RESUME AND SUMMARY OF DISCUSSION: This application proposes to investigate risk factors for and subclinical and clinical consequences of early childhood obesity and sleep problems. In particular, the project will evaluate the prospective relationships between childhood sleep related factors and obesity in young adulthood, the longitudinal association between baseline obesity and cardiometabolic, sleep and neurobehavioral outcomes at follow-up, the cross-sectional association between obesity and relevant clinical and subclinical cardiometabolic and sleep abnormalities at follow-up, and whether sleep disordered breathing (SDB) in adolescence is age-dependent. The project will also assess the associations between independent variables in the obesity and sleep domains and three interrelated health outcomes involving cardiometabolic, sleep, and neurobehavioral systems. The topic has potential public health and clinical significance and impact. The investigators are qualified to conduct the proposed study, and the environment is appropriate. Many concerns from the previous review have been satisfactorily addressed. However, while the application has these and other strengths, there are some remaining concerns. Issues which were emphasized during the discussion included a need to further address followup of children (i.e., persons under 21 years of age) who may go to college (in light of an intended 100 percent followup), a need to further address exclusion criteria (including obesity at baseline), a need to further address coordinating methods with the proposed hypotheses, a need to further address non-linear changes with age and how Tanner staging scores would be used, a need to further address how DEXA scores would be used, and other methodologic aspects of the approach. Overall, however, the strengths of the application outweigh the weaknesses, and it is likely that informative findings would result from this project.

DESCRIPTION (provided by applicant): We propose to conduct an 8-year follow-up examination of a population-based sample of 700 young adolescents. The recruitment and baseline exam of this cohort was conducted when they were 5-12 years old. Our overall objective is to assess a wide range of risk factors for and subclinical and clinical consequences of early childhood obesity and sleep problems. Specifically, we propose to evaluate the following three specific aims: 1) the prospective relationships between childhood sleep related factors and obesity in young adulthood; 2a) the longitudinal association between baseline obesity and cardiometabolic, sleep and neurobehavioral outcomes at follow-up; 2b) cross-sectional association between obesity and relevant clinical and subclinical cardiometabolic and sleep abnormalities at follow-up; and 3) whether SDB in adolescence is age-dependent. We plan to assess the independent associations between independent variables in the obesity and sleep domains and three inter-related health outcomes involving cardiometabolic, sleep and neurobehavioral systems. Obesity both in adults and children has become epidemic and is a major public health problem given its association with CVD, the leading cause of death, and other metabolic diseases. However, there are limited data assessing the risk factors for, and outcomes of, childhood obesity. Recent data from our group and others are supportive of a systematic prospective investigation of our hypotheses, and these evidence include: (1) Sleep duration has been recently identified as a novel risk factor for obesity, and the association is modified by factors such as age, gender, stress, physical activity, and socioeconomic status. In our data, we observed a cross-sectional association between sleep duration and obesity based on subjective but not objective reports; (2) Obese adults that are stressed frequently have mild hypercortisolism and are at risk for stress-induced visceral obesity and metabolic syndrome. Our data, from the child and adult samples, support this hypothesis; (3) Obesity in adults is a strong risk factor for cardiovascular disease. In our child sample, we have reported that obesity and SDB are strong and independent risk factor for higher levels of BP and impairment of cardiac autonomic modulation; (4) In adults it is hypothesized that obesity leads to higher risk of CVD via metabolic syndrome pathway and there is increasing concern that metabolic factors are elevated in obese children as well. We and others have reported that SDB in adults is associated with increased risk of the metabolic syndrome. In our child data, SDB was cross-sectionally associated with an increased risk for several metabolic abnormalities; (5) We and others have reported that impaired autonomic modulation is significantly associated with CVD mortality and morbidity. In our children sample, we have reported significant synergistic interactions between SDB-HRV and obesity-HRV on elevated BP, indicative of complex inter-relationships between sleep, obesity, and cardiometabolic...
health occurring early in life. Finally, in our child data the age distribution of SDB suggested a possible age-dependent relationship within adolescence.

PUBLIC HEALTH RELEVANCE: Obesity in childhood has become an epidemic and a major public health problem. This prospective study will assess a wide range of novel risk factors for and subclinical and clinical consequences of early childhood obesity and sleep problems. The knowledge gained from this study will better position our intervention strategies to reduce the public health burden of childhood obesity.

CRITIQUE 1

Significance: 1
Investigator(s): 2
Innovation: 2
Approach: 1
Environment: 2

Overall Impact:

Strengths

- Results from this longitudinal study will have impact on the broader understanding of how obesity in developing adolescents is related to sleep and sleep disordered breathing (SDB) and, conversely, how sleep and SDB impact obesity
- Results from this longitudinal study will have impact on the broader understanding how sleep and SDB are related to cardiovascular function, markers of inflammation and stress, glucose control and behavioral measures in developing adolescents

Weaknesses

- Numbers of children with severe SDB at Baseline is relatively small, but the impact of this on the study of incidence is not a detriment for the current study design, since measurements of sleep, SDB and obesity will be available at both times of measurement.

1. Significance:

Strengths

- Large (N = 700) cohort of children sampled from a single identified county in rural Pennsylvania followed Best Practices for engaging a public school system, which resulted in very high initial questionnaire response rate response rate; study then proceeded to carefully characterize SDB and sleep with in-lab, continuously monitored polysomnography, thus creating a unique and indispensable resource to be followed over time.
- Existing cross-sectional data investigating relationship of elevated blood pressure to SDB are impressive in implicating AHI as a risk factor for hypertension at levels below those customarily considered for adults (AHI’s between 1 and 5).
- Measures of Heart Rate Variability (HRV) during sleep in a population based study of adolescents in relation to SDB suggests sensitivity of these measures in a far younger age group than is usually considered at risk for changes in cardiovascular function

Weaknesses

- Preliminary data did not always corroborate what other researchers have reported regarding the association between SDB and tonsil size (assessed visually) and between SDB and cognitive impairment; unclear whether these represent substantive weaknesses or whether the findings may be reflecting unique features of this particular pediatric population
2. Investigator(s):

**Strengths**
- Strong research group with Multiple Principal Investigator leadership, consisting of a highly experienced, established investigator in sleep research (Bixler) and a strong methodologist/epidemiologist with particular skills in computerized analyses of the EKG (Liao).
- Other Co-investigators (Vgontzas, Calhoun) provide important complementary skill sets.
- Note is made of inclusion of a Co-investigator with specific background in actigraphic measurements of physical activity (Elavsky)

**Weaknesses**
- None obvious. This team has worked together effectively for some time.

3. Innovation:

**Strengths**
- Most cohorts examining morbidity of SDB have been adult or geriatric populations
- Of those few existing population-based (non-clinic) cohorts of children arguably none have had sleep and physiology as well characterized as this population.
- High retention rate is a distinguishing feature.
- Inclusion of orthostatics in adolescents is novel
- Application of study of autonomic balance during sleep to this age group is unique; may hold promise in understanding how short sleep durations and/or complaints of poor sleep manifest physiologically

**Weaknesses**
- None obvious.

4. Approach:

**Strengths**
- Application has been quite responsive to prior Summary Statement from the IRG.
- Several modifications have been offered in the current application, including expansion of measures of physical activity to include actigraphy, deletion of echocardiography, and further specification of EKG data to be available and how such data will be used.
- Timeline of recruitment, calendar years of initial data collection, age of children when originally studied have all been clarified with new Tables on page 54 and 61
- Justification for DXA has been described and neuropsychological battery has been shortened
- Questions regarding bi-directionality of relationships have been elucidated explicitly to indicate that sleep (both duration and SDB) is conceptualized as a risk factor for the development of follow-up obesity, taking into account baseline measurement, as well as examining how adiposity is related to incident SDB. Hypotheses reflecting this bi-directionality are now included.
- Follow-up estimates (85%) are high but clearly justified by Preliminary Data of a follow up of 150 participants from the original study that are committed to participating in the follow-up.

**Weaknesses**
- Although the Investigators will include the obese subjects in Baseline, a possible reduction in power exists if children with prevalent hypertension or abnormal sympathetic/parasympathetic balance on those initial measurements are included in the study of incidence; thresholds for such abnormalities not yet defined in the application, although the Investigators do make it clear that baseline measures
(e.g., HRV) are to be used as covariates

5. Environment:

Strengths

- The sampling framework (public school system of Dauphin County, Pennsylvania) is a unique resource, given the very high initial rates of participation and preliminary data suggesting that call back retention will be very high as well.
- Setting for the research (Penn State Medical Center in Hershey) is well-accepted into the community

Weaknesses

- The population is fixed by composition of original sample, which is about 80% Caucasian.

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

- Adequate

Inclusion of Women, Minorities and Children:

Both Genders, Acceptable
Minority and Non-minority, Acceptable
Children and adults, Acceptable

- Acceptable scientifically

Resubmission:

- This is a resubmission of an application previously reviewed in February 2009; many concerns have been addressed.

Budget and Period of Support:

Recommend as Requested

Resource Sharing Plans:

Acceptable