IJHAS
International Journal of Health and Allied Sciences
Official Publication of JSS Academy of Higher Education and Research (JSS AHER), Mysuru

Manuscript 1058

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ORIGINAL STUDY

"Cost-effective Markers to Identify Metabolically Healthy/Unhealthy Individuals and Their Future Risk for Cardiovascular Disorders"

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Abstract

Background: **With the rising prevalence of metabolically healthy obese, it becomes essential to identify markers to differentiate them from metabolically unhealthy obese and their future risk for cardiovascular disorders (CVD). The study aims to identify suitable markers for risk stratification of metabolically healthy/unhealthy individuals and their risk for CVD.**

Method: **Total 84 individuals aged 18–60 years of age without any comorbidities were enrolled. Their demographic details along with anthropometric measurements were noted. The biochemical parameters like fasting glucose, insulin, lipid profile, and serum adipokines were estimated. Insulin resistance (IR) markers and atherogenic indices were calculated. The data were analyzed on Microsoft Excel 2010 lnk sheet. P-value of <0.05 was considered statistically significant.**

Results: **Parameters between obese and non-obese were divided into obese and non-obese, males and females, IR and IS (insulin sensitivity). We found neck circumference (NC), IR markers, triglyceride/high density lipoprotein (TGL/HDL), lipid accumulation product (LAP) index had significant results with P-value of <0.05 to differentiate between metabolically healthy and metabolically unhealthy individuals.**

Conclusion: **The NC, TGL/HDL, and LAP index can be used as cost-effective markers to detect metabolically healthy/unhealthy individuals and their risk for CVD.**

Keywords: Obese, Insulin resistance, Metabolically healthy, Metabolically unhealthy, CVD

Message

In this article, we have identified the cost-effective markers for risk stratification of metabolically healthy/unhealthy individuals and their risk for future cardiovascular disease. We had included healthy individuals in the study and assessed the anthropometric measurements, biochemical parameters, and insulin resistance markers between obese and non-obese individuals. Further these were divided into insulin resistant and insulin-sensitive individuals and cost-effective markers have been identified to predict the future risk for cardiovascular disease.

1. Background

Obesity is a growing burden with a prevalence of 40.3% in India, highest in the south (46.51%), and lowest in the east (32.96%) [1]. Early screening of obesity with less expensive, valid, and reliable methods may reduce the morbidity and mortality associated with obesity. Few studies have also shown that NC may also be used in routine clinical practices because of its ease of measurement and detection of cardiometabolic risks in obese and overweight and its correlation with WC and BMI. Nevertheless, all these measurements have their

Received 25 July 2023; accepted 2 September 2023.
Available online 15 November 2023

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https://doi.org/10.55691/2278-344X.1058

limitations [2,3]. The anthropometric indicators do not differentiate between different body components and body fat contents. The body fat contents expressed as fat mass index (FMI) to measure adiposity seems to be an accurate measure to detect metabolic disorders [4]. In most individuals the basal metabolic rate (BMR), the daily energy expenditure accounts for 60–70% of total energy. In overweight and obese, BMR is higher than the non-obese individuals [5].

Obesity is not always associated with metabolic complications in all [6]. These subsets of obese individuals without any metabolic complications are referred to as metabolically healthy obese (MHO) [7]. The prevalence of MHO ranges between 4.2% and 13.6% [8]. When compared to metabolically unhealthy obese (MUO), MHO is characterized by low liver and visceral fat, high leg fat, higher level of cardiorespiratory fitness, normal inflammatory markers, insulin sensitivity (IS), and normal adipose tissue function [9]. Lipoprotein a [Lp(a)] is an independent risk factor for CVD and can also be used along with BMI for risk stratification [10].

MHO individuals are at 96%, 49%, and 7% increased risk of developing heart failure, coronary artery disease, and cerebrovascular disease, respectively [9,11]. Hence, this cannot be considered benign and early interventions are required to reduce the metabolic risk. The complex regulation of the inflammatory status and insulin response in obese individuals appears to be a fundamental step in developing complications. Thus homeostatic model assessment of insulin resistance (HOMA-IR), the marker of homeostatic model assessment of β-cell function (HOMA-β), and the quantitative insulin sensitivity check index (QUICKI) may be used as markers to assess insulin resistance (IR) or IS in obese and to predict the risk of cardiovascular disease [12,13]. The lipid accumulation product (LAP) index has been proposed as the better index to identify the over accumulation of lipids concerning central obesity and metabolic risk. The LAP index score of MHO is intermediate between MUO and metabolic healthy normal-weight (MHNW) [14]. The lipid indices like low-density lipoprotein cholesterol (LDL-C)/high-density lipoprotein cholesterol (HDL-C) (AI or Castelli's risk index II [CRI-II]), Triglycerides(TGL)/HDL-C, Total Cholestrol(TC)/HDL-C (CRI-I), non-HDL-C, and atherogenic index of plasma (AIP) are used to measure cardiovascular risk and are better indicators for detecting CVD in addition to lipid parameters [15,16].

Altered adipokine levels lead to an increased risk of developing comorbidities of obesity. Some also debate that it is leptin resistance that leads to cardiovascular disease in obese as leptin cannot function properly [17]. The adiponectin/leptin ratio (A/L) correlates with insulin resistance rather than leptin and adiponectin alone. All the above studies have made use of either a single or a couple of parameters to detect the risk of cardiovascular disease among obese and non-obese. We aim to detect a better marker to predict the risk of CVD in metabolically healthy individuals using anthropometric measurements, biochemical parameters, insulin resistance indicators, and lipid indices.

2. Methodology

2.1. Recruitment of study subjects

The study was approved by the Institutional Ethical Committee via the letter-number XXXX-6062/2020–21 for conducting an exploratory study among the adult population. Subjects aged between 18 and 60 years of age without any comorbidities were included in the study and subjects less than 18 years and above 60 years or subjects having any comorbid conditions were excluded from the study. Written consent was collected from all the study participants. Based on the prevalence of obesity [18], the sample size was calculated to be 84, with a precision of 5% and confidence interval of 98%

2.2. Anthropometric measurements

The age and gender of the study subjects were noted and anthropometric measurements were recorded. Using Hesley weighing scale with advanced bioelectrical impedance analysis (BIA) (Hesley Inc), weight, and fat mass (FM) in kilograms, subcutaneous fat percentage (SF%), visceral fat index (VFI), and BMR was documented. FMI in kg/m^2 was calculated using the formula FM (kg)/height (m^2) and fat-free mass index (FFMI) in kg/m^2 was calculated using the formula BMI − FMI [19].

2.3. Biochemical analysis

The overnight fasting venous blood samples were collected by venepuncture using all aseptic precautions. The serum was separated stored in sterile Eppendorf tubes at −80 °C until further analysis. The fasting blood glucose was estimated using the glucose oxidase peroxidase method on semi auto-analyzer Mispa Viva, Agappe Diagnostic Ltd, India. Fasting insulin was estimated using an electrochemiluminescence method on Cobas 6000 immunoassay analyzer, Roche Diagnostics. To check the insulin sensitivity status well-established IR markers

like HOMA-IR, HOMA-β, and insulin sensitivity index QUICKI were calculated. HOMA-IR was calculated using the formula HOMA-IR = insulin in μU/mL × [glucose in mmol/L/22.5]. Subjects were classified as IR and IS based on HOMA-IR values. HOMA-IR values ≥ 2.5 were considered IR and <2.5 as IS. HOMA-β was calculated by using the equation HOMA-β = 20 × insulin in μU/mL/[glucose in mmol/L −3.5] and QUICKI was calculated as QUICKI = 1/[log(I)+log(G)], where I is fasting insulin in μU/mL and G is fasting glucose in mg/dL. QUICKI value below 0.34 is considered IR and a value below 0.30 is diabetes mellitus [12,20,21].

The lipid profile parameters like TC by cholesterol oxidase peroxidase method, HDL-C by phosphotungstic acid method, TGL by glycerol phosphate oxidase enzymatic method were all measured on semi auto-analyzer Mispa Viva, Agappe Diagnostic Ltd, India. LDL-C was calculated using Friedewald's formula LDL-C = TC − HDL-C − TGL/5, Very low-density lipoprotein cholesterol (VLDL-C) was calculated using the formula VLDL = TGL/5, and non-HDL-C was calculated as non-HDL-C = TC − HDL-C. LAP index was calculated using the formula (WC in cm − 65) × (TGL in mmol/L) for men, and (WC in cm − 58) × (TGL in mmol/L) for women [22,23].

Lp(a) was measured by the Enzyme-linked Immunosorbent Assay (ELISA) kit from ROCHE diagnostics according to the manufacturer's protocol.

2.4. Atherogenic indices

The atherogenic indices like LDL-C/HDL-C, TGL/HDL-C, TC/HDL-C, and AIP were calculated. AIP was calculated using the formula AIP = log (TGL/HDL-C) [24].

2.5. Serum adipokines analysis

Serum leptin and adiponectin were measured by the ELISA Kit (Cloud clone corp.) according to the manufacturer's protocol. Further A/L ratio was calculated.

2.6. Statistical analysis

The data were analyzed on Microsoft Excel 2010 lnk sheet. The Student's t-test was used to compare the means of anthropometric measurements and biochemical parameters between the obese and non-obese. Pearson's correlation was performed to determine the relationship of BMI and HOMA-IR with anthropometric measurements and biochemical parameters. To find the association of BMI and HOMA-IR with other parameters, the logistic regression analysis was done using EPI-Info version: 7.2.5.0. P-value (Probability that the result is true) of <0.05 was considered statistically significant after assuming all the rules of statistical tests.

3. Results

3.1. Comparison between obese and non-obese individuals

A total of 84 individuals aged between 18 and 60 years comprising of an equal number of obese and non-obese, from in and around regions of Mysore District participated in the study. The anthropometric measurements like WHR, NC showed a significant increase in obese than non-obese individuals. Even FMI, FMI, SF%, VFI, and BMR showed significant increase in obese than non-obese individuals. All the subjects included in our study were non-diabetic and fasting insulin showed a significant increase in obese than non-obese with a p-value <0.005, whereas fasting glucose did not show any difference. The IR markers, like HOMA-IR, HOMA-β, and QUICKI showed that the obese individuals were significantly more insulin-resistant than the non-obese individuals. The leptin and A/L ratio showed a statistically significant difference, whereas adiponectin, even though higher in non-obese was not statistically significant. Among lipid profile only LAP index showed a statistically significant increase in obese compared to non-obese. Atherogenic risk calculator indices did not show any significant difference (Table 1).

3.2. Comparison between obese and non-obese, males and females

Further we compared the parameters between obese male (n = 21) and female (n = 21) and non-obese male (n = 21) and female (n = 21). In both groups, WHR, NC, and BMR showed a statistically significant increase in obese and non-obese male with a p-value <0.000. The fasting glucose, insulin, and IR markers did not show any significant difference between both groups. Among lipid profile, LDL-C showed statistically significant increase and TGL and LAP index showed significant decrease in non-obese males than females. However, between obese males and females, lipid profiles did not show any significant difference. The atherogenic risk calculators, TG/HDL-C and AIP showed a significant increase in non-obese males compared to females. The leptin was significantly increased in females

Table 1. Comparison between obese and non-obese individuals.

Study Parameter	Total (n = 84)	Obese (n = 42)	Non-obese (n = 42)	P-value
Age	35.9 (±11.7)	36.09 (±11.51)	35.78 (±11.96)	0.90
Gender	M/F (42/42)	M/F (21/21)	M/F (21/21)	
WHR	0.90 (±0.07)	0.91(±0.08)	0.88 (±0.06)	**0.05**
NC (cm)	34.75(±3.9)	36.70(±3.65)	32.85 (±3.12)	**<0.000**
FMI (kg/m^2)	9.61(±3.98)	12.46(±3.61)	6.75 (±1.52)	**<0.000**
FFMI (kg/m^2)	18.57(±3.35)	21.04 (±2.58)	16.10 (±1.89)	**<0.000**
SF (%)	29.87(±7.57)	33.15(±7.50)	26.59 (±6.06)	**<0.005**
VFI	9.28(±3.81)	12.23(±2.90)	6.33 (±1.79)	**<0.000**
BMR (kcal)	1412.1(±295.29)	1598.97(±263.80)	1225.58 (±186.97)	**<0.000**
Fasting Glucose(mg/dl)	107.02 (±51.11)	108.71(±51.55)	105.33(±50.60)	0.76
Fasting insulin (mU/L)	18.73 (±16.06)	25.10(±18.6)	12.36(±9.2)	**<0.005**
HOMA-IR	4.65 (±3.95)	6.22(±4.29)	3.90(±2.81)	**<0.000**
HOMA- β	72.17 (±67.21)	96.33(±80.41)	48.02(±37.43)	**<0.005**
QUICKI	0.31 (±0.03)	0.30(±0.02)	0.33(±0.02)	**<0.000**
TC (mg/dl)	180.33 (±44.37)	178.34(±40.19)	182.31(±48.10)	0.69
HDL-C (mg/dl)	39.85 (±24.05)	43.98(±31.71)	35.73(±10.83)	0.12
LDL-C (mg/dl)	109.08 (±53.59)	100.79(±60.50)	(117.37 ± 44.13)	0.20
TGL (mg/dl)	156.924(±103.66)	167.82(±104.98)	146.02(±101.16)	0.31
VLDL-C (mg/dl)	31.38 (±20.73)	33.56(±20.99)	29.20(±20.23)	0.31
Non-HDL-C	140.47 (±54.03)	134(±59.17)	146.58(±47.57)	0.35
Lipoprotein A (mg/dl)	20.75(±20.89)	22.35(±23.12)	19.14(±18.25)	0.48
LAP Index	257.07 (±206.83)	358.55 (±225.7)	155.60 (±124.9)	**<0.000**
LDL-C/HDL-C	3.44 (±1.90)	3.30(±2.01)	3.59(±1.77)	0.52
TGL/HDL-C	4.87 (±4.09)	5.13(±4.59)	4.62(±3.50)	0.59
TC/HDL-C	5.42 (±2.20)	5.32(±2.34)	5.51(±2.04)	0.72
AIP	0.57 (±0.31)	0.58(±0.33)	0.56(±0.28)	0.80
Leptin (ng/ml)	23.50(±27.22)	36.43(±31.72)	10.53(±11.94)	**<0.000**
Adiponectin (ng/ml)	3.04 (±1.61)	2.9(±1.57)	3.08(±1.6)	0.72
A/L	1.18(±1.93)	0.49(±0.74)	1.88(±2.44)	**0.000**

WHR- Waist hip ratio, NC- Neck circumference, FMI-Fat mass index, FFMI- Fat free mass index, SF%- Subcutaneous fat %, VFI-Visceral fat index, BMR- Basal metabolic rate, HOMA-IR- Homeostasis model assessment-estimated insulin resistance, HOMA- β-Homeostasis model assessment of β-cell function, QUICKI- Quantitative insulin sensitivity check index, TC- Total cholesterol, HDL-C-High density lipoprotein cholesterol, LDL-C- Low density lipoprotein cholesterol, TGL- Triglycerides, VLDL-C- Very low-density lipoprotein cholesterol, LAP index- Lipid accumulation product, AIP- Atherogenic index of plasma, A/L- Adiponectin/leptin ratio.

and A/L significantly increased in males in both the groups (Table 2).

3.3. Comparison between IR and IS individuals

Since we are aiming to study the cardiovascular risk among healthy adults, a total of 84 individuals are divided into IR (n = 55) and IS (n = 29). The NC, BMI, FMI, FFMI, VFI, BMR showed a significant increase in IR compared to IS groups. The fasting insulin showed a statistically significant increase in the IR group whereas fasting glucose even though higher in the IR group was not statistically significant. Also, HOMA-β and QUICKI supported the presence of insulin resistance in the two groups. Except for triglycerides and VLDL, the rest of the lipid profile did not show any significant difference between IR and IS. The LAP index was higher in IR individuals when compared with IS. The atherogenic indices, TG/HDL-C and AIP were significantly higher in IR than IS. Leptin showed a significant increase whereas A/L showed a significant decrease in the IR group (Table 3).

3.4. Comparison between obese and non-obese IR and IS individuals

Later they were divided into obese IR (n = 37) and IS (n = 5) and non-obese IR (n = 18) and IS (n = 24). There were only a few measurements and parameters that showed significant differences between obese IR and IS (Table 3).

3.5. Comparison between male and female IR and IS individuals

As we also wanted to check the anthropometric, biochemical status, atherogenic indices, adipokines levels between males and females with IR and IS, they were divided into male IR (n = 27) and male IS (n = 15) and female IR (n = 28), and the female IS (n = 28).

Between male IR and male IS, NC, BMI, FFMI, VFI, BMR, fasting insulin, HOMA-β, LAP index, and leptin showed a statistically significant increase, whereas QUICKI showed a statistically significant decreased with p=<0.05. Among female IR and IS,

Table 2. Comparison between obese and non-obese, male and female individuals.

Study Parameter	obese (n = 42)			Non-obese (n = 42)		
	Male (n = 21)	Female (n = 21)	P-value	Male (n = 21)	Female (n = 21)	P-value
Age	35.85 (±10.85)	36.33 (±12.13)	0.89	36.33 (±12.13)	35.23 (±11.76)	0.77
WHR	0.97 (±0.08)	0.85 (±0.03)	**<0.000**	0.93 (±0.04)	0.84 (±0.05)	**<0.000**
NC (cm)	39.76 (±1.89)	33.85 (±2.43)	**<0.000**	35.47 (±1.96)	30.23 (±1.37)	**<0.000**
FMI (kg/m^2)	12.68 (±4.06)	12.25 (±3.08)	0.71	6.50 (±1.43)	7.00 (±1.56)	0.33
FFMI (kg/m^2)	21.01 (±2.49)	21.08 (±2.68)	0.93	16.43 (±1.74)	15.76 (±1.98)	0.32
SF (%)	33.80 (±7.88)	32.5 (±7.04)	0.63	25.33 (±5.01)	27.85 (±6.73)	0.25
VFI	11.71 (±2.91)	12.76 (±2.80)	0.31	6.33 (±1.75)	6.33 (±1.83)	1.0
BMR (kcal)	1770.9 (±217.8)	1427 (±180.52)	**<0.000**	1330.38 (±141.98)	1120.09 (±166.27)	**<0.000**
Fasting Glucose (mg/dl)	113.94 (±66.97)	103.48 (±27.86)	0.47	111.14 (±63.99)	99.52 (±30.97)	0.30
Fasting insulin (mU/L)	28.92 (±23.90)	21.28 (±9.87)	0.12	12.96 (±10.76)	11.77 (±7.46)	0.700
HOMA-IR	6.85 (±5.03)	5.58 (±3.26)	0.23	3.02 (±2.13)	3.16 (±3.35)	0.87
HOMA- β	115.31 (±103.82)	77.34 (±37.87)	0.09	52.97 (±48.09)	43.06 (±21.00)	0.41
QUICKI	0.29 (±0.02)	0.30 (±0.02)	0.31	0.33 (±0.025)	0.33 (±0.03)	0.52
TC (mg/dl)	177.50 (±41.01)	179.19 (±39.34)	0.90	185.63 (±44.96)	178.99 (±50.83)	0.65
HDL-C (mg/dl)	40.43 (±24.77)	47.53 (±37.04)	0.51	34.75 (±8.07)	36.70 (±12.94)	0.58
LDL-C (mg/dl)	100.83 (±60.36)	100.76 (±60.63)	0.99	114.67 (±35.83)	120.07 (±50.96)	**<0.000**
TGL (mg/dl)	181.17 (±105.79)	154.47 (±102.45)	0.400	180.97 (±126.96)	111.07 (±43.62)	**0.009**
VLDL-C (mg/dl)	36.23 (±21.15)	30.89 (±20.49)	0.400	36.19 (±25.39)	22.21 (±8.72)	**0.009**
Non-HDL-C	137.06 (±58.26)	131.66 (±59.94)	0.81	150 (±42.64)	142.29 (±51.68)	0.56
Lipoprotein A (mg/dl)	18.28 (±22.84)	26.42(±22.68)	0.26	15.19(±19.14)	23.09(±16.39)	0.168
LAP index	398.36 (±225.83)	318.74 (±223.85)	0.25	193.95 (±155.05)	117.25 (±69.72)	**0.045**
LDL-C/HDL-C	3.49 (±2.16)	3.10 (±1.83)	0.60	3.37 (±1.03)	3.80 (±2.27)	0.41
TGL/HDL-C	5.79 (±4.91)	4.46 (±4.14)	0.33	5.65 (±4.20)	3.58 (±2.18)	**0.046**
TC/HDL-C	5.65 (±2.53)	4.99 (±2.09)	0.46	5.50 (±1.48)	5.52 (±2.49)	0.98
AIP	0.64 (±0.31)	0.51 (±0.34)	0.23	0.64 (±0.29)	0.47 (±0.25)	**0.05**
Leptin (ng/ml)	10.97 (±10.98)	62.65 (±22.70)	**<0.000**	1.298 (±0.944)	19.76 (±10.67)	**<0.000**
Adiponectin (ng/ml)	2.93(±1.16)	2.98 (±1.90)	0.92	2.85(±1.56)	3.30(±1.74)	0.39
A/L	0.86 (±0.84)	0.04 (±0.02)	**0.000**	3.51 (±2.55)	0.25(±0.21)	**<0.000**

NC, BMI, FMI, FFMI, VFI, BMR was significantly increased in female IR compared to female IS. The fasting glucose, fasting insulin, HOMA-β, TGL, VLDL, LAP index, TG/HDL-C, AIP and leptin showed significantly increased in female IR whereas QUICKI was significantly decreased in female IS (Table 4).

3.6. Correlation between BMI and other parameters

BMI showed significant positive correlation with NC, FMI, FFMI, SC%, VFI, BMR, fasting serum insulin, HOMA-IR, HOMA- β, QUICKI, serum leptin levels, and A/L with $P < 0.05$. Whereas, negative correlation was observed with fasting glucose, TC, LDL-C, non-HDL-C, LDL-C/HDL-C, TG/HDL-C, and TC/HDL-C (Table 5).

3.7. Correlation between HOMA-IR and other parameters

HOMA-IR positively correlated with WHR, NC, BMI, FMI, FFMI, VFI, BMR, fasting serum insulin levels, HOMA-β, QUICKI and LDL-C (Table 5).

3.8. Association between BMI and other parameters

Logistic regression analysis was performed to test the association between BMI and other parameters. BMI was used as an outcome variable and others parameters as an independent variable. Results from the logistic regression analysis showed a significant association of BMI with NC, FMI, FFMI, SF %, VFI, BMR, insulin, HOMA-IR, HOMA- β, QUICKI, leptin and A/L. Even though odds ratio was more than 1 for WHR, fasting glucose, HDL-C, LDL-C, TGL, VLDL-C, lipoprotein−A, TG/HDL-C, and AIP the p-value did not show any significance (Table 6a).

3.9. Association between HOMA-IR and other parameters

HOMA-IR was used as an outcome variable and others parameters as an independent variable. Results from the logistic regression analysis showed a significant association of HOMA-IR with NC, BMI, FMI, FFMI, VFI, BMR, fasting insulin, HOMA- β, QUICKI, AIP, leptin, and A/L. Even though the odds ratio was more than 1 for WHR, fasting glucose,

Table 3. Comparison between IR and IS individuals and obese and non-obese IR and IS.

Study Parameter	Total (n = 84)			Obese (n = 42)			Non-obese (n = 42)		
	IR (n = 55) (HOMA-IR>2.5)	IS (n = 29) (HOMA-IR<2.5)	P-value	IR (n = 37)	IS (n = 5)	P-value	IR (n = 18)	IS (n = 24)	P-value
Age	35.72 (±12.32)	36.34 (±10.54)	0.81	36.56 (±11.81)	32.6 (±8.04)	0.41	34 (±13.1)	37.12 (±10.81)	0.42
Gender	27/28 (M/F)	15/14 (M/F)		19/18 (M/F)	2/3 (M/F)		8/10 (M/F)	13/11 (M/F)	
WHR	0.90 (±0.08)	0.89 (±0.07)	0.47	0.91 (±0.08)	0.88 (±0.07)	0.54	0.88 (±0.06)	0.89 (±0.07)	0.75
NC (cm)	35.48 (±3.70)	33.41 (±3.90)	**0.019**	36.63 (±3.52)	37.2 (±4.44)	0.85	33.16 (±2.87)	32.62 (±3.27)	0.58
BMI (kg/m^2)	29.85 (±5.92)	24.92 (±5.04)	**<0.000**	33.38 (±3.52)	34.08 (±5.72)	0.82	22.59 (±1.78)	23.01 (±1.67)	0.45
FMI (kg/m^2)	10.50 (±3.52)	7.92 (±4.23)	**0.008**	12.10 (±3.11)	15.11 (±5.46)	**0.02**	7.19 (±1.36)	6.42 (±1.55)	0.10
FFMI (kg/m^2)	19.38 (±3.59)	17.03 (±2.14)	**0.0003**	21.32 (±2.56)	19.00 (±1.73)	0.053	15.39 (±1.49)	16.62 (±1.98)	**0.031**
SF (%)	30.95 (±6.98)	27.81 (±8.19)	0.09	32.32 (±7.10)	39.28 (±7.52)	0.13	28.14 (±5.77)	25.42 (±6.01)	0.15
VFI	10.38 (±3.88)	7.20 (±2.64)	**<0.000**	12.35 (±2.96)	11.4 (±2.33)	0.48	6.33(±1.91)	6.33 (±1.69)	1.0
BMR (kcal)	1475.53 (±306.41)	1291.8 (±228.9)	**0.003**	1600.56 (±269.18)	1587.2 (±219.63)	0.91	1218.5 (±199.3)	1230.29 (±176.97)	0.84
Fasting Glucose (mg/dl)	113.17 (±56.58)	95.36 (±35.87)	0.08	113.18 (±53.23)	75.63 (±10.83)	**0.001**	113.15 (±62.90)	99.47 (±37.85)	0.43
Fasting insulin (Mu/L)	24.27 (±17.36)	8.23 (±2.76)	**<0.000**	27.06 (±19.06)	10.62 (±1.89)	**<0.000**	18.54 (±11.16)	7.73 (±2.65)	**0.001**
HOMA- β	91.60 (±75.23)	35.32 (±16.62)	**<0.000**	102.27 (±83.76)	52.38 (±14.57)	**0.003**	69.68 (±46.47)	31.77 (±14.71)	**0.004**
QUICKI	0.30 (±0.02)	0.35 (±0.016)	**<0.000**	0.29 (±0.01)	0.34 (±0.00)	**<0.000**	0.31 (±0.02)	0.35 (±0.01)	**<0.000**
TC (mg/dl)	181.69 (±41.91)	177.73 (±48.58)	0.7	182.32 (±40.77)	148.9 (±16.85)	**0.011**	180.40 (±44.13)	183.74 (±50.82)	0.82
HDL-C (mg/dl)	37.67 (±19.66)	43.99 (±30.27)	0.32	40.12 (±22.55)	72.53 (±61.28)	0.35	32.63 (±9.86)	38.05 (±10.94)	0.10
LDL-C (mg/dl)	109.33 (±52.72)	108.61 (±55.22)	0.95	106.85 (±57.27)	55.99 (±64.76)	0.65	114.44 (±41.37)	119.58 (±45.97)	0.71
TGL (mg/dl)	173.44 (±111.08)	125.59 (±78.91)	**0.02**	176.73 (±108.38)	101.85 (±26.76)	**0.002**	166.67 (±116.13)	130.54 (±85.05)	0.28
VLDL-C (mg/dl)	34.688 (±22.21)	25.11 (±15.78)	**0.02**	35.34 (±21.67)	20.37 (±5.35)	**0.002**	33.33 (±23.22)	26.10 (±17.01)	0.28
Non-HDL-C	144.02 (±50.05)	133.73 (±60.29)	0.44	142.2 (±53.33)	76.36 (±67.39)	0.11	147.77 (±42.26)	145.68 (±51.17)	0.88
Lipoprotein A (mg/dl)	19.21(±21.23)	23.65(±19.9)	0.35	21.62(±23.2)	27.8(±21.81)	0.61	14.27(±15.34)	22.79(±19.37)	0.12
LAP index	303.13 (±222.57)	164.04(±138.26)	**0.0005**	376.26 (±227.86)	227.48 (±132.45)	0.067	161.97 (±104.82)	150.83 (±135.51)	0.77
LDL-C/HDL-C	3.58 (±2.00)	3.18 (±1.66)	0.34	3.43 (±1.97)	2.28 (±1.96)	0.31	3.88 (±2.03)	3.37 (±1.52)	0.34
TGL/HDL-C	5.51 (±4.46)	3.66 (±2.91)	**0.02**	5.45 (±4.75)	2.77 (±1.95)	**0.05**	5.65 (±3.79)	3.84 (±3.04)	0.11
TC/HDL-C	5.68 (±2.28)	4.91 (±1.94)	0.11	5.52 (±2.28)	3.83 (±2.31)	0.22	6.01 (±2.26)	5.14 (±1.78)	0.19
AIP	0.63 (±0.29)	0.45 (±0.31)	**0.016**	0.62 (±0.29)	0.28 (±0.42)	0.19	0.65 (±0.29)	0.49 (±0.26)	0.08
Leptin (ng/ml)	28.14 (±28.64)	14.66 (±21.76)	**0.02**	36.03(±31.12)	39.19(±35.71)	0.87	11.86 (±11.08)	9.55 (±12.44)	0.54
Adiponectin (ng/ml)	2.99 (±1.55)	3.06 (±1.75)	0.84	2.91(±1.55)	3.23(±1.70)	0.73	3.14(±1.53)	3.03(±1.76)	0.83
A/L	0.80 (±1.42)	1.9 (±2.47)	**0.03**	0.49(±0.75)	0.50(±0.677)	0.96	1.45(±2.10)	2.19(±2.61)	0.32

Table 4. Comparison between male and female IR and IS.

Study Parameter	Male (n = 42)			Female (n = 42)		
	IR (n = 27)	IS (n = 15)	P-value	IR (n = 28)	IS (n = 14)	P-value
Age	35.96 (±11.92)	36.33 (±0.74)	0.92	35.5 (±12.68)	36.35 (±10.32)	0.821
WHR	0.96 (±0.007)	0.95 (±0.04)	0.57	0.85 (±0.04)	0.83 (±0.04)	0.18
NC (cm)	38.46 (±2.11)	35.93 (±3.27)	**0.013**	32.71 (±2.53)	30.71 (±2.46)	**0.024**
BMI (kg/m^2)	30.02 (±5.70)	25.24 (±6.05)	**0.02**	29.69 (±6.11)	24.58 (±3.63)	**0.002**
FMI (kg/m^2)	10.46 (±3.44)	8.02 (±5.24)	0.13	10.53 (±3.60)	7.80 (±2.75)	**0.012**
FFMI (kg/m^2)	19.55 (±3.45)	17.22 (±1.63)	**0.006**	19.21 (±3.71)	16.83 (±2.56)	**0.023**
SF (%)	30.93 (±6.90)	27.11 (±8.77)	0.17	30.97 (±7.05)	28.57 (±7.43)	0.33
VFI	9.92 (±3.72)	7.4 (±2.72)	**0.019**	10.82 (±3.98)	7.00 (±2.53)	**0.0007**
BMR (kcal)	1637 (±278.31)	1394.4 (±230.47)	**0.005**	1319.35 (±245.05)	1181.92 (±168.24)	**0.045**
Fasting Glucose (mg/dl)	119.01 (±73.87)	100.9 (±44.53)	0.33	107.54 (±31.00)	89.42 (±21.76)	**0.039**
Fasting insulin (mU/L)	27.70 (±22.37)	8.776 (±2.98)	**0.0002**	20.96 (±9.32)	7.65 (±2.35)	**<0.000**
HOMA- β	110.52 (±97.83)	36.655 (±17.64)	**0.0008**	73.36 (±34.79)	33.89 (±15.34)	**<0.000**
QUICKI	0.29 (±0.02)	0.346 (±0.015)	**<0.000**	0.30 (±0.02)	0.35 (±0.01)	**<0.000**
TC (mg/dl)	183.88 (±42.49)	177.398 (±44.20)	0.65	179.59 (±41.23)	178.09 (±52.86)	0.92
HDL-C (mg/dl)	36.97 (±19.39)	38.717 (±17.15)	0.77	38.34 (±19.89)	49.65 (±38.99)	0.33
LDL-C (mg/dl)	107.66 (±53.31)	107.909 (±43.79)	0.98	110.94 (±52.09)	109.37 (±65.27)	0.94
TGL (mg/dl)	196.19 (±124.08)	153.857 (±96.80)	0.24	151.50 (±91.70)	95.31 (±32.95)	**0.007**
VLDL-C (mg/dl)	39.23 (±24.81)	30.771 (±19.36)	0.24	30.30 (±18.34)	19.06 (±6.59)	**0.007**
Non-HDL-C	146.90 (±51.86)	138.680 (±50.47)	0.62	141.24 (±48.08)	128.43 (±68.90)	0.55
Lipoprotein A (mg/dl)	13.03 (±17.95)	23.40 (±24.52)	0.177	25.17 (±22.42)	23.92 (±13.29)	0.826
LAP index	346.55 (±226.67)	205.43 (±171.46)	**0.029**	267.15 (±215.37)	119.70 (±73.59)	**0.002**
LDL-C/HDL-C	3.58 (±1.87)	3.183 (±1.28)	0.43	3.58 (±2.13)	3.19 (±1.98)	0.57
TGL/HDL-C	6.33 (±4.95)	4.633 (±3.53)	0.21	4.73 (±3.77)	2.62 (±1.46)	**0.015**
TC/HDL-C	5.84 (±2.23)	5.109 (±1.66)	0.24	5.53 (±2.32)	4.71 (±2.19)	0.28
AIP	0.68 (±0.30)	0.571 (±0.27)	0.23	0.58 (±0.27)	0.33 (±0.29)	**0.018**
Leptin (ng/ml)	8.12 (±10.48)	1.50 (±1.19)	**0.003**	47.40 (±27.40)	28.82 (±24.33)	**0.038**
Adiponectin (ng/ml)	2.93 (±1.34)	3.08 (±1.68)	0.79	3.4 (±1.83)	3.13 (±1.83)	0.98
A/L	1.76 (±2.23)	3.31 (±2.55)	0.068	0.12 (±0.15)	0.217 ±0.213)	0.16

LDL-C/HDL-C, TG/HDL-C, TC/HDL-C, the p-value did not show any significance (Table 6b).

4. Discussion

Several measurements, biochemical parameters, and models were used to define overweight, obesity, and its complications. But the exact association between the anthropometric measurements, biochemical parameters, and IR markers is still under study. Few obese individuals, MHO, are at lower risk of developing CVD compared to MUO. The exact definition of MHO is still not clear. Our study subjects were healthy obese and non-obese individuals without any comorbidities. First, we compared the parameters between obese and non-obese subjects. The WHR and NC were increased in obese compared to non-obese, which was in line with the previous studies [25]. FMI and FFMI are better than BMI in predicting metabolic risk with FMI being higher in obese than non-obese [26]. We reported an elevated FMI and FFMI in obese compared to non-obese. Few other studies stated that BMI and FMI have equal weightage in detecting obesity and metabolic syndrome, indicating that the location of fat may affect the deregulation of metabolism [27,28]. In our study, SF%, VFI, and BMR were higher in obese than non-obese individuals.

The fasting glucose was within normal limits in both obese and non-obese which is in line with other research [29]. The fasting insulin though within the normal range, was significantly higher in obese than non-obese probably due to insulin resistance [30]. The IR in obese was confirmed further by calculating the IR markers. This was in line with other studies [31,32]. The subjects in our study did not show any significant difference in lipid profile parameters. The LAP-index which is considered a better predictor of IR than HOMA-IR was higher in obese than non-obese indicating the presence of IR in obese. The adipokines, leptin was high in obese than non-obese, however, adiponectin did not show any significant difference. Whereas, the A/L ratio which is better predictor of comorbidities in obese than HOMA-IR was significantly lower in obese, indicating the risk of comorbidities in obese (Table 1).

Further, when the subjects were divided into obese males and females and non-obese males and females, in both groups males showed significantly higher WHR and NC compared to females. Studies

Table 5. Correlation between BMI and HOMA-IR with other parameters.

Study parameter		BMI	HOMA-IR
WHR	Pearson Correlation	0.122	0.25
	P-value	0.268	**0.02**
NC	Pearson Correlation	0.555**	0.30*
	P-value	**<0.001**	**0.005**
BMI	Pearson Correlation	–	0.42**
	P-value	–	**<0.000**
FMI	Pearson Correlation	0.864**	0.31*
	P-value	**<0.001**	**0.003**
FFMI	Pearson Correlation	0.794**	0.39**
	P-value	**<0.001**	**0.0001**
SF %	Pearson Correlation	0.530**	0.16
	P-value	**<0.001**	0.14
VFI	Pearson Correlation	0.837**	0.42**
	P-value	**<0.001**	**<0.000**
BMR	Pearson Correlation	0.719**	0.36**
	P-value	**<0.001**	**0.0006**
Fasting Glucose	Pearson Correlation	−0.030	0.14
	P-value	0.787	0.20
Fasting Insulin	Pearson Correlation	0.442**	0.91**
	P-value	**<0.001**	**<0.000**
HOMA-IR	Pearson Correlation	0.428**	–
	P-value	**<0.001**	–
HOMA- β	Pearson Correlation	0.40	0.77**
	P-value	**0.0001**	**<0.000**
QUICKI	Pearson Correlation	0.53	0.85**
	P-value	**<0.000**	**<0.000**
TC	Pearson Correlation	−0.099	0.12
	P-value	0.369	0.244
HDL-C	Pearson Correlation	0.125	0.11
	P-value	0.257	0.31
LDL-C	Pearson Correlation	−0.143	0.22
	P-value	0.193	**0.03**
TGL	Pearson Correlation	0.013	0.17
	P-value	0.903	0.10
VLDL-C	Pearson Correlation	0.013	0.17
	P-value	0.903	0.10
Non HDL-C	Pearson Correlation	−0.137	0.15
	P-value	0.214	0.15
Lipoprotein A	Pearson Correlation	0.101	0.04
	P-value	0.36	0.6 6
LDL-C/HDL-C	Pearson Correlation	−0.070	0.17
	P-value	0.524	0.12*
TGL/HDL-C	Pearson Correlation	−0.021	0.05
	P-value	0.851	0.62
TC/HDL-C	Pearson Correlation	−0.069	0.12
	P-value	0.535	0.24
AIP	Pearson Correlation	0.004	0.10
	P-value	0.972	0.32
Leptin	Pearson Correlation	0.41	0.21
	P-value	**<0.000**	0.05
Adiponectin	Pearson Correlation	0.019	0.10
	P-value	0.85	0.33
A/L	Pearson Correlation	0.284	0.19
	P-value	**0.008**	0.08

have shown that estrogen decreases the WHR in females and testosterone increases the WHR in males. The hip fat in females which is rich in long-chain polyunsaturated fatty acid is required for the infant brain growth and also low WHR in females is associated with more regular cycles and increased rate of conception than compared with high WHR in females [33]. Even the BMR between the two groups showed males have greater BMR than females, due to more muscle mass and faster metabolism in males. Due to the hormonal effects, females have higher HOMA-IR than males and this insulin sensitivity decreases as menopause is reached [34]. But it has also been stated that there is no sex difference in the HOMA-IR levels [35]. Our study also did not show any sex difference for IR indicators for both groups. Men usually have higher TC, and TGL than women, however, as age advances, these values tend to equalize [36]. We observed no significant difference in the lipid profile parameters between obese males and females, whereas non-obese males showed higher TG and lower LDL-C. Our study showed higher values of the LAP index in non-obese males than in non-obese females. LAP index is superior to IR indicators in predicting IR and metabolic syndrome in non-obese, normoglycaemic subjects [37]. Leptin levels are higher, and adiponectin and A/L levels are lower in females due to the influence of sex hormones (Table 2).

HOMA−IR is one of the important indicators to predict IR and metabolic syndrome. We divided the study subjects into IR and IS with 65% being IR and 35% being IS. The anthropometric measurements like BMI, WC, and NC have been reported to be higher in IR [38–40]. In lean individuals, FMI is directly proportional to fasting insulin and HOMA-IR indicating fatness plays a major role in glucose intolerance [41], whereas, QUICKI is inversely proportional to HOMA-IR [40]. Our study also showed that anthropometric measurements along with IR markers were raised in IR than IS. There is a poor correlation between TC and LDL-C with IR. TGL/HDL is a better predictor of metabolic disease in IR. Furthermore, it has been noted that increased TGL/HDL leads to increased left ventricular wall thickness and is a marker of end-organ damage and it is also an independent risk factor to determine chronic kidney disease [42]. We too did not see any significant difference among the lipid profile parameters except for TGL/HDL between IR and IS. LAP is directly related to IR and it has been stated that LAP is superior to HOMA-IR in predicting metabolic syndrome, type 2 diabetes and cardiovascular disease in the general population and also between sex [43,44]. Adipose tissue hypertrophy is seen in hyperleptinemia and also deficient leptin signaling causes IR. High levels of serum leptin levels are seen in IR [45,46]. It is also known that a reduced A/L ratio is an indicator of an increased risk for

Table 6a. Association between BMI and other parameters.

Term (BMI)	Odds ratio	95%	CI	Coefficient	SE	Z-statistic	P-value
Age	1.0022	0.9664	1.0394	0.0022	0.0186	0.1208	0.9039
WHR	31.986	0.1287	7951.426	3.4653	2.8142	1.2314	0.2182
NC	1.3672	1.1764	1.5890	0.3127	0.0767	4.0775	**0.0000**
FMI	5.2510	2.1966	12.5527	1.6584	0.4447	3.7296	**0.0002**
FFMI	2.8102	1.7571	4.4945	1.0333	0.2396	4.3125	**0.0000**
SF%	1.1523	1.0671	1.2444	0.1418	0.0392	3.6142	**0.0003**
VFI	4.5492	2.0861	9.9203	1.5149	0.3978	3.8085	**0.0001**
BMR	1.0078	1.0043	1.0113	0.0078	0.0018	4.4263	**0.0000**
Glucose	1.0013	0.9929	1.0098	0.0013	0.0043	0.3005	0.7638
Insulin	1.1083	1.0461	1.1741	0.1028	0.0295	3.4908	**0.0005**
HOMA-IR	1.3966	1.1385	1.7130	0.3340	0.1042	3.2048	**0.0014**
HOMA- β	1.0223	1.0083	1.0366	0.0221	0.0071	3.1338	**0.0017**
QUICKI	0.000	0.000	0.0000	−48.5422	11.492	−4.2240	**0.0000**
TC	0.9980	0.9884	1.0077	−0.0020	0.0049	−0.4085	0.6829
HDL-C	1.0175	0.9940	1.0416	0.0174	0.0119	1.4525	0.1464
LDL-C	0.9941	0.9858	1.0024	−0.0059	0.0042	−1.3980	0.1621
TGL	1.0021	0.9978	1.0064	0.0021	0.0022	0.9495	0.3424
VLDL-C	1.0105	0.9889	1.0325	0.0104	0.0110	0.9495	0.3424
Non-HDL-C	0.9958	0.9877	1.0039	−0.0042	0.0041	−1.0289	0.3035
Lipoprotein A	1.0037	0.9941	1.0134	0.0037	0.0049	0.7515	0.4523
LDL-C/HDL-C	0.9224	0.7352	1.1572	−0.0808	0.1157	−0.6981	0.4851
TGL/HDL-C	1.0313	0.9275	1.1468	0.0308	0.0541	0.5696	0.5690
TC/HDL-C	0.9620	0.7921	1.1683	−0.0388	0.0992	−0.3912	0.6957
AIP	1.2070	0.3073	4.7412	0.1881	0.6981	0.2695	0.7875
Leptin	1.0526	1.0241	1.0820	0.0513	0.0140	3.6607	**0.0003**
Adiponectin	0.9366	0.7183	1.2211	−0.0656	0.1353	−0.4843	0.6281
A/L	0.5594	0.3635	0.8609	−0.5809	0.2199	−2.6411	**0.0083**

Table 6b. Association between HOMA-IR and other parameters.

Term (HOMA-IR)	Odds ratio	95%	CI	Coefficient	SE	Z-statistic	P-value
Age	0.9955	0.9582	1.0343	−0.0045	0.0195	−0.2295	0.818
WHR	7.8963	0.0254	2456.05	2.0664	2.9286	0.7056	0.4804
NC	1.1627	1.0244	1.3197	0.1507	0.0646	2.3328	**0.0197**
BMI	1.1808	1.0697	1.3034	0.1662	0.0504	3.2967	**0.0010**
FMI	1.2458	1.0618	1.4616	0.2197	0.0815	2.6958	**0.007**
FFMI	1.276	1.0812	1.506	0.2438	0.845	2.884	**0.0039**
SF%	1.0598	0.9939	1.1302	0.0581	0.0328	1.7719	0.0764
VFI	1.3282	1.1251	1.568	0.2838	0.0847	3.352	**0.0008**
BMR	1.0024	1.0006	1.0042	0.0024	0.0009	2.5962	**0.0094**
Glucose	1.0103	0.996	1.0248	0.0102	0.0073	1.4091	0.1588
Insulin	1.5136	1.2311	1.8608	0.4145	0.1054	3.9326	**0.0001**
HOMA- β	1.0523	1.0255	1.0798	0.051	0.0132	3.8773	**0.0001**
QUICKI	4.5358	1.1486	17.9118	1.512	0.7008	2.1577	**0.031**
TC	1.002	0.9918	1.0123	0.002	0.0052	0.389	0.6973
HDL-C	0.9896	0.9713	1.0083	−0.0104	0.0095	−1.0947	0.2736
LDL-C	1.0003	0.9919	1.0087	0.0003	0.0043	0.0585	0.9534
TGL	1.0063	0.9997	1.013	0.0063	0.0034	1.877	0.0605
VLDL-C	1.0322	0.9986	1.0668	0.0316	0.0169	1.877	0.0605
Non-HDL-C	1.0035	0.9952	1.0119	0.0035	0.0042	0.8257	0.409
Lipoprotein A	0.9959	0.9864	1.0055	−0.0041	0.0049	−0.8415	0.4001
LDL-C/HDL-C	1.1186	0.8766	1.4274	0.1121	0.1244	0.9013	0.3674
TGL/HDL-C	1.1714	0.9899	1.3862	0.1582	0.0859	1.8416	0.0655
TC/HDL-C	1.1787	0.9501	1.4623	0.1644	0.11	1.4948	0.135
AIP	7.316	1.394	38.3954	1.9901	0.8459	2.3527	**0.0186**
Leptin	1.0224	1.0010	1.0443	0.0221	0.0108	2.0497	**0.040**
Adiponectin	0.9465	0.7183	1.2472	−0.0550	0.1407	−0.3904	0.6962
A/L	0.7526	0.5880	0.9633	−0.2842	0.1259	−2.2569	**0.0240**

metabolic syndrome. Our study also showed an altered A/L ratio in IR indicating the risk of comorbidities. IS subjects had a favorable cardiometabolic profile compared to IR. It can also be noted that IR and IS subjects roughly reflect the mirror image of metabolically unhealthy individuals and metabolically healthy individuals.

Further IR and IS subjects were divided into obese IR(88%) and IS (12%) and non-obese IR (43%) and IS (57%). IR indicators, TC, TGL and TG/HDL showed significant difference between obese IR and obese IS. As explained earlier TG/HDL is a better predictor of metabolic disease in IR, our study was also in line with it. However between non-obese IR and IS, only IR indicator showed significant difference between them. This indicates non-obese individuals could be at equal risk of developing CVD (Table 3). Furthermore dividing the study subjects into male IR (64%) and IS (36%) and female IR (66%) and IS (34%), no significant difference between IR and IS was observed (Table 4).

The correlation and association between BMI and other parameters showed that there is a strong positive correlation between BMI and NC, FMI, FFMI, VFI, BMR, Fasting insulin, HOMA-IR, HOMA- β, QUICKI, leptin, and A/L. Also, the correlation and association between HOMA-IR and other parameters showed that there is a strong positive correlation between HOMA-IR and NC, BMI, FMI, FFMI, VFI, BMR, Fasting insulin, HOMA-β, QUICKI (Tables 5 and 6).

Our study clearly states that anthropometric measurements like BMI, WC, WHR, FMI, FFMI, and lipid profile parameters TC, TGL, and HDL-C may not be good markers to predict the future risk of CVD. Though fasting insulin has been significant in identifying at-risk individuals, it is one of the components for calculating the IR indicators and is expensive. Thus, considering the cost-effectiveness we have excluded fasting insulin from the final list of markers. As evident from our study and also from previous studies it can be stated that parameters like NC, TGL/HDL, and LAP index can be used as better markers to detect metabolically healthy and metabolically unhealthy individuals in lean and obese individuals.

Limitations of our study include a smaller sample size and the wide age range to which the study subjects belong to. Thus further multicentric studies are required using a larger sample size and classifying the subjects into young adults (18–25 years), adults (26–44 years), middle-age (45–59 years), old age (60 years and above) categories. The exact cut-off value for NC, TGL/HDL, and LAP index to detect metabolically healthy and metabolically unhealthy individuals need to be determined in each categories. Also, molecular studies like epigenetic and gene expression analysis in all age categories may be required to understand if these modifications occur in early adulthood or later. Early identification of at-risk individuals will help clinicians to advise the lifestyle modifications before the occurrence of any symptoms. This may reduce the national burden of metabolically unhealthy individuals.

Source(s) of support

JSS Academy of Higher Education and Research for funding the project: JSSAHER/REG/RES/URG/54/2011–12/10,392.

Presentation at a meeting

Nil.

Conflicts of interest

There are no conflicts of interest.

Acknowledgement

The authors would like to acknowledge the JSS Academy of Higher Education and Research for funding the project: JSSAHER/REG/RES/URG/54/2011-12/10392 and the Special Interest Group in Human Genomics and Rare Disorders(SIG-HGRD) for their support in the study.

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