Variation of C-Reactive Protein Levels in Adolescents Association With Sleep-Disordered Breathing and Sleep Duration

Emma K. Larkin, MHS; Carol L. Rosen, MD; H. Lester Kirchner, PhD; Amy Storfer-Isser, MS; Judith L. Emancipator, MA; Nathan L. Johnson, MA; Anna Marie V. Zambito, MPH; Russell P. Tracy, PhD; Nancy S. Jenny, PhD; Susan Redline, MD, MPH

Background—There is increasing evidence that sleep-disordered breathing (SDB) is an independent risk factor for cardiovascular disease (CVD) in adults. C-reactive protein (CRP), a marker of systemic inflammation, is an important predictor of future cardiovascular events. The goal of this study was to quantify the associations of SDB, sleep duration, and CRP in adolescents to better understand the role of SDB in CVD risk.

Methods and Results—Adolescents (n=143; age, 13 to 18 years; 36% black; 50% female) with a wide range of SDB severity underwent polysomnography and measurement of high-sensitivity CRP. SDB was quantified with the apnea hypopnea index (AHI) and oxygen desaturation measures. Sleep duration was estimated from 7-day actigraphy. The independent and dose-response associations of SDB with CRP were addressed through linear mixed-effects models. Forty-eight percent were overweight or obese, and 12% had SDB (AHI ≥5). CRP levels varied with increasing body mass index and SDB. After adjustment for body mass index, age, sex, and race, mean CRP levels were 0.50, 0.43, 0.97, and 1.66 mg/L for SDB severity levels of AHI <1, 1 to 4.9, 5 to 14.9, and ≥15, respectively (P=0.0049, AHI ≥15 versus <1). Adjusted mean CRP levels demonstrated a dose response with SDB above a threshold AHI of 5. This association was partially explained by overnight hypoxemia and less so by sleep duration.

Conclusions—In adolescents free of known CVD, an AHI ≥5 is associated with increasing levels of CRP, suggesting that pediatric SDB may confer additional CVD risk beyond that of obesity. (Circulation. 2005;111:1978-1984.)

Key Words: body mass index • C-reactive protein • inflammation • sleep apnea syndromes

Sleep-disordered breathing (SDB), characterized by snoring, repetitive apneic episodes, hypoxemia, sleep disruption, daytime sleepiness, and neurobehavioral dysfunction, is a treatable condition found in 4% to 9% of middle-aged adults.1 In adults, SDB is an independent risk factor for hypertension and is implicated in the initiation and progression of other cardiovascular diseases.2-4 The increased prevalence of hypertension and atherogenesis among SDB patients has been attributed to sympathetic activation and endothelial dysfunction, likely resulting from initiation and propagation of inflammatory responses within the microvasculature.5,6 Consistent with this pathogenesis, C-reactive protein (CRP), a biomarker of inflammation that predicts risk of future cardiovascular events and a potential direct mediator of inflammation in atherosclerotic lesions,7 is elevated in adults with severe SDB, with some evidence that it decreases after SDB treatment.8,9

SDB is a prevalent condition in childhood, affecting 2% of school-aged children.10 Children may be a more ideal population to examine the role of SDB in cardiovascular outcomes using intermediate markers of cardiovascular disease (CVD) such as CRP because children have less confounding from comorbidities and medications and because studies of young cohorts are less likely to be influenced by survivor biases. Delineating the determinants of cardiovascular risk factors in childhood is important, given their predictive abilities for later cardiovascular events and their potential importance of initiating prevention strategies early in life.11-13

To date, most research on adverse outcomes from SDB in children has focused on behavioral and neurocognitive dysfunction with less attention to cardiovascular outcomes. However, a small amount of literature indicates that SDB is associated with higher blood pressure (BP).14,15 BP dysregulation,16 and echocardiographic changes17 in children with SDB. A recent study in 81 snoring children referred for diagnostic testing for suspected SDB reported that CRP was positively associated with the degree of SDB, sleep disruption, and daytime sleepiness18 and supports the feasibility of using this biomarker in pediatric SDB.
This study addresses the role of sleep disorders and CRP levels in adolescents, a group at increased risk for sleep deprivation, which may also trigger proinflammatory processes. We postulated that CRP levels will be augmented in association with degree of respiratory and sleep disturbances. Additionally, we assessed the presence of a physiological threshold or a dose-response relationship between levels of CRP and SDB. Moreover, we explored whether the CRP response to SDB was acute, as reflected by changes in overnight levels of CRP, or a more chronic, sustained elevation.

### Methods

#### Participants and Protocol

This report includes data from 143 adolescents who were 13 to 18 years of age in the TeenZzz Study, an ongoing longitudinal pediatric cohort study evaluating the role of SDB on a wide range of health outcomes. TeenZzz participants represent a sample of children who initially participated in the Cleveland Children’s Sleep and Health Study (CCHS), a nonclinical cohort study of 850 children recruited from the birth records of local area hospitals who underwent sleep and health assessments at 8 to 11 years of age. For the TeenZzz Study, 250 of these children—including all snorers, children with SDB, and a random sample of the remaining cohort—have been targeted for evaluation during adolescence. To increase the range of SDB severity in the original nonclinical CCHS cohort, TeenZzz also has included recruitment of a clinical sample of adolescents from the same community who were referred for evaluation of snoring. The analytic sample consists of 128 of the 130 adolescents studied to date who were recruited via the CCHS cohort (2 adolescents were excluded because of juvenile-onset diabetes) and all 15 adolescents studied to date recruited from the referred sample. Through the use of a standardized research protocol in a dedicated clinical research facility, each child who was free of acute illness had overnight polysomnography, venipuncture both before (at 10PM) and after sleep with overnight fasting (7AM), and various physiological and anthropometric assessments. Informed consent was obtained from the child’s caregiver; written assent was obtained from the child. The governing institutional review board approved the study.

#### Polysomnography and Sleep Data

In laboratory polysomnography (Compumedics E-series) and actigraphy were performed as detailed in the online-only Data Supplement. With polysomnography, SDB was quantified as the apnea hypopnea index (AHI), calculated by summing the total number of respiratory events (apneas and hypopneas) and dividing by total sleep time. SDB was categorized as normal (AHI <1), mild (AHI, 1 to 4.9), moderate (AHI, 5 to 15), or severe (AHI ≥15). When treated as a continuous variable, the AHI was natural log transformed to achieve a distribution close to normality. AHI was also categorized AHI and ln(CRP) were conducted in 3 ways: (1) models that select a value near the bend of the GAM plot and then searching for the threshold effect using a linear mixed-effects model in which ln(CRP) and ln(AHI), after adjustment for age, sex, race, BMI percentile, and other covariates, were lower than the detectable limits and assigned a value of 0.1 or 0.15 on the basis of the assay used. Additional sensitivity analyses were conducted to compare alternative coding values of the lower limit. Because of processing errors, only a single CRP level was available for 40 individuals (16 from morning and 24 from evening sampling). The intraclass correlation coefficient for morning and evening levels was very high (0.92), with no evidence of systematic differences in morning and evening values. CRP, as a skewed variable, was natural log transformed to achieve a distribution close to normality.

#### Other Covariates

Height was measured with a rigid stadiometer, and weight was measured with a calibrated digital scale. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared and converted into age- and sex-adjusted percentiles based on population data from NHANES 2000. Three BP readings at each of 3 measurement times (10 PM and 7 and 10 AM) were obtained following standardized guidelines using a calibrated sphygmomanometer, and the resultant 9 measurements were averaged. Systolic hypertension and diastolic hypertension were defined by values that exceeded the 95th percentile for age, sex, and height based on normative population data. Information on sleep and health habits was obtained from a standardized questionnaire completed by the caregiver. Waist-to-hip ratio (WHR) was calculated by taking the average of 2 waist circumference measurements and dividing by the average of 2 hip circumference measurements. Lipid profiles were determined by automated colorimetric methods at the University of Vermont.

#### Statistical Analyses

SAS version 8.2 and S-PLUS version 6.0 were used for all analyses. Graphs and Spearman rank correlations were used to summarize relationships between continuous variables. Linear mixed-effects models were used to explore the relationship between ln(CRP) and demographic variables. This model allows for the fact that not all participants had both CRP measurements and models the correlation between morning and evening CRP levels in participants who had both measurements. Generalized additive models (GAMs) were used to identify the functional form (dose response) of the relationship between ln(CRP) and ln(AHI), after adjustment for age, sex, race, BMI percentile, and (BMI percentile). The models were fit with a nonparametric loess function of ln(AHI) to describe the functional form. From the results of a plot of the predicted ln(CRP) versus ln(AHI), a threshold dose response was identified and a piecewise linear model was then fit to allow for the threshold effect using a linear mixed-effects model in SAS Proc Mixed. The cut point for a threshold effect was chosen by selecting a value near the bend of the GAM plot and then searching in that neighborhood for a point that produced the lowest Akaike information criterion in a mixed model. Models comparing categorized AHI and ln(CRP) were conducted in 3 ways: (1) models that were unadjusted for any covariates; (2) adjusted models that included age, sex and race (partially); or (3) adjusted models that included covariates for age, sex, race, BMI percentile, and (BMI percentile) (fully). Additional models included oxygen desaturation parameters, arousal index, hypertension status, average sleep duration, and cholesterol levels to determine whether they explained the relationship between SDB and CRP.

To assess whether there were any changes in overnight CRP levels by SDB status, we analyzed the overnight difference divided by the mean of morning and evening levels for individuals who had both measurements available and whose values did not reach the floor for either measurement. A t test was used to compare whether this measure of overnight change of CRP change differed by AHI ≥5 versus AHI <5.

### CRP Levels

Serum CRP was assayed with a high-sensitivity assay. For 81% of the samples, the assay performed had a lower limit of 0.1 and an upper limit of 90 mg/L (Immunoite High Sensitivity CRP, Immulite 2000 Analyzer); the remaining 29% were assayed with a lower detectable limit of 0.15 mg/L (BNII nephelometer [N High Sensitivity CRP, Dade Behring Inc]). Forty-seven measurements (19.1%) were lower than the detectable limits and assigned a value of 0.1 or 0.15 on the basis of the assay used. Additional sensitivity analyses were conducted to compare alternative coding values of the lower limit. Because of processing errors, only a single CRP level was available for 40 individuals (16 from morning and 24 from evening sampling). The intraclass correlation coefficient for morning and evening levels was very high (0.92), with no evidence of systematic differences in morning and evening values. CRP, as a skewed variable, was natural log transformed to achieve a distribution close to normality.

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Results
The sample of 143 children had a mean±SD age of 13.8±0.8 years (range, 13 to 18 years; Table 1), and 36.4% were black. Approximately one third of the sample met the criteria for obesity defined by exceeding the 95% percentile of BMI for age and sex, whereas 19% were at risk for overweight with values between the 85th and 95th percentiles. The prevalence of hypertension was 11.2% on the basis of either elevated systolic (n=13) or diastolic (n=3) measurements. SDB was identified in 17 (11.9%), with 8 (5.6%) having moderate SDB (AHI, 5 to 14.9) and 9 (6.3%) having severe SDB (AHI ≥15).

Variation of CRP Levels by Participant Characteristics
CRP levels by subgroups are shown in Table 2. In unadjusted analyses, CRP levels did not vary significantly by race (P=0.07) or sex (P=0.18). In contrast, adolescents with either systolic or diastolic hypertension had higher CRP levels than nonhypertensives (P=0.04). As continuous measures, however, CRP levels were only weakly correlated with systolic BP (r=0.15, P=0.08) and were not correlated with diastolic BP. CRP levels also varied significantly with BMI, showing little difference in CRP between the first 2 quartiles of BMI percentile (<85%) but increasing levels in the third quartile (BMI, 85% to 97%) and fourth quartile (BMI >97%). CRP level was modestly correlated with total cholesterol (r=0.22, P<0.01) and LDL cholesterol (r=0.26, P<0.01) but not with HDL cholesterol (r=−0.13, P=0.12).

Interrelationship Among BMI, AHI, CRP, and Sleep Variables
Spearman’s correlations show the unadjusted associations among the variables of interest (Table 3). CRP was strongly correlated with BMI percentile (r=0.53); statistically significant but weaker correlations also were demonstrated with AHI, both overnight hypoxemia variables, and average sleep duration. However, there was little evidence of a correlation between CRP and arousal index, a measure of sleep fragmentation. Moderate associations among BMI percentile and the sleep variables were also observed. WHR demonstrated weaker correlations with AHI and CRP than BMI percentile.

Variation of BP With Sleep Indexes
Of the 17 subjects with an AHI ≥5, 5 (29.4%) were classified as hypertensive. The AHI was correlated with both systolic (r=0.40, P<0.001) and diastolic (r=0.20, P<0.02) BP. Systolic but not diastolic BP was correlated with sleep duration (r=−0.27, P<0.001), percentage time at an oxygen

Table 1. Sample Characteristics (n=143)

<table>
<thead>
<tr>
<th>Age, y</th>
<th>13.7±0.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>71 (50)</td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>52 (36)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.2±6.6</td>
</tr>
<tr>
<td>BMI percentile (mean±SD)</td>
<td>73.0±27.1</td>
</tr>
<tr>
<td>BMI percentile category, n (%)</td>
<td></td>
</tr>
<tr>
<td>Normal, &lt;84%</td>
<td>74 (52)</td>
</tr>
<tr>
<td>At risk for overweight, 85%–94%</td>
<td>27 (19)</td>
</tr>
<tr>
<td>Overweight, &gt;95%</td>
<td>42 (29)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>155.4±30.3</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>48.8±13.8</td>
</tr>
<tr>
<td>SDB category, n (%)</td>
<td></td>
</tr>
<tr>
<td>AHI &lt;1</td>
<td>96 (67)</td>
</tr>
<tr>
<td>AHI 1–4.9</td>
<td>30 (21)</td>
</tr>
<tr>
<td>AHI 5–15</td>
<td>8 (6)</td>
</tr>
<tr>
<td>AHI ≥15</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Sleep duration, min</td>
<td>469.2±64.8</td>
</tr>
<tr>
<td>&lt;7 h, n (%)</td>
<td>25 (17)</td>
</tr>
<tr>
<td>&lt;6 h, n (%)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Children with SpO₂ values &lt;90%, n (%)</td>
<td>31 (22)</td>
</tr>
<tr>
<td>SpO₂ nadir (mean±SD), %</td>
<td>90.2±4.4</td>
</tr>
</tbody>
</table>

Table 2. Unadjusted Geometric Mean CRP Levels by Subject Characteristics

<table>
<thead>
<tr>
<th>n</th>
<th>Geometric Mean CRP Level, mg/L</th>
<th>95% CI</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>72</td>
<td>0.63</td>
<td>0.46–0.86</td>
</tr>
<tr>
<td>Female</td>
<td>71</td>
<td>0.47</td>
<td>0.34–0.64</td>
</tr>
<tr>
<td>Nonblack</td>
<td>52</td>
<td>0.46</td>
<td>0.35–0.61</td>
</tr>
<tr>
<td>Black</td>
<td>91</td>
<td>0.72</td>
<td>0.50–1.03</td>
</tr>
<tr>
<td>No hypertension</td>
<td>128</td>
<td>0.50</td>
<td>0.39–0.63</td>
</tr>
<tr>
<td>Hypertension†</td>
<td>15</td>
<td>1.05</td>
<td>0.53–2.06</td>
</tr>
</tbody>
</table>

Table 3. Spearman Correlation Coefficients Relating AHI, BMI Percentile, and CRP With Each Other and Sleep Indexes*

<table>
<thead>
<tr>
<th></th>
<th>BMI</th>
<th>AHI</th>
<th>WHR</th>
<th>Arousal Index</th>
<th>SpO₂ &lt;90%</th>
<th>SpO₂ Nadir</th>
<th>Sleep Duration, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP†</td>
<td>0.53 (&lt;0.001)</td>
<td>0.35 (&lt;0.001)</td>
<td>0.32 (&lt;0.001)</td>
<td>0.07 (0.38)</td>
<td>0.32 (&lt;0.001)</td>
<td>−0.22 (0.010)</td>
<td>−0.29 (&lt;0.001)</td>
</tr>
<tr>
<td>BMI</td>
<td>...</td>
<td>0.50 (&lt;0.001)</td>
<td>0.46 (&lt;0.001)</td>
<td>0.16 (0.06)</td>
<td>0.37 (&lt;0.001)</td>
<td>−0.27 (&lt;0.001)</td>
<td>−0.34 (&lt;0.001)</td>
</tr>
<tr>
<td>AHI</td>
<td>...</td>
<td>...</td>
<td>0.40 (&lt;0.001)</td>
<td>0.27 (0.001)</td>
<td>0.61 (&lt;0.001)</td>
<td>−0.64 (&lt;0.001)</td>
<td>−0.31 (&lt;0.001)</td>
</tr>
</tbody>
</table>

*Data are presented as correlation coefficients with probability values in parentheses.
†Based on the average of morning and evening values, unless only 1 value was available.
TABLE 4. Variation of CRP Levels With SDB

<table>
<thead>
<tr>
<th>AHI Level</th>
<th>Unadjusted</th>
<th>Partially Adjusted</th>
<th>Fully Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI &lt;1</td>
<td>0.42 (0.33–0.54)</td>
<td>0.43 (0.33–0.56)</td>
<td>0.50 (0.40–0.63)</td>
</tr>
<tr>
<td>AHI 1–4.9</td>
<td>0.56 (0.36–0.88)</td>
<td>0.54 (0.34–0.86)</td>
<td>0.43 (0.29–0.66)</td>
</tr>
<tr>
<td>AHI 5–14.9</td>
<td>1.48 (0.62–3.53)</td>
<td>1.37 (0.56–3.34)</td>
<td>0.97 (0.43–2.16)</td>
</tr>
<tr>
<td>AHI ≥15</td>
<td>3.11 (1.38–7.03)</td>
<td>2.73 (1.17–6.37)</td>
<td>1.66 (0.76–3.60)</td>
</tr>
</tbody>
</table>

*Values are geometric means (95% confidence limits) of CRP (mg/L) values in unadjusted and adjusted models.
†Adjusted for age, sex, race, BMI percentile, and (BMI percentile2).
‡Adjusted for age, sex, race, BMI percentile, (BMI percentile2).

Variation of CRP Levels by AHI Level
The variation of levels of CRP by AHI categories is summarized in Table 4 in analyses that were unadjusted; adjusted for age, sex, and race (partial); and adjusted for age, sex, race, BMI percentile, and (BMI percentile2) (full). WHR did not significantly predict ln(CRP) levels after adjustment for BMI. Significant differences between the “severe” SDB group (AHI ≥15) and the unaffected group (AHI <1) were observed in the unadjusted analyses (P<0.0001), partially adjusted models (P<0.001), and fully adjusted models (P=0.0053).

The lines in the Figure show the predicted association between ln(AHI) and ln(CRP), after adjustment for BMI percentile, (BMI percentile2), age, sex, and race from the GAM; the circles indicate raw unadjusted values. Statistical modeling identified a threshold effect at a ln(AHI) of 1.6 (corresponding to an AHI level of ~5). The regression coefficients from the 2-slope mixed-effects linear model that incorporated this threshold effect are reported in Table 5. The first slope assesses the relationship between ln(AHI) and ln(CRP) before the bend (ln(AHI) < 1.6 or AHI <5), whereas the sum of the first and second regression coefficients assesses the relationship between ln(AHI) and ln(CRP) after the bend. There is little evidence of a relationship between ln(AHI) and ln(CRP) for ln(AHI) <1.6 (slope, -0.03; P=0.80). However, at levels of ln(AHI) >1.6, there is a significant linear relationship between ln(AHI) and ln(CRP) (slope, 0.88; P=0.0002). Children with the highest AHI levels had increased levels of CRP whether AHI was expressed as a continuous or ordinal predictor.

To further explore the association between CRP and AHI, considering cholesterol levels (a possible confounder), we added total cholesterol and LDL cholesterol separately as covariates in the above model. The results show a similar significant association between ln(AHI) and ln(CRP) as described above, with the coefficient for cholesterol marginally significant (P=0.075) and the coefficient for LDL less so (P=0.11).

Relationships of CRP With Other Respiratory or Sleep Measures
CRP was also highly associated with overnight hypoxemia expressed as percent of sleep time with SpO2 values <90% (P=0.0008) in a regression model after adjustment for age, sex, BMI percentile, and (BMI percentile2). When terms for both hypoxemia and AHI were simultaneously included in the previously described models, the magnitude of the second slope decreased by 23%, suggesting that a portion of the association between AHI and CRP was explained by SDB-associated hypoxemia. More specifically, with both AHI and hypoxemia terms included in the same model, the second slope remained a significant predictor (P=0.02), whereas the hypoxemia was not a significant predictor. Sleep duration was also significantly associated with ln(CRP) in models adjusted for age, sex, BMI percentile, and (BMI percentile2) (P=0.023). Incorporating both sleep duration and ln(AHI) into the model reduced the magnitude of the ln(AHI) ≥1.6 coefficient by only 9%. Controlling for the arousal index did not substantially affect the relationship between ln(AHI) and ln(CRP).

Overnight Variation in CRP Levels
Visual inspection of the relationship between ln(AHI) and overnight change in CRP level (measured by the overnight difference in CRP divided by the mean) demonstrated no discernible pattern or trend. There was no significant difference in the overnight change in CRP levels in children with...
higher AHI (≥5; n=7) versus lower AHI (<5; n=70) levels (P=0.97). Moreover, the intraclass correlation between morning and evening levels was extremely high (0.92), indicating the absence of “acute” variation in response to overnight SDB or sleep-related stresses.

**Discussion**

This is the first study to extensively model the nature of the dose-response relationship between SDB and CRP in a racially diverse population of adolescents who were relatively free of associated comorbidities that considers the potential impact of sleep deprivation, a common exposure in adolescents. In this sample of adolescents, we demonstrate a relationship between SDB and CRP levels that persisted after adjustment for important covariates. This report extends previous research in adults by providing evidence that SDB may modify CVD risk profile much earlier in life. The pathophysiological basis for the observed association between CRP and SDB may relate to myriad potential adverse physiological effects attributable to SDB (hypoxemia, reoxygenation, hypercapnia, intrathoracic pressure changes, and arousals) that may upregulate systemic inflammation and enhance atherosclerotic processes through intermediary mechanisms, including increased sympathetic activation, vascular endothelial dysfunction, oxidative stress, inflammation, and metabolic dysregulation.

This work extends the research of Tauman et al by clearly discerning a strong association for the relationship between AHI and CRP once a threshold AHI value of 5 is exceeded and identifying no significant relationship in children with an AHI <5. Identification of “threshold” levels of disease that confer increased risk of comorbidity has been a major challenge in understanding the health impact of SDB in both children and adults. Recent data in children have indicated that very mild levels of SDB, including primary snoring, are associated with behavioral comorbidity.27,28 To the best of our knowledge, this is the first study to address the threshold level of SDB in children for an important biochemical marker of inflammation, indicating the potential for cardiovascular comorbidity. Identifying threshold effects is important to help develop treatment guidelines and understand the pathophysiological consequences of SDB of various grades of severity.

There are no established guidelines for what levels of CRP are considered elevated in children. In adults, CRP levels <1 mg/L are considered low risk; 1 to 3 mg/L, medium risk; and >3 mg/L, high risk.29 In our study, 20% of the adolescents had medium-risk levels and 12% had high-risk levels of CRP. The proportions of children in our sample who had those elevated CRP levels ranges were similar to those reported in the NHANES data for 10- to 15-year-old children that found that 15% of the sample had values between 0.9 and 2.7 mg/L and 10% of children had values >2.7 mg/L.30

Compared with adult studies of CRP, our observations were based on children with relatively mild SDB and limited hypoxemia, allowing us to extensively model threshold levels at the milder end of disease severity. Although we cannot exclude the possibility that the elevated CRP levels with SDB are an epiphenomenon, it is possible that the strong associations observed in our sample, even with relatively modest degrees of SDB and overnight hypoxemia, may reflect a special vulnerability of younger individuals to overnight SDB-related stresses. Although limited work has addressed this in humans, animal work has shown that the neurodevelopment of young animals is differentially sensitive to hypoxic exposures at key developmental periods.31 Additionally, the strength of the signals observed among SDB indexes with CRP levels may relate to the better ability to detect biologically meaningful relationships in a sample relatively free of other chronic conditions. Finally, our cohort was likely free of survival biases, which may attenuate the strength of potential relationships in older groups, in which those most susceptible to stresses such as SDB may be less represented.

We identified a relationship between indexes of overnight hypoxemia and CRP, consistent with data suggesting that hypoxemia may augment release of inflammatory cytokines, adhesion molecules, and insulin and contribute to excessive free radical production. Our indexes of oxygen desaturation explained part but not all of the association between AHI and CRP, suggesting that overnight hypoxemia may be one pathway that mediates the association between SDB and inflammation. The persistence of an association between AHI and CRP after considering both indexes of oxygen saturation suggests that the AHI may contain additional information about pattern of desaturation (ie, intermittent falls) or other associated physiological stresses (eg, airway obstruction) relevant to systemic inflammation. The association between AHI and CRP was not changed when levels of total cholesterol and LDL cholesterol also were considered.

Previous studies in adults have suggested that sleep deprivation may trigger inflammatory processes. Adolescents are considered to need >9 hours of sleep, which only 12.1% of our sample achieved. However, the biochemical effects of insufficient sleep of various degrees in adolescents are uncertain. In adults, experimentally induced sleep deprivation (4 hours per night for 10 nights) has been shown to elevate CRP levels.30 Epidemiological studies of adults indicate that average sleep times of <6 to 7 hours are associated with a range of adverse health outcomes, including glucose intolerance and mortality.34 In our sample, sleep duration averaged 7.8 hours, with 17.1% sleeping on average <7 hours. A modest negative correlation was observed between sleep duration and CRP levels, which, however, was attenuated when AHI, a correlate of sleep time, was considered. We might have observed as stronger association between CRP and sleep duration had our subjects been more severely sleep deprived.

We found no evidence for a significant relationship between SDB and overnight change in CRP levels in the subsample with both morning and evening measurements. Although this subanalysis was limited, it suggests that the observed elevation of CRP levels in children with SDB is unlikely to be an acute response to overnight SDB stresses. In healthy adults, CRP levels do not display significant diurnal variation.35 Although the half-life of CRP averages ~14 hours, one may have expected morning levels to increase relative to evening levels if SDB-related stresses were acutely causally related to enhanced inflammation. Rather, the overall increase in both morning and evening levels of CRP...
among adolescents with SDB indicates that SDB is associated with sustained diurnal elevation of inflammatory mediators. This is consistent with research that demonstrated that the increased nocturnal sympathetic nervous system activation resulting from sleep apnea persists into the waking state. Treatment studies demonstrating a reduction in CRP levels with the reversal of SDB are necessary to support a causal association between SDB and CRP levels.

The strength of the present study includes the selection of children with a wide spectrum of SDB. The analysis of a younger population reduces the impact of strong confounders such as age, other comorbidities, and medication use on the relationship and survival biases. A study limitation is that inferences were made on relatively small numbers of adolescents with severe SDB. Nonetheless, the total number of adolescents with SDB (n = 17) is comparable to the sample size of adult “cases” reported in the literature. Despite the relatively small numbers of affected children, we were able to detect consistent changes in CRP levels with several measures of SDB and sleep time. Table 2, which explores subgroup differences in CRP, was not adjusted for multiple comparisons.

Another potential limitation of our study is confounding by obesity. The importance of obesity as a contributor to CRP levels is supported by our data showing that 77% of the children without SDB and with elevated CRP levels (defined by CRP > 0.971 mg/L) were obese. Although the association between AHI and CRP persists after adjustment for both BMI percentile and a BMI percentile-squared term, it is possible that this statistical adjustment was incomplete. There has been considerable debate on how best to measure adiposity in adolescents. BMI percentiles for age and sex were used for their ease in interpretability, although results were similar when BMI and ln(BMI) were used. There was no evidence that inclusion of WHR, a measure of central obesity, altered the findings. However, we cannot exclude the possibility that better measures of obesity, particularly visceral obesity, may lead to an improved understanding of the relationship between SDB and AHI. Our analyses should not be misinterpreted by suggesting that CRP levels, which are elevated in association with a multitude of conditions (including obesity), can be used as a screening tool for SDB.

In summary, our analyses show that modest degrees of SDB are associated with elevated CRP levels in an adolescent population. It has been well documented that obesity is associated with inflammation and that adolescent obesity predicts morbidity and mortality in adulthood. However, because obesity is also a risk factor for SDB, it is important to consider that SDB and obesity may be part of a negative risk profile that extends into adulthood. The epidemic rise in obesity in the United States and Europe suggests that there will be a concomitant rise in SDB in children and adults. Treating obesity should be an important role in primary health care; however, it is also important for practitioners to consider SDB in children and teens as a treatable factor that may exacerbate obesity-associated health conditions.

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References


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