARES™ Unicorder.

Analysis of Respiratory Data from ARES: Data from the monitor will be autoscored and then manually reviewed by a single trained sleep technician at NYU SOM. Data from ARES will be de-identified; only the study ID will be used in monitoring. Apneas will be scored when there is a reduction in airflow to less than 10% of baseline. We have extensive experience using the ARES device and have validated it against NPSG (Nocturnal Polysomnography) in over 300 subjects in multiple research studies.

SA3. Relate nasal resistance to CPAP adherence in patients with OSA and show that reduction of expiratory pressure using Cflex will improve CPAP adherence. Patients with OSA will be randomized in a double blind cross over design to receive CPAP or CPAP_Flex and adherence will be measured as average hours of use over 2 weeks.

Protocol for SA3
1. From the ARES studies, we expect to identify ~500 subjects with OSA. We expect about 10% to refuse to even try CPAP. All others would be recruited to be randomly assigned to CPAP or CPAP_Flex as a first treatment, and crossed over to the other after completing the first arm of the protocol.

2. Initially, the subject will be treated using the AutoCPAP program which varies the pressure, generally between 5 and 15 cm water, depending on the obstruction. If used regularly (for at least 4 hours a night for 2 nights), a fixed pressure will be automatically assigned. If the subject does not regularly use CPAP, treatment will continue using the autotitrate program. The technician will monitor CPAP treatment to ensure adequate treatment when the subject uses CPAP. The automated AHI is monitored to ensure efficacy of therapy (AHI of <10 events per hour of sleep). If the AHI is >10 events per hour of sleep the data is reviewed by a designated sleep physician and the pressure is modified or the patient is recommended for an in laboratory sleep study if indicated.

3. Adherence monitoring will be made from the CPAP machine for 1 month with first intervention, then switched to the alternate intervention and adherence monitored for another month. Data from last 2 weeks of each period will be used for objective adherence comparisons between interventions. Periods of reported non-use by the subject due to illness or travel will not be included in the treatment periods. The trial periods may be extended for up to 1 month due to instrument (CPAP machine or modem) failure. Instrument failure is not expected to exceed 10% of the users.

4. Subjective assessment of sleepiness, quality of life and satisfaction with therapy will be obtained using questionnaires administered at the start and end of each period.

Procedures for SA3

Initiation of Therapy: Within 6 months of the home monitoring identify OSA, subjects will return to the clinic for CPAP therapy and will undergo mask fitting and desensitization and CPAP education during this visit. CPAP education will follow a written protocol common to both sites. During the first two weeks of therapy, the research co-coordinator will call the patients each week to discuss any mask or CPAP related issues. If the subject experiences any problems, he/she may
return to the clinic for additional support or mask replacement. If more than 6 months elapse after the home monitoring and the subject wishes to participate in the CPAP trial, the subject will be asked to repeat the initial assessment including questionnaires, rhinomanometry, nasal lavage, and home sleep testing.

**Randomization and Blinding:** OSA patients will be randomly allocated to CPAP or CPAP\textsubscript{Flex} stratified by site and low (log[Reff]≤1.0) and high (log[Reff]>1.0) resistance by the statistician. This will be accomplished by generating an allocation table of randomly permuted blocks of assignments to study condition (CPAP vs CPAP\textsubscript{Flex}) for each site. Outcome of the randomized choice of treatment will be provided to an unblinded individual (one at each site) who is not part of the analysis of the study data, and who will set the allocated CPAP device at the start of each treatment period. Devices will be tracked by serial number. Although subjects will be blinded to the therapy type, they may be able to perceive a difference in the mask pressure during expiration. CPAP and CPAP\textsubscript{Flex} machines are identical otherwise and no feedback will be provided to subjects regarding the type of treatment. The unblinded individual (not the PI) will maintain a master file containing numbered sealed envelopes containing the serial number, patient ID and designation code for each treatment period and subject. Except in an emergency situation these envelopes will not be opened until the study has been completed and all data have been entered/cleaned. The unblinded individual will document any premature unblinding that may occur. All data review relevant to adherence/titration scoring will be presented to the scorer as a flow signal alone, keeping the pressure data unvisualized so as not to reveal the presence of CPAP\textsubscript{Flex}. The automated report will indicate if there are significant deviations from prescribed pressure.

**Monitoring of CPAP Efficacy and Adherence:** Efficacy will be evaluated by (i) reviewing residual AHI and inspiratory flow limitation at optimal pressure as recorded on the device and (ii) review of raw airflow signal. Nightly adherence at the optimal pressure is recorded on the device and also transmitted to the sleep center.

**Cross over to alternate therapy:** Four weeks after the first intervention (ie CPAP or CPAP\textsubscript{Flex}), the device will be switched to the alternate mode by remote modem connection. The switch will take place after the subject has completed the telephone satisfaction questionnaire.

**Subjective Assessment:** At the end of each intervention period subjects will fill out ESS, Functional Outcomes of Sleep Questionnaire (FOSQ) and a satisfaction questionnaire.\textsuperscript{59} At the second clinic visit (for the CPAP training and mask fitting), subjects will be given two stamped envelopes, addressed to the research coordinator. The envelopes will each contain one copy of the ESS and FOSQ. After approximately 3 weeks of the first therapy mode, the subject will be called by a member of the study team. The investigator will interview the subject to complete the satisfaction questionnaire by phone. The satisfaction questionnaire must be completed prior to the switch to the alternate treatment period. The investigator will also remind the subject to complete the ESS and FOSQ and return it by mail. This will be repeated for the second therapy mode. The satisfaction questionnaire must be completed to conclude the CPAP trial. At the end of each the end of each treatment period, a study investigator will attempt to reach the subject at least 3 times to complete the satisfaction questionnaire. If the subject cannot be contacted, a letter will be sent requesting the subject to contact the investigator. During this contact period, the treatment period will be extended. If the subject does not respond within two weeks, he/she will be considered lost to follow-up.
3.1. Duration of Study
The study period is four years.

3.2 Study Sites

Environmental and Occupational Health Institute (EOHSI), Piscataway, NJ, Mt. Sinai School of Medicine, New York and NYU School of Medicine, New York. Only de-identified data will be shared between the study sites.
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3.5.1 Inclusion Criteria
Subjects identified as new onset snoring (pre-post-9/11 score of ≤2 to 3-4) or non-snorer (score of ≤2 to ≤2).

3.5.2 Exclusion Criteria
(i) Gross skeletal alterations affecting the upper airway (eg. micrognathia) (ii) Unstable chronic medical conditions known to affect OSA (CHF, stroke) (iii) Pregnancy or intent to become pregnant within the period of the protocol (iv) Inability to sign informed consent form (v) Habitual snorer or diagnosis of OSA prior to 9/11/01 (pre-9/11 score of 3-4) (vi) A perforated septum (vii) Treatment for sleep apnea including surgery, current (within the past 2 months) use of a mandibular advancement device, or current (within the past 2 months) use of CPAP (viii) First WTCHP monitoring visit after 2/1/13.

3.5.3 Subject Recruitment
Two recruitment methods for the WTCHP responders at Rutgers Robert Wood Johnson Medical School (RWJMS) may be used for the study.

Clinic recruitment
The primary recruitment for the WTCHP responders at Rutgers RWJMS will be in-person during a clinic visit. Prior to each appointment, the WTCHP staff mail appointment packets to responders. The packets contain a letter confirming their appointment, a copy of the WTCHP consent, and approved at-home questionnaires. As part of this mailing packet, a pre-visit flyer (Pre-Visit Study Announcement) announcing the study will be included. As WTC responders return to the clinic for an annual monitoring or treatment exam, the clinic staff will check the medical chart for eligibility. A member of the clinic staff will confirm that the patient has agreed to be contacted for future studies and that the subject had not reported habitual snoring (snoring several nights a week) prior to 9/11. A study flyer will be placed in the file. If the patient appears to be eligible, a nurse or physician will inform the patient about the study, give the patient a copy of the approved flyer and ask if they are interested. If the patient is interested in participating, they will be asked to provide their name, email/street address, and phone number on a postcard so that a member of the research team can speak with him/her about the research study. A box labeled with the study name will be placed in the waiting room to collect postcards from interested patients. The box is under observation by clinic staff and will be emptied by the research staff each day. If the patient cannot be reached by phone and did provide their street address, a follow up letter will be mailed to them. The letter will ask the patient to contact the research staff if he/she is still interested in the study. If the email address was provided, an approved email will be sent asking the subject to contact the research staff.

Interested patients will also be given the option of speaking with a study investigator during the clinic visit. The study investigator (the research coordinator/assistant) will meet with him/her in a private area to inform the potential subject about the study and go through the screening script. In addition, flyers and postcards will be placed in the clinic waiting room. Information about the study will also be posted on the EOHSI website (http://eohsi.rutgers.edu/content/research-volunteers).
Mail recruitment
If the recruitment rate of WTCHP responders at Rutgers RWJMS via clinic visit is insufficient to meet recruitment goals, names of WTCHP responders at Rutgers RWJMS (the same study population) will be recruited by mail. Under WTCHP guidelines, for any mailing, names of responders at Rutgers RWJMS must be obtained from the Data Coordinating Center (DCC) for the WTCHP. Once the DCC has mailed the names to Dr. Udasin, the medical records will be checked to select responders who did not report habitual snoring prior to 9/11/01. The responders who did not snore will be sent a letter from Dr. Udasin, the principal investigator and medical director of the Rutgers RWJMS Clinical Center of the WTCHP. The letter will give the responders information about the study and let them know that they will be called by one of the study investigators. The letter will be followed by a phone call within a few weeks. This will give the responder some time to consider the study prior to being called by the study investigator.

To supplement the two recruitment methods, information about the study will be posted on the EOHSI website (http://eohsi.rutgers.edu/content/research-volunteers).

3.5.4 Consent Procedures

Clinic Recruitment: If the subject has asked to be contacted about the study (placed a contact card in the clinic box), a study investigator (research assistant, research coordinator) will call the subject and read the study screening script for clinic contacts.

Mail Recruitment: If the subject has been recruited by mailing, a member of the clinic staff will call the subject and read the study screening script for DCC contacts.

After reading the script (either for clinic contacts or DCC contacts), if the subject is interested in participating, their contact information will be recorded, a copy of the consent form will be mailed, and an appointment will be made for the first clinic visit. The subject will be called the preceding workday to confirm the appointment. The subject will be asked if he/she is experiencing seasonal allergies or had a recent cold. If yes, the appointment will be re-scheduled so that all symptoms have subsided at least 2 weeks prior to the appointment.

Clinic contacts only: If the subject is in the clinic and requests information about the study, the screening may be done in-person, in a private office. If eligible, the subject will be given a consent form to read. After reading it, the investigator will review the study and answer any questions. The consent form will be signed by the subject and the investigator. The subject will be given a copy of the signed document. An appointment will be made for the clinical visit.

If the subject wishes to think about participating, he/she will be given a copy of the consent form to take home. The investigator will record contact information and contact the subject in a few days. If the subject wishes to participate, an appointment will be made for the clinic visit. Consent will be obtained on the day of the clinic visit as outlined below.

Consent Signature
Clinic and DCC contacts: Subjects may return the signed consent form by mail. Once the consent form is received, an investigator will call the subject, answer any questions, and confirm participation. These subjects may then do the home sleep monitoring prior to their first clinic visit.
The monitor will be mailed with a signed copy of the consent form. If the clinic visit is scheduled first, on the day of the clinic visit, the consent form will be reviewed with the subject by a member of the study team. All questions will be answered. If the subject wishes to enroll, he/she will be asked to sign and date the consent form. The study investigator will also sign and date the consent form. The subject will be given a copy of the signed document.

### 3.5.5 Subject Costs and Compensation

After the completion of the clinic visit and the ARES home monitoring, subjects will be provided payment of $100 dollars as compensation for their time. Subjects who have been diagnosed with sleep apnea and placed on CPAP will be allowed to keep the machine after completion of the study, if desired. Subjects will have an opportunity to refuse to participate at any time during the study.

## 4. Study Variables

### 4.1 Independent Variables or Interventions

Both CPAP and CPAPFlex are standard treatments for sleep apnea. This study will test the efficacy of each treatment based on independent measures of nasal resistance.

### 4.2 Dependent Variables or Outcome Measures

Evaluation of sleep apnea will be based on sleep study performed in the home.

### 4.3 Risk of Harm

The physical risks to the study are minimal. All procedures are non-invasive and often performed in clinical settings. Participants may experience slight discomfort from the pressure of the strap of the ARES monitor. The strap may be loosened. Additionally, in rare cases (<0.5%), participants have had a mild skin allergy to the synthetic fabric on the strap. The participants will be instructed to discontinue use of the monitor if any skin reaction is suspected. Some participants may be concerned about the diagnosis of sleep apnea. These subjects will discuss the diagnosis with the study physician and receive treatment with CPAP. Some people find CPAP uncomfortable. The subject may choose to continue or discontinue the use of CPAP. The other risk of the study is the disclosure of PHI. Every effort will be made to keep all PHI confidential.

### 4.4 Potential for Benefit

Patients with OSA will receive treatment. They will have an opportunity to evaluate two modes of treatment with CPAP (CPAP and CPAPFlex) and select the most comfortable mode. Subjects diagnosed with OSA will be allowed to keep their CPAP machines following the study period, unless they specifically indicate that they do not wish to use it, in which case the devices will be returned to the sleep laboratory. Normal subjects will not benefit directly from participation in this study. However, the data from the study will provide new knowledge about conditions common to WTC exposed individuals.
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Evaluation of standard therapies in this population will help provide guidelines to physicians caring for these patients.

5. Data Handling and Statistical Analysis

Statistical analysis plan
All data (questionnaires, results of physical exams) will be de-identified (coded by study ID) and entered into electronic files on password-protected computers. Only study team members will have access to the data. The link between PHI and the study identifier will be kept in a password-protected file on a password-protected computer in the research coordinator's office. The link will be maintained for a period of 6 years after the closure of the study. Signed consent forms and subject contact sheets will be kept in a locked cabinet in the research coordinator's private office. Research data will not be included in the subject's medical records.

Statistical analysis will be primarily performed on an intent-to-treat basis. For all analyses, the statistical significance will be defined by a p-value < 0.05, unless specified otherwise. Bonferroni corrections will be applied to multiple testing, where appropriate.

SA1: Examine the relationships between post-9/11 OSA, upper airway disease and body mass index.
We will cross-tabulate the distributions of OSA and UAD to calculate the frequencies and proportions. Logistic regression analysis, with OSA as the dependent variable and UAD as the independent variable, will be subsequently used to evaluate the association of OSA and UAD without and with controlling for age, gender, weight gain, smoking and alcohol use. We will use a two-sample t-test to compare BMI between OSA subjects with vs. without UAD, followed by the linear regression analysis controlling for age, gender, weight gain, smoking and alcohol use. In subjects with both UAD and OSA, we will calculate and test the correlation coefficient of BMI and AHI to check if they are not correlated.

SA2: Determine the relationship between post-9/11 OSA, upper airway disease, nasal inflammation and nasal resistance.
We will first explore the distribution of nasal resistance and each of the inflammatory markers (cell count, IL-8, IL-6, TNF-alpha, interferon gamma; IL-4 and IL-10; eosinophil cationic protein (ECP)) by calculating the histograms, means, standard deviations and medians, etc., and compare these measures between subjects with vs. without UAD using the two-sample t-test. To evaluate the association of UAD with nasal resistance and inflammatory markers, we will use logistic regression analysis with UAD (yes/no) as the dependent variable, and nasal resistance and inflammatory markers as the independent variables. Subsequent subset analysis will be performed to test the individual association of UAD vs. nasal resistance and each inflammatory marker. Analysis will also be conducted without and with controlling for age, gender, BMI, AHI, smoking status, alcohol use and use of nasal steroids. Similar statistical methods will be used with OSA as the dependent variable. We will evaluate whether the association between UAD and OSA is attributed to both increased nasal resistance and inflammation. To do this, we will fit a logistic regression model with OSA as the independent variable, UAD, nasal resistance and inflammation as the dependent variable.

SA3. Relate nasal resistance to CPAP adherence in patients with OSA and show that reduction of expiratory pressure using CPAP Flex will improve CPAP adherence.
We will first explore the distributions of nasal resistance and adherence of CPAP, both in continuous scale and the discrete scale. We will calculate the correlation between nasal resistance and CPAP when both are treated continuous measures, and use chi-square test when both are...
6. Data and Safety Monitoring
All procedures in the study are minimal risk. Both CPAP and CPAPFlex have equal efficacy for the treatment of OSA. The PI will monitor this study for all patient safety issues. The PIs, Dr. Sunderram along with Dr. Ayappa (MSSM), will review these data as soon as they are available on each subject. Subjects will be given an access number to call during the work day during the study. Aggregate data reviews will be conducted annually at a minimum, and presented for review by the Rutgers-RWJMS, MSSM IRB and NYU IRB.

7. Reporting Results

7.1 Individual Results
All patients will be given the results of their overnight sleep monitoring. Those diagnosed with OSA will be asked to meet with the study physician to review the results and discuss the diagnosis and treatment options. At the end of the study, those subjects who participated in the CPAP evaluation will be given a report documenting the appropriate titration for treatment and recommendations for follow-up. Subjects will also be asked if they wish to share the study results with the WTCHP clinic. If so, the subjects will be asked to sign an authorization allowing the study staff to release the records to the WTCHP clinic. No release of study information will be made without a written authorization.

7.2 Aggregate Results
Subjects will be given the option to receive a summary of the study results. Additionally, the summary results will be available on ClinicalTrials.gov.

7.3 Professional Reporting
Results of the study will be published in peer-reviewed journals and may be presented at professional meetings. A description of this clinical trial will be available on ClinicalTrials.gov, as required by U.S. Law.

8. Bibliography
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32. McNicholas WT. The nose and OSA: variable nasal obstruction may be more important in pathophysiology than fixed obstruction. *Eur Respir J.* Jul 2008;32(1):3-8.


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