Reduced Heart Rate Variability as A Risk Factor for Cardiovascular Disease in Young Healthy Adults with Low and High Body Mass Indexes – A Descriptive Study

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ABSTRACT

Background: Heart rate variability (HRV) is a used to assess autonomic nervous system input to the heart. Studies on the impact of HRV on underweight are limited.

Aims/Objectives: To evaluate HRV in age matched young adults of different BMI category.

Methodology: This cross-sectional study was done among healthy young adult volunteers between 18 and 25 years of age. Anthropometric variables were measured. ECG was recorded in lead II configuration for 5 minutes. Heart rate variability was analysed with Kubios HRV analyzer.

Results: HRV indices were reduced in underweight (UW), overweight (OW) and obese group compared to normal weight (NW) BMI group. Second order polynomial regression between BMI and HF log power in both genders shows an inverted U-shaped relationship with BMI. The association between BMI, waist circumference and body fat (percentage) with HRV indices shows a significant relation to heart rate variability among which waist circumference (WC) shows a greater association with HRV indices than BMI. Comparison of HRV parameters among men and women of different BMI group shows female had greater heart rate variability compared to males across BMI

Conclusions: underweight individual also have increased cardiovascular risk like obese group and abdominal obesity is better indicator of cardiovascular risk than BMI.

Key-words: Thinness, Overweight, Heart Rate variability, Waist circumference, Heart Disease Risk Factors

INTRODUCTION

Heart rate variability (HRV) is a non-invasive marker of cardiac autonomic activity, an increase in HRV represents the heart's flexibility to any stress whilst a reduction indicates decreased vagal control and is associated with cardiac arrhythmias and sudden deaths.[1-4] Many cardiac autonomic studies focuses on obesity but underweight is often neglected.[5-8] Indian population have double burden of disease with high prevalence of underweight (males 20.9% and females 22.9%) and overweight/obesity (18.9% male and 20.6 % in female).[9,10]

The association between BMI and HRV is controversial.[11-13] Visceral or abdominal adipose tissue are metabolically active which indicates, measurement of fat distribution is important than the overall measure of obesity. Asian Indians have thinner limbs with lesser muscle mass but they are centrally obese.[14] Waist Circumference a surrogate measure of body fat is extremely sensitive to the distribution of body fat and body size and also correlates with BMI.[15]

We aimed to evaluate HRV in age-matched under-weight, normal, overweight, and obese young adults and to compare the strength of association between HRV and WC to that of HRV and BMI.

METHODOLOGY

Study Design and participants: This cross-sectional study was done among 160 (80 males and 80 females) young adult volunteers between 18 and 25 years of age who were recruited by a convenient random sampling technique. The sample size was calculated using open Epi software using the mean ± standard deviation of the HRV parameter LFnu of 40.35 ±17.52 in normal weight and mean ± standard deviation 47.75±15.76 values of overweight subjects from a study done among young Indian adults with confidence interval 95% and 80% power.[12]

Inclusion criteria: Healthy volunteers between 18 and 25 years of age.

Exclusion criteria: Those subjects with a known history of hypertension, cardiovascular diseases, diabetes, smoker, endocrine disorders, autonomic neuropathies, and those who are on long-term drug therapy like steroids, anticholinergic, sympathomimetic or para sympathomimetic agents were excluded.

Written informed consent was obtained from all the participants for voluntary participation in the study. The subjects were instructed not to ingest beverages with caffeine or alcohol and not to perform physical exercise 24 hours before evaluations. Female participants were evaluated during the early follicular phase of their menstrual cycle. All the ECG recording were done between 9 AM- 11AM in Autonomic function test lab of Sri Venkateshwaraa Medical College, Puducherry.

Measurement tools and methods: Anthropometric variables like height (measured using stadiometer in centimeters), weight (measured using a digital weighing scale in Kilograms), Waist circumference (measured at the midpoint between the lowest rib and iliac crest in the standing position at the end of a gentle expiration), hip circumference (measured around the point with a maximum circumference over the buttocks), skinfold thickness (measured using skinfold calliper in the right side of the subject in triceps by measuring a vertical fold on the posterior midline of the upper arm halfway between the acromion and olecranon process with the arm held freely to the side of the body. Suprailiac skinfold is measured by diagonal fold above iliac crest in anterior axillary line, The subscapular skin fold is measured by taking diagonal fold, 2 cm below inferior angle of the scapula) were measured

Body Mass Index was calculated using the formula weight in kilogram divided by height in meters squared. Subjects were stratified by BMI as Underweight (UW) (<18.5 kg/ m²), Normal weight (NW) (18.5-24.9 kg/ m²), overweight (OW) (25-29.9 kg/ m²) and obese (≥30 Kg/m²). The waist hip ratio was calculated by the formula (waist circumference/hip circumference). Body fat % was calculated by using Durnin and Womersley's equation with the values of skinfold thickness of triceps, suprailiac, and subscapular region[16]

Cardiovascular parameters such as blood pressure (BP) and heart rate were recorded using digital BP apparatus in the right arm in a sitting position after 5 minutes of rest. ECG recording was done using PHYSIOPAC -PP4 MEDICAID system, CHANDIGAR in a quiet and temperature-controlled room. After 10 minutes of rest in a sitting position, ECG was recorded in lead II configuration for 5 minutes. Heart rate variability was analyzed with Kubios HRV analyser.

Statistical analysis: Statistical analysis was done using SPSS 17.0 (IBM Corp., Armonk, NY, USA) software. Shapiro–Wilk test was done to check for data normality. All normally distributed data was represented as mean and standard deviation (SD), HRV indices were log transferred and expressed as Mean ± SD. Levene's test of Homogeneity of variance was done for the whole group and was not significant p>0.05. Differences between the groups were assessed using ANOVA. Post Hoc Tukey test was done. Association between HRV indices with BMI, waist circumference and, %fat in males and females done by Pearson correlation. An Independent T-test was used to assess gender differences in HRV indices.

Approval of Institutional Ethical Committee was obtained. (Institute human ethical committee of Sri Venkateshwaraa Medical College Hospital, Puducherry. (SVMCH/IEC/2018-September, Dated: 03.09.2018)

RESULTS

Descriptive characteristics of participants are summarized in Table 1 which shows the four groups were similar by age but significantly different by BMI, waist circumference and body fat %.

Table 2 showed Heart rate was higher in obese group. There was no significant difference in Heart rate between UW, NW and OW group by Post hoc Tukey test. Compared to Normal BMI group OW and obese group have significantly higher systolic and Diastolic BP (p<0.05). There was no difference between UW and Normal group in systolic and Diastolic BP by Post hoc Tukey test (p> 0.05).

HRV indices (SDNN log, RMSSD log, log Power HF nu, log Power LF nu) in UW, OW, and obese were significantly different compared to normal BMI group. Statistically significant difference was found in LF/HF ratio among OW, obese groups compared to the normal BMI group, indicating the autonomic imbalance in OW and obese group compared to normal. LF/HF ratio was not statistically different in UW and NW groups by Post hoc Tukey test.

**Table 1: Characteristics of study group based on BMI (Mean ± SD)**

Parameter	Underweight (n=40)	Normal weight (n=40)	Overweight (n=40)	Obese (n=40)	P value (ANOVA)
Age (years)	19.50 ±1.58	19.65±2.11	20.48±2.17	19.53±1.94	0.089
Weight (kg)	47.40±6.3	59.53±7.48	70.90±7.66	90.75±13.48	0.000*
Height (Cm)	163.83±9.63	165.08±8.22	163.65±8.56	163.10±10.3	0.805
BMI (Kg/m^2)	17.56±0.94	21.92±1.18	26.41±1.08	34.09±3.86	0.000*
Waist circumference (Cm)	65.25±4.80	75.43±5.75	84.13±9.02	100.45±10.48	0.000*
W/H ratio	0.78±0.04	0.80±0.04	0.84±0.72	0.87±0.57	0.000*
Body Fat percentage	18.78±6.22	23.98±6.93	27.88±6.09	31.87±6.42	0.000*

*Statistically significant values

Table 2: Heart rate variability indices in different study group based on BMI (Mean ± SD)

	Underweight (n=40)	Normal weight (n=40)	Overweight (n=40)	Obese (n=40)	P value (ANOVA)
Heart rate (bpm)	80.75±9.56	80.75±11.05	81.48±12.61	90.98±9.92	0.007*
Systolic blood pressure (SBP)	106.75±10.5	112.05±10.13	119.53±10.62	129.53±10.7	0.000*
Diastolic blood pressure (DBP)	72.80±7.81	76.80±7.6	81.63±6.8	87.93±6.0	0.000*
SDNN log	1.81±0.14	1.87±0.1	1.76±0.086	1.67±0.09	0.000*
RMSSD log	1.89±0.10	1.96±0.13	1.86±0.18	1.78±0.15	0.000*
HF log power n.u	1.69±0.08	1.76±0.07	1.74±0.059	1.63±0.09	0.000*
LF log power nu	1.68±0.10	1.602±0.12	1.63±0.08	1.74±0.07	0.000*
LF/HF	0.9 ±0.18	0.8±0.23	1.6±0.15	1.9±0.13	0.006*

*Statistically significant values

Figure 1: Second order polynomial regression between BMI and HF log power in males and female
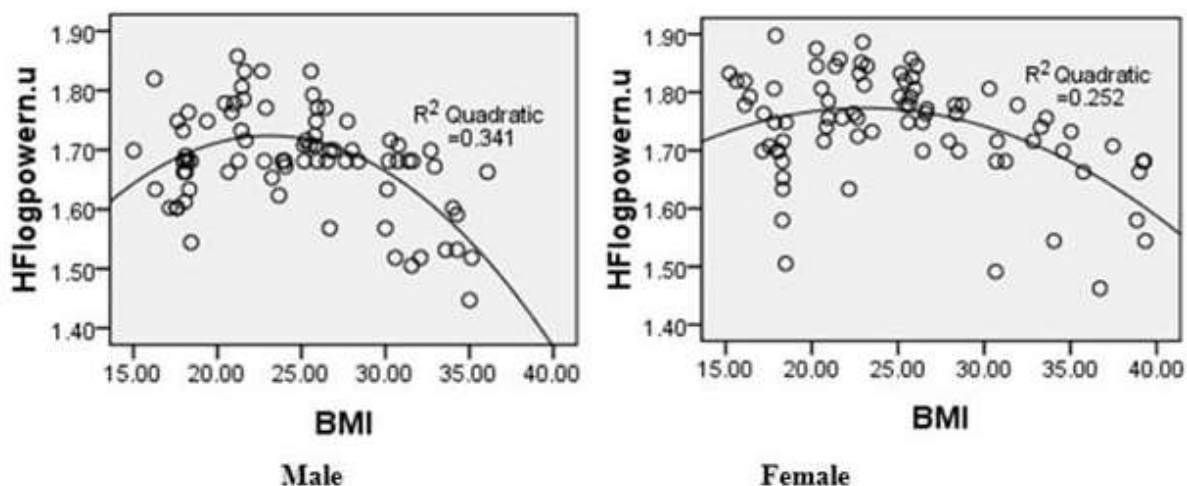
For Males R^2 = 0.341, F=19.94, p<0.01; For females R^2 = 0.252, F=12.90, p<0.01

To assess the relationship between HRV response (HF log power nu, LFlog power nu, RMSSD log, SDNN log) second-order polynomial regression (quadratic) analyses were used, assuming BMI as independent variable.

Figure 1. shows relationship between HF log power nu and BMI, were the lower values of HF log power nu in y-axis-dependent variables were scattered at the edges of the observed x-axis-independent variable, indicating an inverted U-shaped relationship with BMI. So, the HRV indices are not only reduced in the overweight and obese subject but also in the underweight subject in both males and females compared to the normal weight subject. Similar results were obtained for SDNN log, male (r^2= 0.287, F=13.668, P<0.01), female (r^2= 0.383, F=23.937, P<0.01), RMSSD log, male (r^2= 0.187, F=8.109, P<0.05), female (r^2= 0.197, F=9.675, P<0.05), with BMI.

LF log power nu, male (r^2= 0.267, F=14.005, P<0.01), female (r^2= 0.225, F=11.197, P<0.01), showed a U-shaped relationship with BMI indicating higher values were scattered at the edges. Linear regression was significant with less r^2 value compared to second-order polynomial regression (quadratic) analyses.

The association between BMI, waist circumference and body fat (percentage) with HRV indices are presented in Table 3.

Table 3: Association of HRV indices with BMI , waist circumference and %fat in males and females

Parameter	HF log Power (n.u.)		LF logPower (n.u.)		SDNN log		RMSSD log	
	Male (n=80)	Female (n=80)	Male (n=80)	Female (n=80)	Male (n=80)	Female (n=80)	Male (n=80)	Female (n=80)
Body Mass Index (BMI)	0.38**	0.38**	0.33**	0.37**	0.23*	0.60**	0.36**	0.29**
Waist Circumference	0.51**	0.46**	0.43**	0.50**	0.25*	0.60**	0.43**	0.34**
% Fat	0.34**	0.27*	0.29**	0.28*	0.25*	0.55**	0.38**	0.32**

**Significant at level of 0.01; *Significant at level of 0.05

Table 4: Gender difference in HRV indices of different BMI groups

Parameter	Underweight		Normal weight		Overweight		Obese	
	Male (n=20)	Female (n=20)	Male (n=20)	Female (n=20)	Male (n=20)	Female (n=20)	Male (n=20)	Female (n=20)
HF log power n.u	1.66 ±0.06	1.72 ±0.09**	1.736 ±0.06	1.79 ±0.06**	1.71 ±0.054	1.77 ±0.044**	1.61 ±0.08	1.66 ±0.09**
LF log power nu	1.71 ±0.06	1.64 ±0.12**	1.64 ±0.09	1.562 ±0.11**	1.67 ±0.062	1.591 ±0.069**	1.76 ±0.57	1.71 ±0.08**

**significant at level of 0.01

All variables show a significant relation to heart rate variability and WC shows a greater association with HRV indices than BMI. Comparison of HRV parameters among men and women of different BMI groups is presented in Table 4. Which shows female had greater heart rate variability compared to males across BMI.

DISCUSSION

The time domain parameters SDNN (standard deviation of NN intervals) is contributed both by SNS and PNS activity, hence it is an estimate of overall HRV. RMSSD (Root mean square of successive RR interval differences) reflects the beat-to-beat variance in HR and is the primary time-domain measure used to estimate the vagally mediated changes reflected in HRV. Frequency domain parameters, HF (High frequency) component is mainly contributed by Vagal activity whereas LF(Low frequency) component mainly reflects baroreceptor activity during resting conditions and LF/HF estimate the ratio between SNS and PNS activity.[17]

The present study shows a significant change in the time domain and frequency domain parameters of HRV in UW, OW and obese BMI compared to the Normal BMI group. Not only overweight and obese even underweight are associated with reduced HRV indices indicating higher risk factors for cardiovascular disease as there is increased sympathetic inputs and decreased vagal control. Obesity is a well-known risk factor for cardiovascular disease (CVD), but the underweight population of body mass index (BMI) below 18.5 kg/m2 has not been an entity of concern. In a study by Triggiani et al. UW subjects showed a significant reduction in SDNN, LF, and TP, but not in HF values indicating decreased vagal modulations to the heart.[13] A study by Vaz et al. also showed a reduction in HRV indices in UW and undernourished individuals.[11] Sowmya et al. also showed that a slight in-

crease in BMI among low BMI subjects in Indians increased the risk of cardiovascular morbidity and mortality.[18] Our study results contrast with the data published by Krishna et al,[12]Schmid et al[19] and Wu et al.[20] where there was no reduction in HRV indices in UW subjects.

Rossi et al. showed a significant decrease in the RMSSD, HFms, and HFnu indices in the obese group, indicating a decrease in vagal activity and high value of the LFnu index in the obese group pointed to relative sympathetic predominance in obese individuals compared to normal-weight individual similar to our study.[21] Shroney et al. observed decreased HF nu and increased LF nu and LF/HF ratio and our study differed from theirs, where elderly male participants of 40-50years were involved and Asian cutoff criteria for BMI was considered, by which the BMI differed.[22] Rajalakshmi et al. observed significant decrease in total power, high frequency power, and also there is increase in low frequency power compared to normal weight group.[23] Similarly in male subjects Chetan et al. have demonstrated the presence of impaired parasympathetic activity and elevated level of sympathetic activity in obese group.[24] Rohini et al. shows that in obese group there were no predictable changes in cardiovascular autonomic activity as measured by HRV, and also there were no gender differences in autonomic function in obese population.[25] In our study there was no altered sympathovagal balance between UW and normal group whereas OW and obese showed increased LF/HF ratio indicating increased sympathetic activity. Jain et al showed LF/HF was higher in overweight and obese group.[26] Schmid et al showed no difference in LF/HF ratio between underweight and normal weight.[19] Contrary to the results of our study Millis et al. showed high body fat has association with greater vagal activity and also there was significant negative correlation of body fat with LF/HF ratio and this controversy could be attributed to the smaller sample size involved in their study.[27] Adaptive flexi-

bility of the heart rate variability is found to be lesser in UW, OW, and obese subjects compared to NW subjects may represent risk factors for CVD mortality.

The increased CVD risk in the underweight group can be associated with various clinical factors, such as sarcopenia, hormonal imbalances like hypothyroidism as evidences suggests that energy restriction is associated with a reduction in triiodothyronine levels which is associated with altered HRV and it was observed that these HRV changes are reversed by treatment for hypothyroidism. [28,29] In our study we have excluded those with endocrine disorders based on their history hence the change in HRV in our study may not be due to thyroid disorders. Other possible reasons for low HRV in underweight population has been linked to diet and nutritional deficiencies, especially vitamin B12 deficiency and its supplementation reversed lowered HRV.[30] There is evidence from animal models that prenatal under nutrition decreases sympathetic innervation in the long term, at least in the gut.[31] In utero nutritional deficiencies may also reflect changes that have occurred in adult undernourished subjects regarding autonomic disturbances.[32] In low BMI individuals cardiovascular risk may also be attributed to increased visceral adiposity or ectopic fat rather than subcutaneous fat.[33] The detailed mechanisms underlying the alteration of the autonomic function in UW subjects need to be ascertained in future studies.

Obesity increased the sympathetic activity with a reduction in parasympathetic (vagal) tone, indicating poor autonomic cardiac rhythm control in obese individuals.[7] In subjects with increased body mass sympathetic over activity may be explained based on the sympathetic-adrenergic and baroreflex functions in relation to obesity. The mechanism underlying these changes of parasympathetic and sympathetic nervous activities in overweight and obese is unknown. Some of the hormonal signals have been postulated includes leptin, leptin resistance, Insulin, insulin resistance, free fatty acids and other mechanisms like duration of obesity, distribution of fat and so on.[34-37]

BMI has been generally used to diagnose underweight and overweight conditions. It is obvious from this study finding that Waist circumference has a stronger association with HRV markers than BMI, leading to modulation of cardiac autonomic activity. The stronger association between WC with HRV indices compared to BMI could be due to the abdominal obesity existing in the Indian population. BMI cannot differentiate between fat mass and fat-free mass.[15] The other measures which reflect the abdominal adiposity is WC, is better than BMI in predicting CVD risk [38] which is reflected in our study. Thus, indicators of central obesity are more sensitive than the indicator of general obesity. Increased Waist circumference, which indicates visceral adiposity, was strongly associated with reduced cardiac parasympathetic and increased sympathetic activity. Therefore, it would be better to consider Waist cir-

cumference as a stronger obesity marker than BMI in the Indian population. This study indicates that abdominal fat is more negatively associated with indices of HRV suggesting that fat distribution may be an important measure to assess the cardiac autonomic functions. Our study populations were healthy adults without any comorbidity, apart from being underweight and overweight, in spite of it they are at risk of Cardio vascular morbidity. Measurement of the degree of central fat distribution thus appears to be important for the early detection of subsequent health risks, even among those of normal weight. [39]

The Heart rate was significantly higher in the obese group in comparison to the normal weight group. Other studies also support the finding of tachycardia in obese people, and it is due to altered autonomic modulation of the intrinsic heart rate.[21] Our study also confirmed that both SBP and DBP were significantly higher in the OW and obese group as compared to normal weight controls, which is consistent with several other studies indicating autonomic impairment, characterized by a reduction in parasympathetic activity and relative predominance of sympathetic activity in obese individuals.[40,21] The increase in blood pressure in obesity could be attributed to the direct effect of obesity on hemodynamics such as increase in blood volume, stroke volume, cardiac output by the resistance offered to circulatory system by increased adiposity. Besides the mechanical burden offered by obesity by increase in peripheral vascular resistance, obesity mediated inflammatory outcomes such as endothelial dysfunction and effect of cytokines were also implicated in the pathogenesis of obesity related cardiovascular sequel.[41] There is decreased sympathetic activity in females compared to males this can be attributed to the presence of female sex hormones influencing the autonomic activity as the HRV indices are measured during the early follicular phase of the menstrual cycle where there is an increased level of endogenous estrogen.[42] Estrogen has a cardio sympathoinhibitor and vagotonic effect. Hormonal factors may be a cause for decreased sympathetic activity in young adult females compared to males. Other reasons are oxytocin, neural control and differential stress coping provide a functional basis for these gender differences.[43] This could explain the higher risk of cardiovascular disease in males compared to females. Reduced HRV has been reported in our study in low and high BMI individuals, are the indicator of increased risk of cardiovascular morbidity and mortality caused by cardiac autonomic alterations The limitation of our study is we have not considered the physical activity of the subjects since physical exercise can influences cardiac autonomic behavior.

CONCLUSION

HRV indices are reduced in UW, OW, and obese BMI compared to normal BMI group and there is U-shaped association between BMI and HRV indices.

We found not only people with higher BMI, an underweight individual also has increased cardiovascular risk even when they are asymptomatic and with no comorbidities. Further studies are also needed to confirm the pathophysiology behind the decreased HRV indices in the underweight population. The sympathovagal balance is sloped toward sympathetic predominance in the overweight and obese group which is also a predisposing risk factor cardiac morbidity. Waist circumference has a stronger association with HRV markers than BMI which suggests need for assessment of central adiposity along with general adiposity which helps in early recognition of risk factor. We would suggest maintaining normal weight is necessary for reducing cardiovascular risk among UW and OW individuals.

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REFERENCES

1. Dun NJ, Machado BH, Pilowsky PM, editors. Neural mechanisms of cardiovascular regulation. Springer Science & Business Media; 2004 Jan 31.

2. Sztajzel J. Heart rate variability: A noninvasive electrocardiographic method to measure the autonomic nervous system. Swiss Med Wkly. 2004;134(35–36):514–22.

3. Hammoud S, Karam R, Mourad R, Saad I, Kurdi M. Stress and heart rate variability during university final examination among Lebanese students. Behav Sci . 2019;9(1).

4. Nolte IM, Munoz ML, Tragante V, Amare AT, Jansen R, Vaez A, et al. Genetic loci associated with heart rate variability and their effects on cardiac disease risk. Nat Commun. 2017;8(May).

5. Rastović M, Srdić-Galić B, Barak O, Stokić E. Association between anthropometric measures of regional fat mass and heart rate variability in obese women. Nutr Diet. 2017;74(1):51–60.

6. Pal GK, Chandrasekaran A, Hariharan AP, Dutta TK, Pal P, Nanda N, et al. Body mass index contributes to sympathovagal imbalance in prehypertensives. BMC Cardiovasc Disord. 2012;12.

7. Yadav RL, Yadav PK, Yadav LK, Agrawal K, Sah SK, Islam MN. Association between obesity and heart rate variability indices: An intuition toward cardiac autonomic alteration-a risk of CVD. Diabetes, Metab Syndr Obes Targets Ther. 2017;10:57–64.

8. Chen Y, Copeland WK, Vedanthan R, Grant E, Lee JE, Gu D, Gupta PC, et al. Association between body mass index and cardiovascular disease mortality in east Asians and south Asians: pooled analysis of prospective data from the Asia Cohort Consortium. Bmj. 2013 Oct 1;347.

9. Doak CM, Adair LS, Bentley M, Monteiro C, Popkin BM. The dual burden household and the nutrition transition paradox. Int J Obes. 2005;29(1):129–36

10. National Family Health Survey (NFHS-4), 2015-16. Int Inst Popul Sci (IIPS), Mumbai, India. 2017;

11. Vaz M, Bharathi A V., Sucharita S, Nazareth D. Heart rate variability and baroreflex sensitivity are reduced in chronically undernourished, but otherwise healthy, human subjects. Clin Sci. 2003;104(3):295–302.

12. Krishna P, Rao D, Navekar V V. Cardiac autonomic activity in overweight and underweight young adults. Indian J Physiol Pharmacol. 2013;57(2):146–52.

13. Triggiani AI, Valenzano A, Ciliberti MAP, Moscatelli F, Villani S, Monda M, et al. Heart rate variability is reduced in underweight and overweight healthy adult women. Clin Physiol Funct Imaging. 2017;37(2):162–7.

14. Kurpad A V., Varadharajan KS, Aeberli I. The thin-fat phenotype and global metabolic disease risk. Curr Opin Clin Nutr Metab Care. 2011;14(6):542–7.

15. Krakauer NY, Krakauer JC. A new body shape index predicts mortality hazard independently of body mass index. PLoS One. 2012;7(7).

16. Durnin JV, Womersley J. Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. Br J Nutr. 1974 Jul;32(1):77-97. doi: 10.1079/bjn19740060. PMID: 4843734.

17. Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms, Front Public Heal. 2017; 5: 1–17.

18. Sowmya S, Thomas T, Bharathi AV, Sucharita S. A body shape index and heart rate variability in healthy Indians with low body mass index. Journal of nutrition and metabolism. 2014 Jan 1;2014.

19. Schmid K, Schönlebe J, Drexler H, Mueck-Weymann M. Associations between being overweight, variability in heart rate, and well-being in the young men. Cardiol Young. 2010;20(1):54–9.

20. Wu JS, Lu FH, Yang YC, Lin TS, Huang YH, Wu CH, et al. Epidemiological evidence of altered cardiac autonomic function in overweight but not underweight subjects. Int J Obes. 2008;32(5):788–94.

21. Rossi RC, Vanderlei LCM, Gonçalves ACCR, Vanderlei FM, Bernardo AFB, Yamada KMH, et al. Impact of obesity on autonomic modulation, heart rate and blood pressure in obese young people. Auton Neurosci Basic Clin . 2015;193:138–41.

22. Shenoy AR, Doreswamy V, Shenoy JP, Prakash VS. Impact of obesity on cardiac autonomic functions in middle aged males. National Journal of Physiology, Pharmacy and Pharmacology. 2014;4(3):236-9.

23. Rajalakshmi R, VijayaVageesh Y, Nataraj SM, Srinath CG. Heart rate variability in Indian obese young adults. Pakistan Journal of Physiology. 2012;8(1):39-44.

24. Chethan HA, Murthy N, Basavaraju K. Comparative study of heart rate variability in normal and obese young adult males. Int J Biol Med Res. 2012; 3(2):1621-3.

25. Rohini HN, Kudachi PS, Goudar SS. Heart rate variability during deep breathing as an index of autonomic dysfunction in obese medical students-a cross sectional study. Int J Cur Res Rev. 2013 Nov;5(01).

26. Jain N, Choudhary K, Khan I, Parmar J, Chawdhary V. Assessment of cardiac sympathovagal activity with change in body weight in young adult males. Natl J Physiol Pharm Pharmacol. 2020;11(0):1.

27. Millis RM, Austin RE, Hatcher MD, Bond V, Faruque MU, Goring KL, et al.Association of body fat percentage and heart rate variability measures of sympathovagal balance. Life Sci. 2010 Jan 30;86(5-6):153

28. Falcone C, Matrone B, Bozzini S, Guasti L, Falcone R, Benzi A, et al. Time-domain heart rate variability in coronary artery disease patients affected by thyroid dysfunction. International heart journal. 2014:13-98.

29. Karthik S, Pal GK, Nanda N, Hamide A, Bobby Z, D Amudharaj, Pal P. Sympathovagal imbalance in thyroid dysfunctions in fe-

males: correlation with thyroid profile, heart rate and blood pressure. Indian J Physiol Pharmacol.2009; 53: 243 52.

30. Sucharita S, Thomas T, Antony B, Vaz M. Vitamin B12 supplementation improves heart rate variability in healthy elderly Indian subjects. Autonomic Neuroscience. 2012 May 21;168(1-2):66-71.

31. Santer, R. M. and Conboy, V. B. Prenatal undernutrition permanently decreases enteric neuron number and sympathetic innervation of Auerbach's plexus in the rat. J. Anat.1990; 168, 57-62.

32. Sucharita S, Dwarkanath P, Thomas T, Srinivasan K, Kurpad AV, Vaz M. Low maternal vitamin B12 status during pregnancy is associated with reduced heart rate variability indices in young children. Maternal & child nutrition. 2014 Apr;10(2):226-33.

33. Neeland IJ, Ross R, Després JP, Matsuzawa Y, Yamashita S, Shai I, Seidell J, Magni P, Santos RD, Arsenault B, Cuevas A. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. The lancet Diabetes & endocrinology. 2019 Sep 1;7(9):715-25.

34. Popruk S, Tungtrongchitr R, Pongpaew P, et al. Relationship between soluble leptin receptor, leptin, lipid profiles, and athropometric parameters in overweight and obese Thai subjects. J Med Assoc Thai 2005; 88:220-7

35. Emdin M, Gastaldelli A, Muscelli E, et al. Hyperinsulinemia and autonomic nervous system dysfunction in obesity: effects of weight loss. Circulation. 2001;103:513 9.

36. Nagai N, Moritani T. Effect of physical activity on autonomic nervous system function in lean and obese children. Int J Obes Relat Metab Disord 2004 Jan;28(1):27-33.

37. Rabbia F, Silke B, Conterno A, et al. Assessment of cardiac autonomic modulation during adolescent obesity. Obes Res 2003; 11: 541 548.

38. Sabah KMDN, Chowdhury AW, Khan HLR, Hasan ATMH, Haque S, Ali S, et al. Body mass index and waist/height ratio for prediction of severity of coronary artery disease. BMC Res Notes. 2014;7(1):1–7.

39. Farah BQ, Prado WL, Tenório TR, Ritti-Dias RM. Heart rate variability and its relationship with central and general obesity in obese normotensive adolescents. Einstein (Sao Paulo). 2013;11:285-90.

40. Dua S, Bhuker M, Sharma P, Dhall M, Kapoor S. Body mass index relates to blood pressure among adults. N Am J Med Sci. 2014;6(2):89–95.

41. Alpert MA, Omran JA, Bostick BP. Effects of obesity on cardiovascular hemodynamics, cardiac morphology, and ventricular function. Current obesity reports. 2016 Dec;5(4):424-34.

42. Krejza J, Mariak Z, Huba M, Wolczynski S, Lewko J. Effect of endogenous estrogen on blood flow through carotid arteries. Stroke. 2001 Jan;32(1):30-6.

43. Koenig J, Thayer JF. Sex differences in healthy human heart rate variability: A meta-analysis. Neurosci Biobehav Rev. 2016;64:288–310.