Published in final edited form as:
Pediatr Pulmonol. 2009 September ; 44(9): 877–884. doi:10.1002/ppul.21065.

Obesity and obesity related co-morbidities in a referral population of children with asthma

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Abstract

Objective—Although there is mounting evidence that childhood obesity is a risk factor for incident asthma, it remains unclear if there is a distinct "asthma-obesity" phenotype. This study characterized body composition, obesity related co-morbidities, and traditional risk factors for asthma in a cohort of children referred for asthma management in a pulmonary clinic. We hypothesized that children with asthma and obesity would have distinct risk factors and co-morbidities, particularly with respect to metabolic and sleep abnormalities.

Participants and Methods—116 asthmatic children ages 4 to 18 years underwent comprehensive measurements of common asthma risk factors as well as measurements of obesity-related morbidities, including lung function tests, atopy, and assessments of sleep (overnight oximetry and actigraphy), physical activity (accelerometry), and metabolism. Characteristics of children who were obese (BMI $\geq 95^{th}$ percentile) were compared to those who were not obese (BMI $< 95^{th}$ percentile).

Results—Obesity was present in 44% of participants. Obese participants had similar rates of atopy and family history of atopy, lung function, and asthma control at enrollment as their non-obese peers. A significantly higher proportion of obese participants had metabolic syndrome (23% vs 0%) and habitual snoring (60% vs 33%) compared to non-obese participants; insufficient sleep and nocturnal desaturations tended to be more prevalent among obese subjects.

Conclusions—Obesity and obesity related co-morbidities were common in a referral population of children with asthma. The specific influence of metabolic abnormalities on asthma morbidity and management is still uncertain and likely will need to be addressed in prospective studies.

Keywords

obesity; asthma

Background

Asthma appears to be determined by multiple interacting genetic and environmental factors. Asthma phenotyping, or identification of subgroups of asthma with distinct risk factors, co-morbidities, pathophysiology, and response to treatment, is not part of the standard evaluation

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Disclosures: The authors have no disclosures relevant to the material in this manuscript.

and treatment of childhood asthma. Obesity is a particularly common co-morbidity that may adversely affect asthma inception, severity, and response to therapy. There is mounting evidence that childhood obesity is a risk factor for the development of asthma, including cross sectional [1,2] and prospective studies [3,4], and recent studies have also suggested that obese asthmatics respond differently to standard therapies than their non-obese counterparts [5,6].

The first goal of this study was to determine the prevalence of obesity and obesity-related complications in children with asthma referred to a tertiary care asthma center. A secondary goal was to determine if there were phenotypic differences with respect to traditional asthma risk factors (atopy, family history), and asthma severity and control at the time of referral among asthmatics who were obese compared to those who were not obese. We hypothesize that obesity and obesity related complications are common co-morbidities in children referred for asthma care, and these co-morbidities influence asthma control. It is possible that the pathophysiology of asthma in obese children is influenced by the oxidative and inflammatory environment incited by excess visceral adipose tissue and intermittent hypoxia due to obesity-related sleep disordered breathing. This results in a distinct "asthma-obesity" phenotype, characterized by metabolic derangements, less atopy, and more difficulty gaining control of symptoms with standard therapies. Accordingly, we performed comprehensive measurements of common asthma risk factors as well as measurements of obesity-related morbidities in study participants, including measurement of metabolic syndrome and its components. In addition, objective measures of sleep and physical activity were used to attempt to better understand how obesity and asthma may be linked through a shared association with sleep disorders, including nocturnal desaturations, snoring, and insufficient sleep, a risk factor for obesity and obesity related metabolic abnormalities [7,8].

Materials and Methods

Study Population

This was a prospective, observational study performed at Rainbow Babies and Children's Hospital in Cleveland, OH. Sequential enrollment of children ages 4–18 years seen between May 2006 and April 2008 in the pediatric pulmonology clinic who were diagnosed with asthma by a pediatric pulmonologist, on the basis of recurrent or chronic symptoms of cough, wheeze, or shortness of breath that responded to bronchodilators and/or inhaled corticosteroids. Exclusion criteria included cystic fibrosis, sickle cell disease, chronic lung disease of prematurity, interstitial lung disease, and cerebral palsy. Children were ineligible if the parent/guardian was unable to provide informed consent, or they were not able to participate in follow up visits. For those who were eligible but declined participation, the reasons for refusal were recorded. Written informed consent was obtained from the parent or the patient if they were 18 years of age. Assent was obtained from children 7 and older. The study was approved by the local Institutional Review Board.

Study Protocol

Participants underwent physiological, anthropometric, and biochemical study assessments at a clinical research center. In addition, monitoring of physical activity, sleep patterns, and overnight oximetry was performed in the participant's home. Routinely collected health data were extracted from the clinical records, including a medical history and physical exam, allergy skin scratch testing, and spirometry.

Specific measurements

Anthropometry: Height was measured using a wall-mounted stadiometer, weight with a calibrated scale (Healthometer), and waist circumference by a tape measure. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared, normalized for age and

sex using Centers for Disease Control growth percentiles. If the biological mother was the consenting parent, her weight, height, and waist circumference were measured. Bioelectric impedance (BIA, assessing percentage body fat) was obtained on the child with a Quantum X® (resistance/reactance accuracies ±1ohm), applying electrodes to the right hand, wrist, foot and ankle while the subject was supine on a firm bed, after voiding, with arms and legs at a 45° to each other. Percent body fat was calculated using published equations (under 10 years of age [9], 10 years and over [10]). All anthropometric measures were made twice (with 3rd measures if the 1st 2 did not agree); the averages are reported.

Blood Pressure: Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by trained nurses in triplicate 30 seconds apart, sitting, and using a cuff appropriate for arm circumference. Pre-hypertension and hypertension were defined as SBP or DBP ≥ 85th percentile for age and sex or ≥ 95th percentile for age and sex respectively.

Pulmonary Function and Atopy: Exhaled nitric oxide was measured using Niox equipment according to published guidelines [11]. Allergy skin scratch testing included positive (histamine) and negative (saline) controls, and tested for sensitivity to alternaria tenus, aspergillus fumigatus, cat, dog, dust mite (Dermatophagoides farinae and D. pteronyssinus), feather mix, tree mix, grass mix, ryegrass, weed mix, ragweed, and cockroach. A wheal size of 4 mm or greater with a negative control was considered positive. When skin test results were unavailable, atopy was characterized by positive specific IgE to foods or aeroallergens, or by positive skin test results from another provider. Participants were classified as atopic if they had one or more positive skin test or specific IgE. Spirometry was performed on Jaeger spirometers (calibrated daily) by trained personnel in a pediatric pulmonary function laboratory using American Thoracic Criteria acceptability criteria. Percent predicted values calculated using published equations [12].

Activity and Sleep-Related Measurements: The child and parent(s) were instructed on the use of and sent home with a Uni-axial accelerometer (CSA, Ft Walton Bch, FL), wrist actigraph (Octagonal Sleep Watch 2.01; AMI, Ambulatory Monitoring Inc., Ardsley, NY), and pulse oximeter (RAD-8 Masimo oximeter, with cable model 1006 and LNOP finger sensor). The child was asked to wear the actigraph for 5–7 days, including at least 2 weekdays and 2 weekend days to quantify sleep patterns and activity levels, and asked to wear a finger pulse oximeter while asleep for 1–2 nights to identify and quantify nocturnal desaturations; heart rate while asleep was also recorded. The accelerometers provided movement counts per minute; counts were averaged over the time worn. Sleep patterns were assessed from the wrist actigraphy using the Action-W software and the Time Above Threshold algorithm [13]. Mean sleep duration and mean sleep efficiency, defined as the percentage time in bed estimated to be asleep, were calculated. Insufficient sleep was defined as mean sleep duration of less than eight hours per night.

Metabolic Measurements: Total cholesterol, HDL, LDL, triglycerides, glucose were measured in a fasting blood sample, using standard enzymatic methods. Insulin was measured by radioimmunoassay. The homeostatic model assessment (HOMA-IR) was calculated as a function of the product of fasting insulin and glucose [14].

Questionnaires: The patient and guardian were asked to complete the Sleep and Health Questionnaire (SHQ), Asthma Control Test (ACT, childhood version for participants under 12)[15,16], and a 5–7 day diary in which the participant recorded sleep and wake times, and physical activities.

Definition of metabolic syndrome

Metabolic syndrome (MetSyn) was defined using previously described criteria [17] adapted from the National Cholesterol Education Program Adult Treatment Program III for a pediatric population. Subjects who met at least three of the following criteria were defined as having MetSyn: (1) waist circumference ≥ 90th percentile for age and sex; (2) triglycerides ≥ 110 mg/dl; (3) HDL ≤ 40 mg/dl; (4) fasting glucose ≥ 100 mg/dl; (5) mean systolic or diastolic blood pressure ≥ 90th percentile for age, sex, and height.

Statistical methods

The proportion of children eligible to participate in the study with BMI ≥ 95th percentile was used to estimate the prevalence of obesity. To examine the "asthma-obesity" phenotype, characteristics of children who were obese (OB, BMI ≥ 95th percentile) were compared to those who were not obese (NOB, BMI < 95th percentile). Bivariate comparisons were made using the student's t-test for appropriately distributed continuous variables, Wilcoxon rank-Sum for skewed continuous variables, and Chi-square or Fisher's exact test for categorical variables. As there is evidence that the effect of obesity on asthma severity may vary by sex, exploratory analyses stratified by sex were also performed. Exploratory analyses included restricted cubic spline models and ordinary least squares regression to assess the association between BMI percentile and 3 key components of metabolic syndrome: triglycerides, HDL and fasting insulin levels. Analyses were performed using SAS version 9.1.3 (SAS Institute, Inc., Cary, NC). For comparisons made in which more than 10% of the sample had missing data, the number of participants included in the analysis is specified.

Results

Out of 228 subjects with a confirmed diagnosis of asthma who were available for recruitment, 116 (51%) consented to participate and 112 declined. Reasons for refusal included being too busy or not having enough time (73%), and concerns about missed school (14%) or work (12%). Compared to those who declined, participants were similar in terms of age, race, and sex (Table 1). Although not statistically significant, participants had a higher mean BMI than non-participants. Overall, 37% of children eligible to participate had a BMI ≥ of 95th percentile, nearly twice recent estimates of the prevalence of obesity in American children and adolescents (13.9 to 18.8%) [18].

The mean age was 9.1 (± 3.4) years, approximately half were reported to be non-Caucasian (predominantly Black), and more were males (67.2%). Over 40% were from households with an income of less than $20,000 per year. There was a high prevalence of obesity in the study population; 44% had a BMI ≥ 95th percentile and 18% had a BMI ≥ 99th percentile. Table 2 shows the characteristics of the cohort stratified by children who are OB compared to children who are NOB. BMI was correlated with an alternative measure of adiposity derived from BIA, percent body fat ($r=0.62$, $p<0.001$). There were no differences between groups in demographic variables, including age, race, and household income. A significantly higher proportion of participants who were obese had biological mothers who were obese, both by BMI and waist circumference. No differences in physical activity levels were seen between groups.

The prevalence of traditional risk factors for asthma, including atopy and family history of atopy, did not significantly differ between groups. The two groups had similar proportions with uncontrolled asthma (ACT ≤ 19 [16]). Spirometry and exhaled nitric oxide levels also did not differ between OB and NOB subjects. Exploratory analyses stratified by sex also did not show significant differences in spirometry or ACT scores between OB and NOB participants.

Obesity-related complications were prevalent in this sample. Metabolic syndrome was present in 23.1% of participants who were obese and none of the NOB children. Most individual components of the metabolic syndrome (high blood pressure, high waist circumference, high triglycerides, and low HDL) were also more prevalent in the obese children. Although no participants had fasting hyperglycemia, the median fasting insulin of the OB group was nearly twice that of the NOB group (8.3 vs 4.3, $p < 0.0001$). Median HOMA-IR was also higher in children who were obese, and a higher proportion had evidence of insulin resistance with HOMA-IR >3 [19]. Participants who were obese also had higher mean systolic blood pressure by 6.7 mmHg on average, and more met criteria for hypertension (15.4 vs 3.1%, p= 0.04).

We also pursued the hypothesis that obesity would be associated with higher rates of sleep disorders, including snoring, insufficient sleep, and nocturnal desaturation. Obese children were twice as likely to report habitual snoring and experience five or more desaturations of 4% or more per hour of sleep. However, only the former reached statistical significance (60.4 vs 32.8%, p=0.004). There was a trend towards decreased sleep per night in those who were obese, with nearly twice as many obese children sleeping fewer than 8 hours per night (33 vs 18%, p=0.07). Mean heart rate during sleep was higher in OB participants, and sleep efficiency was lower, although still in the normal range.

Exploratory analyses were undertaken to assess the association between BMI percentile as a continuous measure with 3 key components of metabolic syndrome: triglycerides, HDL and fasting insulin levels. The results suggested a quadratic relationship with triglycerides (U-shape) and HDL (inverted U-shape) such that the best lipid levels (lowest levels of triglycerides and highest levels of HDL) were observed among participants with BMI ~60th percentile. BMI percentile had a piecewise linear association with fasting insulin that was consistent with a threshold effect of excess weight; no association was observed among participants with BMI < 85th percentile and a statistically significant positive linear association was seen among subjects with BMI ≥ 85th percentile. These results did not appreciably change after adjusting for age. Additionally, to explore whether these effects varied by age, two-way interactions between age and BMI percentile were tested and were not statistically significant

Discussion

The demographic characteristics of the described cohort are consistent with previously described urban samples of children with asthma [20,21], with a high proportion of children of minority race and living in poverty. In addition to high rates of traditional risk factors for asthma, obesity and obesity-related co-morbidities were strikingly prevalent. The most recent update of the Expert Panel Report guidelines for the diagnosis and management of asthma addresses obesity as a co-morbid condition for the first time, but in a limited manner [22]. The high rates of obesity and the metabolic consequences of obesity in this cohort of young asthmatics highlight the need to better understand how these two inflammatory conditions interact.

Metabolic syndrome, characterized by visceral adiposity and a cluster of abnormalities in glucose and lipid regulation, is a risk factor for future cardiovascular morbidity in both adults[23] and children [24]. Along with obesity, the prevalence of metabolic syndrome has risen dramatically in children in adolescents, increasing from 4.2% to 6.4% over a 10 year period [25] in adolescents in the United States. Similar to obese populations of adolescents described in the literature [17], the prevalence of metabolic syndrome in the overweight children in our cohort was approximately 23%, particularly concerning given the mean age of the population of approximately 9 years. Children with metabolic syndrome are at increased risk for developing diabetes, which is associated with long term increased risk of cardiovascular disease and impaired pulmonary function[26]. Recently published data in adults suggests that

metabolic syndrome and abdominal obesity are associated with lung function impairment, independent of BMI[27]. Longitudinal studies will be needed to determine if abnormalities in lipid and glucose regulation also exacerbate or influence the pulmonary function of obese asthmatic children.

The prevalence of signs and symptoms suggestive of sleep disordered breathing (SDB) in this referral population of asthmatics was also high. More obese children reported habitual snoring, and trends for insufficient sleep time and increased desaturation frequency at night were also observed, consistent with the presence of sleep disordered breathing (SDB). Pediatric SDB has been linked to numerous adverse health and behavioral outcomes, including impulsivity, attention deficit, abnormal blood pressure regulation and increased levels of inflammatory cytokines [28]. Thus, SDB may exacerbate the inflammatory and metabolic effects of obesity. In addition, behavioral effects of SDB may influence adherence to medications or influence health behaviors that may impact asthma management. Sleep requirements change throughout childhood, so a conservative definition of insufficient sleep of less than eight hours per night that would apply to the entire study population was chosen. The etiology of decreased sleep time in the obese group is not clear, but irrespective of the etiology, insufficient sleep has been associated with metabolic syndrome [29], hyperlipidemia [30], and hypertension [31] independent of body mass index. Insufficient sleep has been postulated to be linked to these metabolic derangements through sympathetic nervous system overactivity [32, 33]. In the current study, overweight children had evidence of sympathetic nervous system activation with higher heart rates during sleep.

Contrary to our hypothesis, we did not find significant differences in traditional risk factors for asthma between obese and non-obese participants, with similar rates of atopy and a family history of asthma in both groups. Although a larger sample may be needed to better define the relative influence of traditional versus obesity-related risk factors in asthma, these data suggest that the underlying risk factors in asthma occurring in obesity are similar to those that occur in non-obese children, and perhaps, that obesity alone was not a sufficient risk factor for asthma development. Measures of asthma severity, including lung function and scores on the ACT, also did not differ between obese and non-obese participants. The ACT is a useful and validated tool, but it does not take into account the level of therapy needed to achieve control. Although there is evidence obesity influences asthma incidence in a gender specific manner [34,35], we did not see a similar differential effect of obesity on asthma severity. These findings should be interpreted with caution as the small number of girls in this study limited our power to detect such differences. It is also possible that obesity-related differences in pulmonary function may have been attenuated by the aggressive management approaches available to all children in this referred sample.

Study strengths include the use of objective measures of body composition, metabolic syndrome, pulmonary function, sleep, and physical activity. Limitations include the relatively high refusal rate, lack of a control group, and inability to address the potential interaction between age and metabolic outcomes. The cohort was recruited from a specialty clinic to minimize the likelihood that children without asthma would be included, but this strategy may also limit the generalizability of our findings to asthmatics referred for specialty care. Of those approached about the current study, there was a trend for overweight children to be more likely to consent to participate, likely due to the number of obesity related evaluations in the study. This study would have been strengthened by the inclusion of a control group of children who were obese but did not have asthma; unfortunately, such a control group was not available within the scope of this study. However review of the literature suggests that the rates of obesity in all eligible participants (even those who did not consent to participate) was still higher than recent estimates of obesity in a nationally representative population [18]. These observations suggest an opportunity for health care providers caring for children with asthma to assess for

obesity and obesity related conditions during scheduled asthma encounters, and to make appropriate treatment recommendations or referrals for this increasingly important public health problem.

For the primary analyses, we divided participants into categories of non-obese and obese based on BMI percentile as is the convention in studying childhood obesity. Whether the classically used thresholds are valid in studying the relationship between obesity and lung disease remains to be determined, however. Therefore, we performed some post hoc exploratory analyses using BMI as a continuous variable. Quadratic, or U-shaped, relationships between BMI and components of the metabolic syndrome as were seen in our study have been reported previously in children[36] and Asian populations[37]. While the relationship between BMI and cholesterol and triglycerides was fairly complex, the piecemeal linear relationship seen between BMI and insulin suggested a threshold effect at a BMI of the 85th percentile (overweight), rather than the 95th percentile. Further longitudinal studies will be needed to determine which threshold, if any, is relevant with respect to asthma morbidity or pulmonary function. In other exploratory analyses, we examined whether the association between BMI percentile and components of metabolic syndrome varied by age. While the two-way interactions between age and BMI percentile were not statistically significant, it is possible that these analyses were underpowered to detect interactions. While the ages of participants in the study ranged from 4 to 17, 75% of the participants were under 12 years of age, further limiting our ability to detect age-related differences.

The primary objective of this report was to describe the prevalence of obesity in a referral population of children with asthma, and to compare obese and non-obese children with respect to traditional risk factors for asthma and obesity-related co-morbidities. Although the markers of asthma severity and airway obstruction and inflammation that were assessed were not found to be different among groups, the influence of obesity on asthma severity and control may be better addressed in longitudinal studies.

The extent to which current asthma treatment guidelines can be personalized is limited, in large part due to limited evidence for how co-morbidities affect asthma severity and control. In this study, we found that obesity and metabolic abnormalities are common co-morbid conditions in children seeking treatment for asthma in a sub-specialty setting. This report highlights the need to better understand how obesity and asthma influence one another, and whether characterizing the phenotype of obesity with respect to metabolic abnormalities is an important step. Clinicians who care for asthmatics spend a great deal of time educating children and their families about their disease. Our study underscores the importance of addressing additional issues of weight management and healthy sleep habits children with asthma who are obese and appear also to be at high risk for these morbidities which can have immediate and long term health consequences. The specific influence of metabolic abnormalities on asthma management is still uncertain and likely will need to be addressed in prospective studies.

Acknowledgments

The authors would like to thank Kristen Barrett, RN, for her assistance with data collection, and Dianne DeSatnik, RN, Virginia Gonzalez, RN, Heather Richmond, RN, and our physician colleagues for their help with recruitment.

This work was supported by grants from the Cleveland Foundation (Grant Number L2005-0254- Individualized Health Care for Children with Common Chronic Conditions), and NIH grants KL2RR024990, 1 U54 CA116867, M01 RR00080 and UL1 RR024989 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH) and its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH.

Abbreviations

BMI	body mass index
BIA	bioelectric impedance
SBP	systolic blood pressure
DBP	diastolic blood pressure
HOMA-IR	homeostatic model assessment
ACT	Asthma Control Test
OB	obese
NOB	non-obese
SDB	sleep disordered breathing

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Table 1

Sample Characteristics of Participants and Non-Participants

	Participants (n=116)	Non-participants (n=112)
Age (years)	9.1 ± 3.4 (4.0 – 17.4)	9.5 ± 3.4 (4.1 – 17.4)
Male Gender	67.2%	67.6%
Non-Caucasian Race	50.9%	61.0%
BMI	21.6 ± 6.0 (13.8 – 42.7)	20.8 ± 6.4 (13.3 – 44.4)
BMI Category		
< 85th percentile	41.4%	53.1%
85–95th percentile	14.7%	17.7%
≥95th percentile	44.0%	29.2%

Data are presented as means ± SD (range) for continuous variables or proportions for categorical variables. There were no statistically significant differences between participants and non-participants.

Table 2

Subject Characteristics for the Analytic Sample & Stratified by Weight Status

	Not Obese (BMI <95th percentile) (n=64)	Obese (BMI ≥ 95th percentile) (n=52)
Participant Demographics		
Age (years)	9.0 ± 3.4	9.2 ± 2.9
Non-Caucasian Race	50.0%	52.0%
Male Gender	67.2%	67.3%
Percent Body Fat**	23.2 ± 6.7%	34.3 ± 6.7%
Parent/family characteristics		
Household size (individuals)	4 (3, 5)	4 (3, 5)
Household income (n=106)		
< $20,000	39.6%	47.9%
$20,000 to < $50,000	32.8%	22.9%
$50,000 to < $75,000	6.9%	12.5%
≥$75,000	20.7%	16.7%
Maternal BMI >30 (n=99)*	51.0%	72.9%
Maternal waist circumference (n=96)**	95.6 ± 16.3	108.4 ± 23.4
Family history of asthma	53.1%	53.8%
Family history of atopic disease	65.6%	63.5%
Asthma Control/Atopy		
Asthma Control Test score	21 (16, 23)	20 (16, 23)
Poor Asthma Control (ACT ≤ 19)	42.4%	45.1%
Atopy	77.6%	76.1%
Lung Function/Inflammation		
FEV_1 % predicted (n=78)	97.2 ± 17.2	95.6 ± 18.8
FVC % predicted (n=78)	105.1 ± 15.6	102.6 ± 19.5
FEV_1/FVC (n=78)	81.1 ± 7.8	81.4 ± 6.9
FEV_1/FVC less than 0. 80 (n=78)	40.5%	41.6%
Exhaled nitric oxide (pbb) (n=95)	14.9 (8.0, 33.2)	11.4 (6.6, 38.4)
Metabolic Syndrome – Cook criteria		
Metabolic Syndrome**	0%	23.1%
Waist circumference ≥ 90th percentile**	6.4%	80.8%
Systolic or Diastolic BP ≥ 90th percentile*	12.5%	28.9%
Triglycerides ≥ 110 mg/dl*	6.5%	23.1%
HDL ≤ 40 mg/dl*	14.5%	30.8%
Metabolic Characteristics		
Total Cholesterol mg/dL	151.2 ± 26.5	154.8 ± 18.7
HDL mg/dL*	52.8 ± 12.9	47.2 ± 10.4
Triglycerides mg/dL**	45.5 (33.0, 71.0)	62.5 (45.5, 97.5)

	Not Obese (BMI <95th percentile) (n=64)	Obese (BMI ≥ 95th percentile) (n=52)
Fasting insulin mg/dL**	4.3 (2.6, 6.7)	8.3 (5.1, 14.0)
Fasting glucose mg/dL	84.0 (20.0, 87.0)	87.0 (81.0, 89.0)
HOMA-IR**	0.9 (0.5, 1.4)	1.6 (1.1, 2.9)
HOMA-IR ≥ 3**	7.1 %	23.5%
Hypertension/heart rate		
Systolic BP**	101.8 ± 9.8	108.5 ± 9.1
Diastolic BP	64.5 ± 8.7	67.0 ± 9.5
Hypertension Category*		
Normal	87.5%	71.1%
Pre-Hypertension	9.4%	13.5%
Hypertension	3.1%	15.4%
Mean Heart Rate during sleep*	78.4 ± 9.7	82.4 ± 9.3
Sleep Characteristics		
Hours sleep per night	8.7 ± 0.9	8.3 ± 1.0
Sleep less than 8 hrs/night	18.8%	33.3%
Habitual snoring**	32.8%	60.4%
Mean Oxygen Saturation	98.2 ± 1.0	98.2 ± 0.9
5 or more desaturations/hr (4%)	5.1%	9.3%
Mean Sleep Efficiency*	96.1 (94.6, 97.7)	95.2 (92, 96.9)
Physical Activity:		
Minutes active per day		
Mean minutes moderate activity/d	65.6 (42.6, 102.7)	57.8 (21.9, 100.6)

Data are presented as mean (±SD) for variables with approximately normal distribution, median (interquartile range) for skewed variables, and proportions for categorical variables.

* denotes p-value <0.05,

** p-value <0.01 for obese vs not obese.