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Obesity is associated with impaired cardiac autonomic modulation in children

Sol M. Rodríguez-Colón¹, Edward O. Bixler², Xian Li¹, Alexandros N. Vgontzas², and Duanping Liao¹

¹Department of Public Health Sciences, Penn State University College of Medicine 600 Centerview Dr. Suite 2200, A210, Hershey, PA 17033

²Sleep Research & Treatment Center, Department of Psychiatry, Penn State Milton S. Hershey Medical Center, Penn State University College of Medicine, P.O. Box 850, H073, Hershey, PA 17033-0850

Abstract

Objective—To examine the cross-sectional association between measurements of obesity and subclinical impairment of cardiac autonomic modulation (CAM) in a population-based sample of children.

Methods—Data from 616 grade K-5 children randomly selected from Central Pennsylvania were utilized. Obesity was defined using the International Obesity Task Force (IOTF) age and sex specific cut off criteria and classified as normal weight, overweight, and obese. CAM was measured by heart rate variability (HRV) analysis of beat-to-beat RR intervals, including time domain measures i.e., the standard deviation of all RR intervals (SDNN), the square root of the mean of the sum of squares of differences between adjacent RR intervals (RMSSD), and mean heart rate (HR); and frequency domain measures i.e., high frequency power (HF), low frequency power (LF), and LF/HF ratio.

Results—The prevalence of obesity and overweight in children was 12.3%, and 16.5%, respectively. Age, race, sex, and sleep disorder breathing (SDB) adjusted means (SE) of SDNN were 98(1.24), 90.2(2.58), and 81.9(3.03) milliseconds (ms) in normal weight, overweight, and obese groups, respectively; and that for (log) HF were 6.83(0.04), 6.56(0.08), and 6.35(0.09) ms², respectively. Comparing the magnitude of effects from BMI, weight, and height percentiles, and waist circumference on HRV indices revealed that body weight was the strongest correlate of HRV indices.

Conclusion—Childhood obesity is significantly associated with lower HRV, indicative of sympathetic overflow unopposed by parasympathetic modulation. These findings support the need to target childhood-obesity, before traditional “high risk age” for cardiac events.

Keywords

Obesity; Cardiac Autonomic Modulation; Heart Rate Variability; Population-based Study

Corresponding Author: Duanping Liao, MD, PhD, Department of Public Health Sciences, Penn State University College of Medicine, 600 Centerview Dr. Suite 2200, A210, Hershey, PA 17033, dliao@psu.edu, Tel: 717-531-4149, Fax: 717-531-5779.

Conflict of Interest statement:

There is NO conflict of interest and NO off-label or investigational use of drugs.

Introduction

It is well-known that obesity is a risk factor for cardiovascular disease in adults (1). Today, an obesity epidemic is occurring in children. In 2003–2006, sixteen percent of 2–19 year old children were overweight, and 16.3% were obese (2). Among school age children in North and South America, by 2010, an estimated 16% will be overweight and another 15.2% will be obese (3). Previous studies have reported that childhood obesity substantially increases the risk of coronary heart disease and other chronic diseases, like type 2 diabetes, hyperlipidemia, and hypertension at adulthood (4). The effect of obesity on cardiac autonomic modulation (CAM) in children has not been well examined, although impaired CAM in adults has been associated with higher risk of incident cardiovascular disease (5–10).

Cardiac autonomic activity can be measured by using the Heart Rate Variability (HRV) method. HRV is the variation of RR intervals over a period of time and is broadly used as a noninvasive method to assess the overall CAM quantitatively (5–7, 11–21). The autonomic nervous system (ANS) controls the heart rate by balancing sympathetic and parasympathetic activity (5–35). Published studies using HRV method to measure the CAM effect in obese children, have reported that obese children have lower parasympathetic modulation than normal weight children (36–40). However, limited population-based data from children are available to investigate obesity-related subclinical abnormalities, such as CAM. Thus, we carried out this cross-sectional study to examine the association between various measurements of obesity and subclinical impairments of CAM in a large population-base sample of children.

Methods

Study population

The study population was from the Penn State Children Cohort (PSCC). The PSCC is a population-based study of the prevalence and correlates of sleep-disordered breathing (SDB) in children. The study sample was selected through a two-phase sampling process, with Phase I consisting of the collection of general information from the parents about their child's sleep and behavioral patterns. Phase II of the study consisted of the collection of more detailed data from a one night sleep study in our General Clinical Research Center (GCRC). The study was reviewed and approved by our Institutional Review Board (IRB) as well as the GCRC review board. Briefly, in Phase I, a self-administered questionnaire was sent home to be completed by the parents of all elementary school (grade K-5) children in three school districts in Dauphin county, central Pennsylvania. We sent home 7,312 questionnaires and 5,740 were returned, with a response rate of 79%. In Phase II of sampling, each year, we randomly selected 200 children from those who returned our questionnaires in Phase I to participate in our GCRC sleep study. The Phase II examination was carried out between 2002 and 2006. We stratified this sampling based on the severity of risk for SDB as reported by parents in the Phase I questionnaire, and by grade and gender. We selected 1,000 children to participate in the Phase II sleep laboratory evaluation and 700 children participated, with a response rate of 70% (41, 42).

During Phase II, each child underwent a standardized physical examination and their parent completed a set of standardized questionnaires. The measurements derived from the physical examination included height, weight, waist and neck circumferences, blood pressure, a visual evaluation of the nose and throat by an ear, nose and throat (ENT) specialist, and an evaluation of the respiratory function by a pediatric pulmonologist. All measurements were based on standardized procedures and protocols, and were subject to established quality control procedures. Each child received a 9-hour fixed protocol nighttime polysomnogram

(PSG). During the PSG sleep evaluation, each child, in the presence of a parent, spent a night in a sound-attenuated, temperature-and-light-controlled room located in our GCRC. The child's sleep was continuously monitored for nine hours, including electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), respiration (nasal pressure and thermocouple, thoracic and abdominal strain gauges), hemoglobin oxygen saturation, and objective snoring (41, 42). During this time a single-channel electrocardiogram (ECG) was recorded continuously with the voltages, at a sampling rate of 100 Hz from the PSG.

Classification of obesity status

Participants wearing light clothing were weighed with a standard pediatric scale with an accuracy of 0.01 pound. Standing height without shoes was measured with a standard pediatric height scale with an accuracy of 0.1 centimeter. The scales were subject to daily calibration before each use. Waist circumference was measured at the top of the iliac crest in the standing position. From the height and weight measurements, we calculated BMI (kg/m^2) as weight in kg/height in meter squared. Obesity was defined using the International Obesity Task Force (IOTF) age and sex specific cut off criteria of Normal Weight, Overweight, and Obese (43).

Cardiac autonomic modulation (CAM) measures

Overnight 9-hour continuous ECG data were collected at the baseline sleep laboratory study. After converting the 1 channel ECG voltage data into a beat-to-beat ECG waveform file, we identified the peak of each QRS complex as the R wave point. Then, the beat-to-beat RR intervals from the entire ECG recording were calculated after applying an artifacts identification and removal algorithm to the entire RR interval data. This algorithm identified and removed any RR interval as artifacts if a RR interval is less than 375 ms, or longer than 1200 ms, or RR interval ratio from two adjacent RR intervals is less than 0.8 or greater than 1.2. The HRV Analysis Software (44) was used to apply HRV analysis to the above described "artifact free" RR interval files if the total length of the "artifact free" RR interval file was more than 6.5 hours (corresponding to approximately 75% of the total recording time) (42). Fast Fourier Transformation (FFT) was used to perform frequency domain HRV analysis. Briefly, the adjacent RR interval data were interpolated using a piecewise cubic spline interpolation approach, with a 2 Hz sampling rate. The FFT was performed on the equidistantly interpolated RR time series. We used 2nd order polynomial model to remove the slow nonstationary trends of the HRV signal. We calculated the following time domain HRV indices: SDNN, the standard deviation of all RR intervals (ms); RMSSD, the square root of the mean of the sum of the squares of differences between adjacent RR intervals (ms); and mean HR (BPM). These time domain HRV variables were used to measure the total variability of RR intervals with a lower value indicating imbalance between parasympathetic and sympathetic effect. We calculated the following frequency domain HRV: high frequency power (HF, 0.15 – 0.40 Hz), which represents the parasympathetic modulation; low frequency power (LF, 0.04 – 0.15 Hz), which represents a mixture of the sympathetic and parasympathetic modulation; and LF/HF ratio, which represents the balance of sympathetic and parasympathetic modulation.

Covariables

At Phase II, demographic and physical variables were collected from participants conforming to the standardized clinical examination. The following covariables were included in this study: age, gender, race, % Rapid Eye Movement (REM)-defined as the proportion of sleep time spent in the REM stage, sleep efficiency-defined as the proportion of the recorded time that the child was asleep, snore and SDB.

Statistical analysis

The characteristics of the study population (mean, standard deviation, and proportions) were calculated. Analysis of covariance (ANCOVA) was used to calculate age, sex, race, and SDB status adjusted means and standard errors of HRV indices at each obesity status. Since the age- and sex- specific percentiles of BMI, weight, and height are normally distributed in our data, we used standardized multivariable linear regression models to assess the effect-sizes on HRV indices associated with a one standard deviation increase of the obesity measures, including BMI percentile, weight percentile, height percentile, and waist circumference. Thus, the interpretations of the same distribution-based increases in each measure are comparable even when they are measured in different scales. According to the convention of HRV analysis (21), LF and HF were log-transformed in the statistical analysis. All analyses were performed by weighting the sampling process. SAS 9.1 software was used for all statistical analyses.

Results

Characteristics of study population

From the PSCC study (700 children), we excluded 84 individuals who did not have sufficient ECG data for HRV analysis (persons with less than 6.5 hours of normal RR interval data). Thus, the effective sample size for this study was 616 children (88% of the original 700 children). The characteristics of the study population, overall and stratified by obesity status, are shown on Table 1. Out of the 616 children in the entire cohort, 420 were normal weight, 105 were overweight, and 91 were obese. Based on IOTF criteria to define overweight and obesity, after accounting for sampling weight, the prevalence of overweight and obesity in this population was 16.5% and 12.3%, respectively. The prevalence of obesity for white boys, white girls, non-white (Black, Hispanic, and Asian) boys, and non-white girls, was 9.3%, 7.7%, 18.2% and 27.0%, respectively. The mean (SD) age of the entire cohort was 9.0 (1.7) years old, with 49% male and 25.3% non-white. In addition, the mean (SD) BMI percentile and waist circumference (cm) of the entire study population was 60.8 (29.4) percentile, and 65 (10.3) cm, respectively. The diastolic and systolic blood pressure (mean (SD)) were higher among overweight (67 (8.0)/116 (11.7) mmHg) and obese (68 (7)/117 (12) mmHg) than normal weight (65 (8.1)/108 (11) mmHg) children. All HRV indices, with the exception of LF/HF ratio and HR, were lower in the obese group than the overweight and normal weight groups.

Multivariable adjusted means (SE) of HRV indices at each obesity status

The age, sex, race and SDB status adjusted mean (SE) levels of HRV indices across the three obesity categories, as well as the *P* values for linear trend and *P* values for comparing obese vs. normal weight and obese vs overweight, are presented in Table 2. These results indicate a clear dose-response relationship between obesity and CAM, in the direction of obesity being associated with lower levels of HF, LF, RMSSD, and SDNN, and with higher levels of LF/HF ratio and HR.

Association between obesity measurements and HRV indices

To assess the strength of the association between different obesity measurements and HRV indices, we used linear regression models to calculate the multivariable adjusted regression coefficients per a one standard deviation (SD) increase of BMI percentile, height percentile, weight percentile, and waist circumference. These results are summarized on Table 3. After adjusting for age, sex, race, and SDB, all four anthropometric measures were associated with HRV indices. Most importantly, among the three directly comparable percentile measures (BMI, weight, and height), the associations with HRV indices were strongest for a one SD

increase in body weight percentile. Although waist circumference was not measured as age and sex specific percentiles, as other anthropometric measures were, a one SD increase in waist circumference had similar adverse effects on HRV indices as a one SD increase in body weight percentile.

Discussion

There are two major findings from the present study. First, there is a graded significant association between the levels of obesity and the impairment of CAM as measured from 9-hour beat-to-beat HRV. Second, the magnitude of the effects from obesity measures on the impairment of CAM is the largest for body weight percentile, compared to BMI percentile and height percentile. These findings, based on the largest population-based study of young children that investigates the associations between obesity measures and CAM, highlight the significant impact of obesity on cardiovascular system in children, far before they reach the traditional “high risk” age for cardiovascular disease.

We examined the association between obesity and CAM by using several HRV indices as measures of the parasympathetic and sympathetic modulation. The significant progressive decrease of HF power and RMSSD, which are thought to reflect parasympathetic modulation, across normal weight, overweight, and obese groups is indicative of reduced parasympathetic modulation associated with obesity. There was also a significant decrease of LF power and SDNN in the obesity group compared to other two groups, reflecting lower parasympathetic and sympathetic modulation in obese children. In addition, we found that the LF/HF ratio and HR are increased significantly in the obese group compared to the other two groups, which suggests an impaired balance of CAM towards a sympathetic overflow and reduced parasympathetic modulation in obese children. Studies have shown that a modest increase in HR is apparent in some obese populations (45, 46) due to a diminished autonomic reflex control of the HR as a result of either increased sympathetic tone and/or lower cardiac parasympathetic modulation (47, 48).

Our findings are consistent with those published by others in small clinical samples (36–38). Martini and colleagues (36) reported that RMSSD was significantly lower, whereas HR was significantly higher, in the obese group than in the lean children. They also found lower frequency domain measures of HRV in the obese children. Kaufman and coworkers studied the different HRV variables in 36 normal weight, overweight, and obese children with an average age of 11.5 years old and they found no differences between normal weight and overweight children for all HRV variables. However, the obese group had significantly higher normalized LF power ($P=0.001$) and LF/HF ratio ($P=0.003$), and significantly reduced HF power ($P=0.001$) as compared with the normal weight children (36). Rabbia et al. demonstrated that children (mean age 13.9 years old) even with a short (<4 years) history of obesity had a sympathovagal imbalance, characterized by low parasympathetic activity and increased indices of sympathetic activity. Low parasympathetic modulation was also observed in children with a longer (>7 years) history of obesity (38). Overall, these findings suggest that there is a lower parasympathetic modulation in obese compared to lean children (37).

In this population, we found that body weight percentile is a stronger correlate to impaired CAM than height percentile or BMI percentile, and that waist circumference is adversely associated with CAM, in a similar pattern and magnitude as body weight percentile. These findings suggest that the overall impact of obesity or central obesity due to weight gain (as opposed to height) has the most adverse effects on CAM. Weight gain has been associated with increased cardiac sympathetic tone in humans (48), and, in a dog model, where it was found that high-fat diet in dogs could decrease HF band of HRV (52). Most importantly,

previous studies of obese children and adults have shown that physical training or weight loss may result in an improvement of the HRV indices (49–51). Gutin et al. reported that obese children that underwent 4 months of intense physical training enhanced their cardiovascular health by elevating the parasympathetic activity and decreasing the sympathetic activity (49). However, this benefit was lost in the 4 month period following cessation of physical activity. In addition, in obese adults a short-term weight reduction over 10%, as a result of a very low-calorie conventional diet, improved parameters related to HRV in an obese subject, especially an increase of HF components, an indicator of parasympathetic activity (51). These findings in combination support the hypothesis that regular exercise or weight loss can boost or increase the parasympathetic and decrease sympathetic modulation in obese children (50). Considering that the effects of obesity on CAM can be reversed by reducing obesity, and/or exercise, various interventions should be designed to target overweight and obesity, in order to improve CAM in these children before they reach the “high risk” age for clinical cardiovascular disease.

A few limitations of this study should be recognized. First, the ECG data was acquired at nighttime during sleep. It is well known that in humans, the autonomic activity shows a circadian rhythm with an increase in parasympathetic activity during the night and a prevalence of sympathetic activity during the day. Therefore, the sleep period is characterized by a low level of sympathetic dominance, and the parasympathetic influence could reduce the heart rate which reaches its lowest point after 5–6 hours of sleep (53, 54). Thus, it is possible that HRV indices collected at evening/nighttime while sleeping may not be representative of day-time HRV. Second, the ECG data were collected digitally at a sampling rate of 100Hz from one-ECG channel. At that sample frequency, it is possible that some degree of random misclassification of the R wave may exist. Third, because the ECG data were collected from one channel only, if an artifact occurred, there was not adjudication that we could have done using other ECG channels. To resolve this problem, we implemented a set of statistical criteria for the identification and removal of those RR intervals (RR interval <375ms, or >1200ms or RR interval ratio from two adjacent RR interval <0.8 or >1.2), which in some cases shortened total available data for HRV analysis. However, there are several strengths of this study: (1) it is the largest population-based sample of children to investigate the association between obesity and CAM; (2) the successfully acquired HRV analysis on 88% of the original PSCC sample (616 out of 700); and (3) long duration of continuous ECG recording (at least 6.5 hours of normal RR interval data).

In summary, these findings highlight once again the increasing burden of the obesity epidemic in the child population in the US. At such a young age (average of 9 years), obesity is already significantly associated with a lower HRV, indicative of impairment of CAM in the direction of sympathetic overflow and reduced parasympathetic modulation. These data support the need to target obesity, especially childhood obesity, even before it reaches the traditional “high risk age” for clinical cardiovascular disease.

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References

1. Kaplan NM. The deadly quartet: upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. *Arch Intern Med.* 1989; 149:1514–20. [PubMed: 2662932]
2. Ogden CL, Carroll MD, Flegal KM. High Body Mass Index for Age among US children and adolescents, 2003–2006. *JAMA.* 2008; 299(20):2401–2405. [PubMed: 18505949]

3. Wang Y, Lobstein T. Worldwide trends in childhood overweight and obesity. *IJPO*. 2006; 1:11–25. [PubMed: 17902211]
4. Dietz WH. Overweight in childhood and adolescence. *N Engl J Med*. 2004; 350:855–7. [PubMed: 14985480]
5. Martin GJ, Magid NM, Myers G, et al. Heart rate variability and sudden death secondary to coronary artery disease during ambulatory electrocardiographic monitoring. *Am J Cardiol*. 1987; 60:86–89.
6. Tsuji H, Larson MG, Venditti FJ Jr, et al. Impact of reduced heart rate variability on cardiac events, The Framingham Heart Study. *Circulation*. 1996; 94:2850–2855. [PubMed: 8941112]
7. Liao D, Cai J, Rosamond W, et al. Cardiac autonomic function and incident CHD: A population based case-cohort study - The ARIC Study. *Am J Epidemiol*. 1997; 145:696–706. [PubMed: 9125996]
8. Dekker JM, Crow RS, Folsom AR, et al. Low heart rate variability in a two minute rhythm strip predicts risk of coronary heart disease and mortality from several causes -- The ARIC Study. *Circulation*. 2000; 102:1239–1244. [PubMed: 10982537]
9. Liao D, Carnethon MR, Evans GW, et al. Lower Heart Rate Variability Is Associated with the Development of Coronary Heart Disease in Individuals with Diabetes - The ARIC Study. *Diabetes*. 2002; 51:3524–3531. [PubMed: 12453910]
10. Liao D, Jianwen Cai, Barnes RW, et al. Cardiac autonomic function and the development of hypertension -- The ARIC Study. *Am J Hypertens*. 1996; 9:1147–1156. [PubMed: 8972884]
11. Pfeifer MA, Cook D, Brodsky J, et al. Quantitative evaluation of cardiac parasympathetic activity in normal and diabetic man. *Diabetes*. 1982; 31:339–45. [PubMed: 7152130]
12. Bigger, JT. Spectral analysis of R-R variability to evaluate autonomic physiology and pharmacology and to predict cardiovascular outcomes in humans. In: Zipes, D.; Jalife, J., editors. *Cardiac Electrophysiology: From the Cell to the Bedside*. 2. Philadelphia, PA: WB Saunders Co; 1995. p. 1151-70.
13. Akselrod S, Gordon D, Ubel FA, et al. Power spectrum analysis of heart rate fluctuation: A quantitative probe of beat-to-beat cardiovascular control. *Science*. 1981; 213:220–22. [PubMed: 6166045]
14. Pomeranz B, Macaulay RJ, Caudill MA, et al. Assessment of autonomic function in humans by heart rate spectral analysis. *Am J Physiol*. 1985; 248:H151–53. [PubMed: 3970172]
15. Hayano J, Sakakibara Y, Yamada A, et al. Accuracy of assessment of cardiac parasympathetic tone by heart rate variability in normal subjects. *Am J Cardiol*. 1991; 67:99–04. [PubMed: 1986515]
16. Pagani M, Lombardi F, Guzzetti S, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-parasympathetic interaction in man and conscious dog. *Circ Res*. 1986; 59:178–93. [PubMed: 2874900]
17. Kamath MV, Ghista DN, Fallen EL, et al. Heart rate variability power spectrogram as a potential noninvasive signature of cardiac regulatory system response, mechanisms, and disorders. *Heart Vessels*. 1987; 3:33–41. [PubMed: 3305472]
18. Malik M, Camm AJ. Heart rate variability. *Clin Cardiol*. 1990; 13:570–76. [PubMed: 2204508]
19. Ori Z, Monir G, Weiss J, et al. Heart rate variability - Frequency domain analysis. *Cardiol Clin*. 1992; 10:499–37. [PubMed: 1504981]
20. Kleiger RE, Miller JP, Bigger JT Jr, et al. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol*. 1987; 59:256–62. [PubMed: 3812275]
21. Vaishnav S, Stevenson R, Marchant B, et al. Relation between heart rate variability early after acute myocardial infarction and long-term mortality. *Am J Cardiol*. 1994; 73:653–57. [PubMed: 8166060]
22. Lombardi F, Sandrone G, Pernpruner S, et al. Heart rate variability as an index of sympathovagal interaction after acute myocardial infarction. *Am J Cardiol*. 1987; 60:1239–45. [PubMed: 3687775]
23. Malik M, Farrell T, Camm AJ. Circadian rhythm of heart rate variability after acute myocardial infarction and its influence on the prognostic value of heart rate variability. *Am J Cardiol*. 1990; 66:1049–54. [PubMed: 2220630]

24. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart Rate Variability: Standards of measurement, physiological interpretation, and clinical use. *Circulation*. 1996; 93:1043–1065. [PubMed: 8598068]
25. Williams EF III, Woo P, Miller R, et al. The effects of adenotonsillectomy on growth in young children. *Otolaryngol Head Neck Surg*. 1991; 104:509–516. [PubMed: 1903865]
26. Liao D, Barnes RW, Chambless LE, et al. Population based study of heart rate variability and prevalent myocardial infarction: The ARIC Study. *J Electrocardiol*. 1996; 29:189–198. [PubMed: 8854330]
27. Liao D, Creason J, Shy C, et al. Daily variation of particulate air pollution and poor cardiac autonomic control in the elderly. *Environ Health Perspect*. 1999; 107:521–525. [PubMed: 10378998]
28. Liao D, Sloan RP, Cascio WE, et al. The multiple metabolic syndrome is associated with lower heart rate variability: The ARIC Study. *Diabetes Care*. 1998; 21:2116–2122. [PubMed: 9839103]
29. Carnethon MR, Liao D, Evans GW, et al. Does the Cardiac Autonomic Response to Postural Change Predict Incident Coronary Heart Disease and Mortality? The Atherosclerosis Risk in Communities Study. *Am J Epidemiol*. 2002; 155:48–56. [PubMed: 11772784]
30. Carnethon MR, Liao D, Evans GW, et al. Correlates of the shift in heart rate variability with an active postural change in a healthy population sample: The Atherosclerosis Risk In Communities study. *American Heart Journal*. 2002; 143:808–13. [PubMed: 12040341]
31. Carnethon MR, Anthony MS, Cascio WE, et al. Prospective Association between Hormone Replacement Therapy and Heart Rate Variability: The Atherosclerosis Risk in Communities Study. *J Clin Epidemiol*. 2003; 56:565–71.
32. Carnethon MR, Golden SH, Folsom AR, et al. Prospective investigation of autonomic nervous system function and the development of type 2 diabetes: the Atherosclerosis Risk in Communities study, 1987–1998. *Circulation*. 2003; 107:2190–5. [PubMed: 12695289]
33. Schroeder EB, Welch VL, Couper D, et al. Lung Function and Incident Coronary Heart Disease - The Atherosclerosis Risk in Communities Study. *Am J Epidemiol*. 2003; 158:1171–1181. [PubMed: 14652302]
34. Schroeder EB, Liao D, Chambless LE, et al. Hypertension, Blood Pressure, and Heart Rate Variability: The Atherosclerosis Risk in Communities (ARIC) Study. *Hypertension*. 2003; 42:1106–1111. [PubMed: 14581296]
35. Liao D, Duan Y, Whitsel EA, et al. Higher Ambient Criteria Pollutants are Associated with Impaired Cardiac Autonomic Control – A Population-based Study. *Am J Epidemiol*. 2004; 159:768–777.
36. Kaufman CL, Kaiser DR, Steinberger J, et al. Relationship of cardiac autonomic function with metabolic abnormalities in childhood obesity. *Obesity*. 2007; 15(5):1164–70. [PubMed: 17495192]
37. Martini G, Riva P, Rabbia F, et al. Heart rate variability in childhood obesity. *Clin Auto Res*. 2001; 11:87–91.
38. Rabbia F, Silke B, Conterno A, et al. Assessment of cardiac autonomic modulation during adolescent obesity. *Obe Res*. 2003; 11:541–8.
39. Yakinci C, Mungen B, Karabiber H, et al. Autonomic nervous system functions in obese children. *Brain & Development*. 2000; 22:151–153.
40. Nagai N, Matsumoto T, Kita H, et al. Autonomic nervous system activity and the state and development of obesity in Japanese school children. *Obes Res*. 2003; 11:25–32. [PubMed: 12529482]
41. Bixler EO, Vgontzas AN, Lin HM, Liao D, et al. Blood pressure associated with sleep-disordered breathing in a population sample of children. *Hypertension*. 2008; 52(5):841–6. [PubMed: 18838624]
42. Liao D, Liu J, Vgontzas A, Rodriguez-Colon S, et al. Cardiac Autonomic Modulation and Sleep-Disordered Breathing in Children. *Sleep Med Clin*. 2009; 4:27–36.
43. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ*. 2000; 320:1240–43. [PubMed: 10797032]

44. The Biomedical Signal Analysis Group, Department of Applied Physics, University of Kuopio, Finland. [Accessed November 3, 2009] The HRV Analysis Software. (<http://bsamig.uku.fi/research/hrv.shtml>)
45. Peterson HR, Rothschild M, Wienberg CR, et al. Body fat and the activity of the autonomic nervous system. *N Engl J Med*. 1998; 318:1077–1083. [PubMed: 3352710]
46. Rossi M, Marti G, Ricordi L, et al. Cardiac autonomic dysfunction in obese subjects. *Clin Sci*. 1989; 76:567–572. [PubMed: 2736876]
47. Grassi G, Seravalle G, Cattaneo BM, et al. Sympathetic activation obese normotensive subjects. *Hypertension*. 1995; 25:560–563. [PubMed: 7721398]
48. Arone LJ, Mackintosh R, Rosebaum M, et al. Autonomic nervous system activity in weight gain and weight loss. *Am J Physiol*. 1995; 169(pt 1):R222–R225. [PubMed: 7631897]
49. Gutin B, Owens S, Slavens G, et al. Effect of physical training on heart-period variability in obese children. *The Journal of Pediatrics*. 1997; 130:938–943. [PubMed: 9202616]
50. Gutin B, Barbeau P, Litaker MS, et al. Heart Rate Variability in Obese Children: Relations to Total Body and Visceral Adiposity, and Changes with Physical Training and Detraining. *Obesity Research*. 2000; 8:12–19. [PubMed: 10678254]
51. Akehi Y, Yoshimatsu H, Kurokawa M, et al. VLCD-induced weight loss improves heart rate variability in moderately obese Japanese. *Exp Biol Med*. 2001; 226(5):440–5.
52. Verwaerde P, Sénard JM, Galinier M, Rougé P, et al. Changes in short-term variability of blood pressure and heart rate during the development of obesity-associated hypertension in high-fat fed dogs. *J Hypertens*. 1999; 17(8):1135–43. [PubMed: 10466469]
53. Emdin M, Gastaldelli A, Muscelli E, et al. Hyperinsulinemia and autonomic nervous system dysfunction in obesity: effects of weight loss. *Circulation*. 2001; 30;103(4):513–9.
54. McCaffrey PM, Riddell JG, Shanks RG. An assessment of the partial agonist activity of Ro 31-1118, flusoxolol and pindolol in man. *Br J Clin Pharmacol*. 1987; 24(5):571–80. [PubMed: 2893634]

Table 1

Study Population Characteristics Using Mean (SD) Levels or Proportion of Major Covariables

Variables	Entire cohort (n = 616)	Obesity Status		
		Normal Weight ^a (n = 420)	Overweight ^a (n = 105)	Obese ^a (n = 91)
Age	9.0 (1.7)	8.8 (1.8)	9.3 (1.6)	9.2 (1.5)
Male (%)	48.6	49.6	47.3	44.3
Race (% non-white)	25.3	21.1	26.0	48.0
Blood Pressure:				
Systolic (mmHg)	111 (12)	108 (11)	116 (11.7)	117 (12)
Diastolic (mmHg)	65 (8.0)	64.7 (8.1)	67 (8.0)	68 (7.1)
HRV Indices:				
Log HF (ms ²)	6.7 (0.84)	6.8 (0.80)	6.5 (0.82)	6.3 (0.92)
Log LF (ms ²)	6.6 (0.66)	6.66 (0.62)	6.4 (0.71)	6.25 (0.65)
LF/HF Ratio	0.98(0.52)	0.94 (0.49)	1.05 (0.57)	1.12 (0.61)
SDNN	94 (27.4)	98 (27)	90 (26)	79.2 (25)
RMSSD	73 (34)	77 (34.5)	65.4 (30.1)	58.8 (30.7)
HR (bpm)	77 (8.2)	76.1 (8.0)	77.9 (8.14)	81.5 (7.9)
Obesity Measurements:				
Waist (cm)	65 (10.3)	60.5 (5.7)	71.3 (6.7)	82.5 (10.8)
Weight (kg)	35 (12.3)	29.9 (7.1)	42 (8.9)	55 (14)
Weight for age percentile	61.6 (29.7)	49 (26.2)	88.7 (10.7)	97.8 (3.6)
Height (cm)	136 (12)	134.4 (11.4)	140.4 (10.5)	143 (12.3)
Height for age Percentile	59 (29.7)	53.9 (29.8)	68.1 (27)	75.5 (24.6)
BMI (kg/m ²)	18.4 (4.0)	16.3 (1.6)	21 (1.8)	26 (3.1)
BMI percentile	60.8 (29.4)	47 (24)	91.8 (3.4)	98 (0.76)

Abbreviations: BMI, body mass index; HRV, heart rate variability; HF, high frequency power; LF, low frequency power; SDNN, the standard deviation of all RR intervals; RMSSD, the square root of the mean of the sum of the squares of differences between adjacent RR intervals; and HR, mean heart rate.

^aStratified by obesity status using IOTF age and sex specific cut off criteria of Normal Weight; Overweight; and Obese.

Table 2

Adjusted Mean (SE) levels of HRV Indices According to Obesity Status Defined by IOTF age and sex specific cut off criteria.

Obesity Status	HF	LF	LF/HF	SDNN	RMSSD	HR
Normal Weight ^{a,b} (n = 420)	6.83 (0.04)	6.66 (0.03)	0.94 (0.02)	98.1 (1.24)	77.8 (1.55)	75.9 (0.36)
Overweight ^{a,b} (n = 105)	6.56 (0.08)	6.47 (0.06)	1.03 (0.05)	90.2 (2.58) ***	67.3 (3.22)	78.3(0.75) ****
Obese ^{a,b} (n = 91)	6.35 (0.09) **	6.33 (0.07) **	1.12 (0.06) **	81.9 (3.03) **	61.8 (3.79) **	81.5 (0.89) **
P linear trend ^b	<0.01	<0.01	0.01	<0.01	<0.01	<0.01

Abbreviations: HRV, heart rate variability; HF, high frequency power; LF, low frequency power; SDNN, the standard deviation of all RR intervals; RMSSD, the square root of the mean of the sum of the squares of differences between adjacent RR intervals; and HR, mean heart rate.

*and ** $P < 0.05$ and $P < 0.01$, respectively, comparing obese with normal weight.

and * $P < 0.05$ and $P < 0.01$, respectively, comparing obese with overweight

^aStratified by obesity status using IOTF age and sex specific cut off criteria of Normal Weight; Overweight; and Obese.

^b Adjusted for age, sex, race, sleep disorder breathing and sampling weight.

Table 3
Regression Coefficients (SE) of HRV Indices Associated with a One Standard Deviation Increase of Obesity Measures in Children

Obesity Measurements	HRV Indices					
	HF (log)	LF (log)	LF/HF Ratio	RMSSD	SDNN	HR
BMI Percentile ^a	-0.122 (0.033) **	-0.100 (0.025) **	0.033 (0.021)	-4.47 (1.32) **	-3.81 (1.06) **	1.22 (0.312) **
Height Percentile ^a	-0.114 (0.033) **	-0.065 (0.025) **	0.069 (0.021) **	-4.88 (1.31) **	-3.20 (1.06) **	0.468 (0.314)
Weight Percentile ^a	-0.145 (0.032) **	-0.112 (0.025) **	0.049 (0.021) *	-5.71 (1.31) **	-4.50 (1.06) **	1.12 (0.312) **
Waist (cm)	-0.148 (0.036) **	-0.105 (0.028) **	0.054 (0.023) *	-4.83 (1.45) **	-4.46 (1.16) **	1.56 (0.34) **

Abbreviations: BMI, body mass index; HRV, heart rate variability; HF, high frequency power; LF, low frequency power; SDNN, the standard deviation of all RR intervals; RMSSD, the square root of the mean of the sum of the squares of differences between adjacent RR intervals; and HR, mean heart rate.

* $P < 0.05$

** $P < 0.01$

^a Adjusted for age, sex, race, sleep disorder breathing and sampling weight.