© Kamla-Raj 2019 J Hum Ecol, 65(1-3): 1-11 (2019)
PRINT: ISSN 0970-9274 ONLINE: ISSN 2456-6608 DOI: 10.31901/24566608.2019/65.1-3.3131

Association of Body Mass Index with Non-communicable Diseases: Polycystic Ovary Syndrome, Type 2 Diabetes Mellitus and Coronary Artery Disease

Battini Mohan Reddy* and S.A.A. Latheef

Department of Genetics, Osmania University, Hyderabad, India

KEYWORDS Body Mass Index. Disease Specific Cut Offs. Gender Specific Cut Offs. Logistic Regression. ROC Based Cut Offs. 95 Percentile Cut Offs

ABSTRACT We investigated the role of Body mass index (BMI) in non-communicable diseases- polycystic ovary syndrome (PCOS), type 2 diabetes (T2DM) and coronary artery disease (CAD). Using a case control design, we compared mean BMI and its categories, in gender and disease specific samples, and computed odds ratios as well as receiver operator characteristic (ROC) curve. The 95 percentile cut off values were also determined but only for controls. We found mean BMI and prevalence of obesity to be higher in PCOS and T2DM and lower in CAD cases than controls. The ROC analysis suggested gender specific cut-off values are more sensitive than pooled sample. The area under the ROC curve which is highly significant suggests predictive utility of the BMI cut off values both for PCOS and T2DM.

INTRODUCTION

Abnormal or excess accumulation of fat in adipose tissue to the extent that it leads to the impairment of health is known as obesity (Ofei 2005). Of the two types of obesity, general obesity is assessed by using body mass index (BMI) and central obesity by different measurements: waist-hip ratio, waist circumference, waist-height ratio, sagittal abdominal diameter etc. (Okafor et al. 2011).The BMI is calculated as a ratio of weight to height (Weight in kgs/height in meters^2) and the cut off value of BMI for defining obesity has been variable depending on the ethnic group. Globally, Obesity was reported to be responsible for 3.4 million deaths, loss of 3.9 percent years of life and 3.6 percent of disability adjusted life years in the year 2010 (Ng et al. 2014). Increasing obesity was documented for the past three decades globally but marked differences were observed across the countries which were attributed to the increased intake of calories, altered composition of diet and altered gut microbiome and reduced physical activity (Ng et al. 2014). In India, higher prevalence of obesity was observed in urban residents, high income groups, sedentary/physically inactive people and women and the increasing prevalence was attributed to increasing urbanization, use of mechanized transport and labour saving devices, sedentary life styles and consumption of processed and energy dense foods (Pradeepa et al. 2015). About 5 percent of the patients with non-communicable diseases were estimated to have been associated with obesity (Banjare and Bhalerao 2016). Obesity was also shown to exacerbate other intermediate risk factors and non-communicable diseases and increase the risk of disability and mortality (Manning et al. 2016).

Menstrual abnormalities, long-term difficulty for conception and close association with insulin resistance were observed among obese women with polycystic ovary syndrome (PCOS). In a meta-analysis, Babu et al. (2018) observed significant association of obesity with type 2 diabetes mellitus (T2DM). Though obesity is associated with cardiovascular diseases such as heart failure, coronary artery disease (CAD), sudden cardiac death, atrial fibrillation and reduced survival but some studies also have shown that obese people with aforementioned clinical problems were found to have better prognosis than non-obese subjects (Lavie et al. 2009). Further, it is not clear from the literature whether same cut-off value of BMI can be applied for predicting the risk of all non-communicable diseases and if the cut-off values are different for males and females. It is also not clear if the cut off values obtained from ROC curve and the 95th percentile of the BMI data from the control sample are different and if the odds ratios obtained

Address correspondence to:
Professor B.M. Reddy
ICMR Emeritus Medical Scientist
Department of Genetics
Osmania University
Hyderabad 500 007, India
E-mail: bmrisi@gmail.com

based on these cut offs of BMI, reflecting association with non-communicable diseases, will be different. We analysed three sets of case-control data of BMI for T2DM, PCOS and CAD in order to address the above issues.

Objectives

1. To determine the disease and gender specific cut off values of BMI and test if they are different.
2. To compare the cut off values obtained by ROC curve and 95 percentile value to gauge relative predictive utility of BMI based on the two methods.
3. To obtain the odd ratios based on the quantitative BMI and its cut off values to gauge relative significance of association in case of each these syndromes.

METHODOLOGY

The BMI and other data for the study were collected as part of three plan projects of the Indian Statistical Institute (PCOS, T2DM and CAD) undertaken by BMR during 2007-2016 and the details on the sampling, inclusion criteria etc. can be found in a series of publications dealing with genetic susceptibility of the three NCDs (Dasgupta et al. 2012; Dasgupta et al. 2013; Umajyothi et al. 2013; Uma Jyothi and Reddy 2015; Pranavchand and Reddy 2016; Pranavchand et al. 2016, 2017). For the sake of ready reference, the number of case and control samples analysed for PCOS, T2DM and CAD are furnished in Table 1. Suffice to say that while the cases were recruited from different hospitals in Hyderabad, the controls (broadly matched for age and ethnicity) were drawn from Hyderabad and its vicinity, recruiting from different organizations and by conducting health camps. Body mass index (BMI) was calculated using the formula: weight (kg) / height (m^2). The subjects having BMI >25 were considered as obese, following the guidelines of Indian consensus group on obesity (Misra et al. 2009).

Statistical Analysis: All continuous variables were presented as mean and standard deviation. Data distribution was checked using Shapiro-Wilks test. Due to non-normal distribution of data, Mann-Whitney U test was used to compare the medians of the groups. Cut-off values of BMI were obtained by employing receiver operator characteristic curve analysis and also by calculating 95 percentiles of controls. Association of BMI with dependent variables (PCOS, T2DM and CAD) were investigated by logistic regression analysis. All statistical analyses were performed by using SPSS ver 20 of IBM Corporation and Medcalc software ver 16.

Ethical clearance was obtained for the study from the Indian statistical institute review committee for protection of research risks to humans with reference to each of the three projects from which data were drawn. Written consent of the subjects was obtained before collecting the information.

RESULTS

Gender wise and pooled sample means and SDs of BMI for patients and controls of PCOS, T2DM and CAD are given in Table 2. While mean BMI is found to be significantly much higher in the PCOS and T2DM patients when compared to the respective controls (P=0.000), CAD patients showed significantly lower mean BMI (p = 0.013) when compared to the controls. Further, while we observed significantly higher mean BMI in male and female T2DM patients when compared to same gender controls (P=0.000), no such pattern, higher or lower, was apparent in CAD patients.

Table 1: Details of sampling and sample sizes for different case and control cohorts

S. No.	*Cohorts*	*Male*	*Female*	*Total*	*Sampling locations*
1.	PCOS cases	-	170	170	Gynecology Clinic of Osmania hospital and Anu's Infertility Clinic, Hyderabad
2.	PCOS controls	-	238	238	Family Planning Centre of Osmania Hospital and from the general population, Hyderabad
3.	T2DM cases	441	260	701	J.P. Endocrine centre, Hyderabad
4.	T2DM controls	397	224	621	Free health camps in different organizations in Hyderabad
5.	CAD cases	180	70	250	Care hospitals, Hyderabad
6.	CAD controls	287	220	507	Free health camps in and around Hyderabad

Table 2: Mean and SDs of BMI in case and control cohorts of PCOS, T2DM and CHD

	Polycystic Ovary Syndrome Cases vs Control		
Cases (n=170)	Control (n=238)	Total (n=408)	P value
27.35 ± 5.66	22.59 ± 3.64	24.74 ± 5.03	0.000
	Type 2 Diabetes Mellitus Cases vs Control		
Cases (n=701)	Control(n=621)	Total (n=1322)	P value
26.83 ± 5.24	24.65 ± 4.81	25.81 ± 5.16	0.000
	Male Cases vs Control		
Cases (n=441)	Control (n=397)	Total (n=838)	P value
26.01 ± 5.07	24.34 ± 4.38	25.22 ± 4.83	0.000
	Female Cases vs Control		
Cases (n=260)	Controls (n=224)	Total (n=484)	P value
28.23 ± 5.22	25.21 ± 5.46	26.83 ± 5.54	0.000
	Coronary Artery Disease Cases vs Control		
Cases (n=250)	Control (n=507)	Total (n=757)	P value
26.12 ± 3.76	26.86 ± 4.54	26.62 ± 4.31	0.013
	Male Cases vs Control		
Cases (n=180)	Control (n=287)	Total (n=467)	P value
25.91 ± 3.33	26.31 ± 4.21	26.15 ± 3.90	0.208
	Female Cases vs Control		
Cases (n=70)	Control (n=220)	Total (n=290)	P value
26.68 ± 4.68	27.59 ± 4.85	27.37 ± 4.82	0.161

The results on the test of homogeneity of frequencies of different BMI categories between cases and controls in different age groups and in the pooled sample are presented in Table 3 for PCOS, T2DM and CAD. Over all, statistically significant heterogeneity in the frequency of BMI categories was observed between the PCOS, T2DM (P=0.000) and CAD (P=0.008) cases and their respective controls. The difference in the prevalence of BMI categories between PCOS patients and controls were found to be highly significant in all the age groups (P=0.000). Similarly significant difference in the prevalence of BMI categories was also observed between T2DM patients and controls (P=0.000) in all but the 30-40 years age group. On the other hand, significant heterogeneity in the prevalence of BMI categories between CAD patients and control (P=0.003) was observed only in the age group of 51-60 years.

Gender specific and for the pooled sample of males and females the prevalence of BMI categories is furnished in Table 4 for patients and controls of PCOS, T2DM and CAD. Concurrent to the above observations, while the prevalence of obesity was found to be significantly higher in PCOS and T2DM patients when compared to their re-

Table 3: Test of homogeneity of the frequency of BMI categories in different age groups of PCOS, T2DM and CAD cases and controls

Polycystic ovary syndrome

Age group	*PCOS (n=168)*				*Age group*	*Controls (n=233)*				*P value* (χ^2)
	BMI categories					*BMI categories*				
	<18.5	18.5-22.9	23-24.9	>25		<18.5	18.5-22.9	23-24.9	>25	
15-25 (n=91)	5 (5.49)	24 (26.37)	9 (9.89)	53 (58.24)	15-25 (n=166)	18 (10.84)	97 (58.43)	36 (21.68)	15 (9.03)	0.000
26-35 (n=76)	0 (0.00)	13 (17.10)	9 (11.84)	54 (71.05)	26-35 (n=54)	2 (3.70)	27 (50.00)	10 (18.51)	15 (27.77)	0.000
36-45 (n=1)	0 (0.00)	0 (0.00)	0 (0.00)	1(100)	36-45 (n=13)	0 (0.00)	1 (7.69)	3 (23.07)	9 (69.23)	0.000

Type 2 diabetes

Age group	*T2DM (n=700)*				*Age group*	*Controls (n=620)*				*P value* (χ^2)
	BMI categories					*BMI categories*				
	<18.5	18.5-22.9	23-24.9	>25		<18.5	18.5-22.9	23-24.9	>25	
30-40 (n=70)	1 (1.42)	8 (11.42)	14 (20.00)	47 (67.14)	30-40 (n=2)	0 (0.00)	0 (0.00)	0 (0.00)	2 (100.00)	0.810
41-50 (n=236)	9 (3.81)	33 (13.98)	30(12.71)	164 (69.49)	41-50 (n=323)	21 (6.50)	72(22.29)	72 (22.29)	158 (48.91)	0.000
51-60 (n=275)	3 (1.09)	47 (17.09)	50(18.18)	175 (63.63)	51-60 (n=228)	19 (8.33)	48(21.05)	29 (12.71)	132 (57.89)	0.000
61-70 (n=100)	2 (2.00)	12 (12.00)	14(14.00)	72 (72.00)	61-70 (n=48)	17 (35.41)	13(27.08)	7 (14.58)	11 (22.91)	0.000
71-80 (n=19)	0 (0.00)	2 (10.52)	2(10.52)	15 (78.94)	71-80 (n=19)	6 (31.57)	11(57.89)	0 (0.00)	2 (10.52)	0.000

Coronary artery disease

Age group	*CAD (n=248)*				*Age group*	*Controls (n= 496)*				*P value* (χ^2)
	BMI categories					*BMI categories*				
	<18.5	18.5-22.9	23-24.9	>25		<18.5	18.5-22.9	23-24.9	>25	
30-40 (n=12)	0 (0.00)	2 (16.66)	2 (16.66)	8 (66.66)	30-40 (n=77)	1 (1.29)	10 (12.98)	8 (10.38)	58 (75.32)	0.866
41-50 (n=40)	2 (5.00)	7 (17.50)	7 (17.50)	24 (60.00)	41-50 (n=212)	4 (1.88)	37 (17.45)	27 (12.73)	144 (67.92)	0.522
51-60 (n=103)	1 (0.97)	21 (20.38)	25 (24.27)	56 (54.36)	51-60 (n=125)	5 (4.00)	20 (16.00)	11 (8.80)	89 (71.20)	.003
61-70 (n=75)	0 (0.00)	9 (12.00)	19 (25.33)	47 (62.66)	61-70 (n=64)	2 (3.12)	11 (17.18)	13 (20.31)	38 (59.37)	0.330
>71 (n=18)	1 (5.55)	2 (11.11)	3 (16.66)	12 (66.66)	>71 (n=18)	2 (11.11)	5 (27.77)	6 (33.33)	5 (27.77)	0.139

spective controls (p=0.000), it was lower in case of CAD (p=0.01).The prevalence of obesity in both male and female T2DM patients was significantly higher than their gender specific controls, but in other categories of BMI the opposite trend was seen. Significant heterogeneity in the prevalence of BMI categories was observed between male and female CAD patients (P=0.004). Similarly, significant heterogeneity in the prevalence of BMI categories, particularly in overweight and obese people, was observed between male and female T2DM patients (P=0.000).

Pooled and gender specific BMI Cut-off values for PCOS, T2DM and CAD are given in Table 5 and the respective ROC curves depicted in Figures 1-3. Irrespective of the disease, the cut-off values of pooled and gender specific samples were found to be different. The area under curve, which reflects the predictive ability of the cut-off value was found to be highly significant and relatively large for PCOS (AUC ~0.77) and T2DM (AUC ~0.63), not for CAD (AUC ~ 0.55). The results of the logistic regression analysis of the quantitative BMI and its cut-off values (based on (1) 95 percentile value of the controls and (2) ROC curve) in the PCOS, T2DM and CAD cases and controls are given in Table 6. BMI and its cut-off values obtained from ROC curve were found to explain relatively higher percentage of variation in PCOS and T2DM, when compared to

Table 4: Gender wise prevalence of BMI categories in the cases and controls of PCOS, T2DM and CAD

Polycystic ovary syndrome

BMI Categories	*Cases (n=168)*	*Controls (n=233)*	*P value (χ^2)*
Underweight (<18.5)	5 (2.97)	20 (8.58)	0.000
Normal (18.5-22.9)	37 (22.02)	125 (53.64)	
Overweight (23-24.9)	18 (10.71)	49 (21.03)	
Obesity (>25)	108 (64.28)	39 (16.73)	

Type 2 diabetes

BMI categories	*Cases*			*Controls (χ^2)*			
	Male (n=440)	*Female (n=260)*	*Total (M+F) (n=700)*	*Male (n=396)*	*Female (n=224)*	*Total (M+F) (n=620)*	*P value* (χ^2)*
Underweight (<18.5)	9 (2.04)	5 (1.92)	14 (2.00)	38 (9.59)	25 (11.16)	63 (10.16)	0.000
Normal (18.5-22.9)	78 (17.68)	24 (9.23)	102 (14.57)	97 (24.49)	47 (20.98)	144 (23.22)	
Overweight (23-24.9)	82 (18.59)	29 (11.15)	111 (15.85)	76 (19.19)	32 (14.28)	108 (17.41)	
Obesity (>25)	271 (61.45)	202 (77.69)	473 (67.57)	185 (46.71)	120 (53.57)	305 (49.19)	

P value (χ^2)between male and female cases=0.000;
P value (χ^2)between male cases and male controls=0.0000001;
P value (χ^2)between female cases and female controls=0.0000001
P value between male and female controls= 0.217
;

Coronary artery disease

BMI categories	*Cases*			*Controls*			
	Male (n=179)	*Female (n=69)*	*Total (M+F) (n=248)*	*Male (n=280)*	*Female (n=216)*	*Total (M+F) (n=496)*	*P value* (χ^2)*
Underweight (<18.5)	0 (0.00)	4 (5.79)	4 (1.61)	9 (3.21)	5 (2.31)	14 (2.82)	0.01
Normal (18.5-22.9)	32 (17.87)	9 (13.04)	41 (16.53)	50 (17.85)	33 (15.27)	83 (16.73)	
Overweight (23-24.9)	45 (25.13)	11 (15.94)	56 (22.58)	42 (15.00)	23 (10.64)	65 (13.10)	
Obesity (>25)	102 (56.98)	45 (65.21)	147 (59.27)	179 (63.92)	155 (71.75)	334 (67.33)	

P value between male and female cases=0.004;
P value between male cases and male controls= 0.902;
P value between female cases and female controls=0.304;
P value between male and female controls=0.295

**Between pooled cases (M+F) and Controls*

Table 5: Cut-off values of pooled and gender specific BMI with CAD, T2DM and PCOS

Variable	*Cut-off value*	*AUC*	*95 percent CI, p-value*	*Sen*	*Spe*
		Polycystic Ovary Syndrome			
BMI in total subjects	>24.52	0.767	0.723-0.807, 0.0001	67.65	80.67
		Type 2 Diabetes			
BMI in total subjects	>24.80	0.629	0.602-0.655, 0.0001	68.90	50.16
BMI in males	>23.30	0.604	0.570-0.637, 0.0001	77.32	38.89
BMI in females	>24.70	0.666	0.622-0.708, 0.0001	80.38	45.54
		Coronary Artery Disease			
BMI in total subjects	<27.68	0.555	0.519- 0.591,0.0101	73.60	42.01
BMI in males	<26.57	0.535	0.488-0.581, 0.1983	67.78	44.25
BMI in females	<27.70	0.556	0.497-0.614, 0.1557	67.14	50.45

Sen: sensitivity; **Spe**: specificity

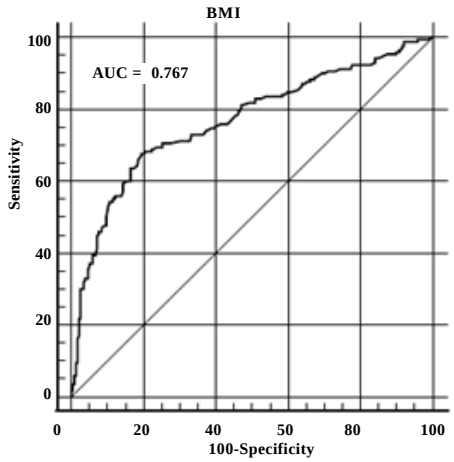


Fig. 1. Receiver operator characteristic curve analysis of BMI in PCOS

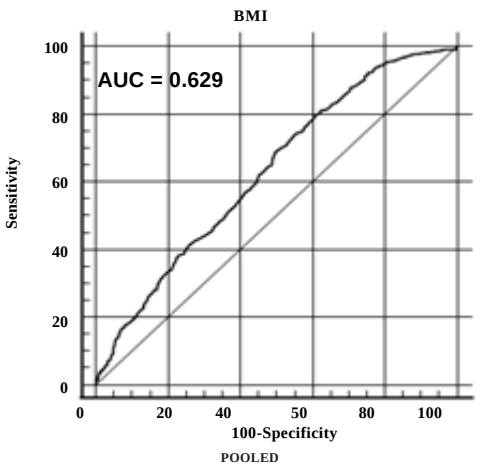
that based on the 95 percentile value. Further, BMI emerges as better predictor of risk of PCOS as compared to T2DM (Nagelkerke R^2: Cut off values obtained by ROC explain ~30 percent of variation in PCOS as against 5 percent in case of T2DM and 1 percent in case of CAD). However, similar degree of association was observed when logistic regression analysis was done either with quantitative BMI values or with cut-off value obtained through ROC in case of both PCOS or T2DM.

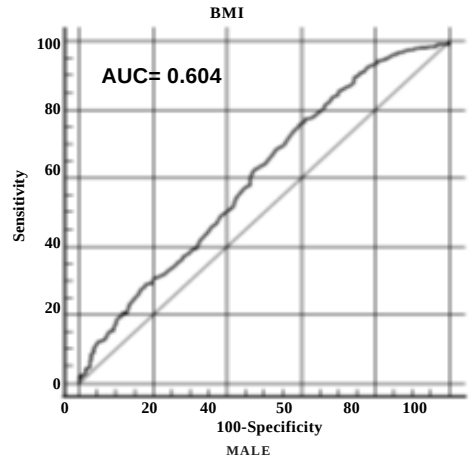
DISCUSSION

Polycystic Ovary Syndrome

Higher mean BMI and prevalence of obesity in PCOS patients when compared to controls that we observed in the present study is consistent with earlier finding among both Indian (Sharma and Majumdar 2015; Garg et al. 2016; Chitme et al. 2017; Thangavelu et al. 2017) and non-Indian (Beydoun et al. 2009; Chitme et al. 2017) populations. Significantly higher prevalence of obesity with increasing age among patients when compared to controls suggest that age has an influence on increasing prevalence of obesity in PCOS. To the best of our knowledge no cut-off value of BMI for predicting the risk of PCOS in the Indian context is hitherto determined. In our study of south Indian women from Hyderabad, a cut-off value of BMI >24.52 kg/m^2 for PCOS with sensitivity of 67.65 percent and specificity of 80.67 percent was observed. The AUC of 0.767 obtained through ROC analyses suggests that BMI has a highly significant predictive value in assessing the risk of PCOS. The cut-off value obtained for PCOS is similar to the cut-off value of BMI obtained for T2DM in females from the same geographic region. Given the common clinical feature of insulin resistance for both these diseases, this finding is somewhat expected. In terms of contribution of BMI in explaining the variation in the dependent variable, PCOS, cut-off value obtained through ROC analysis and the quantitative trait BMI explained almost similar proportion of variation (28.8 VS 28%), which is much higher than that explained by the 95 percentile value obtained from the control sample (~20.5 %).

The proposed mechanisms of obesity causing PCOS are insulin resistance and consequent hyperinsulinemia (Legro 2012). Insulin acts as a co-gonodotropin and stimulates ovaries to produce androgens. Laprauchaunism, a characteristic feature of hyperandrogenimia was seen in women with insulin resistance and hyperinsuline-





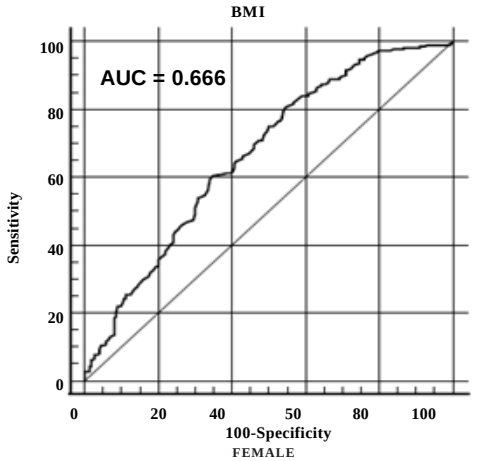
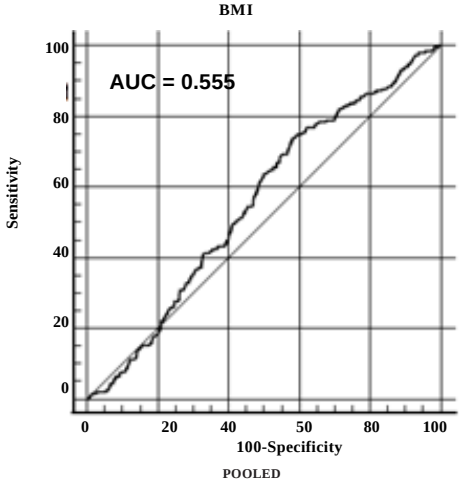
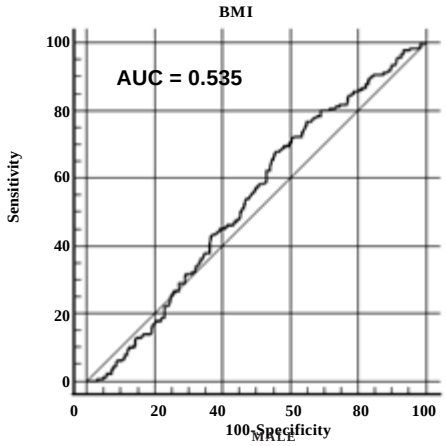


Fig. 2. Receiver operator characteristic curve analysis of BMI in T2DM





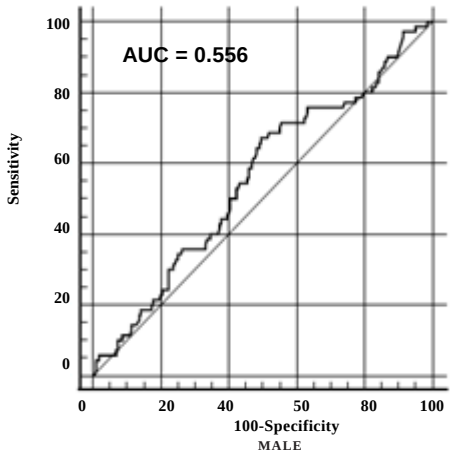


Fig. 3. Receiver operator characteristic curve analysis of BMI in CAD

Table 6: Association of quantitative BMI and its cut-off values with PCOS, T2DM and CAD, adjusted for age and gender

Variable	*B*	*S.E*	*Wald*	*OR*	*95 percent CI*	*P value*	*Nagel kerke R^2*
Polycystic ovary syndrome							
BMI	0.234	0.029	64.30	1.263	1.193-1.338	0.000	0.280
BMI 95percentile >28.79	2.421	0.348	48.408	11.256	5.691-22.262	0.000	0.205
BMI cut-off value >24.52	2.147	0.232	85.452	8.561	5.430-13.498	0.000	0.288
Type 2 diabetes							
BMI	0.093	0.013	55.22	1.098	1.071-1.125	0.000	0.062
BMI 95 percentile >32.19	0.744	0.224	11.05	2.104	1.357-3.263	0.001	0.012
BMI cut-off value >24.8	0.811	0.115	49.70	2.250	1.796-2.819	0.000	0.051
Coronary artery disease							
BMI	-0.041	0.108	4.891	0.960	0.926-0.995	0.027	0.009
BMI 95Percentile >34.59	-0.933	0.496	3.534	0.393	0.149-1.040	0.060	0.008
BMI cut-offvalued <27.68	0.703	0.169	17.230	2.020	1.449-2.815	0.000	0.033

mia. Administration of insulin to women with type1 diabetes or normal ovaries increased the concentration of ovarian androgens. Treatment directed to decrease insulin or to improve insulin action with antidiabetic drugs lowered the circulatory levels of androgens and accelerated ovulation rates. It was also observed that increased levels of growth factors and inflammatory factors found in obese people elevate the secretion of ovarian androgens or prevent the aromatization of androgens to estrogens. Irregular secretion of gonadotropin was observed in insulin resistance or hyperinsulinemia due to their influence on hypothalamus. Selective knocking of insulin receptor on pituitary gland of obese mice resulted in normal secretion of gonadotropin and improved fertility (Brothers et al. 2010). Further, in Anorexia nervosa or hypothalamic amenorrhea, gonadotropin secretion is suppressed or ovulatory function is lost. Administration of leptin resulted in the restoration of gonadotropin levels and follicle development or ovulation in women with hypothalamic amenorrhea (Welt et al. 2004). Obesity was shown to influence the peripheral metabolism and regulation of sex steroids. The aromatase present in the adipose tissue stimulates the excess secretion of bioactive oestrogen from androgens into the circulation and increases the levels of oestrogen contributing to the anovulation and development of endometrial hyperplasia (Kaaks et al. 2002). Hyperandrogenism and insulin resistance suppresses the secretion of sex hormone binding globulin (SHBG) and this leads to increased levels of androgen in the periphery, pilosebaceous unit and liver. The Clamiphene (oestrogenic substance), oral contraceptives, insulin sensitizing agents and pregnancy were shown to increase the concentration of SHBG (Legro 2012).

Type 2 Diabetes

Higher mean BMI (Ganz et al. 2014; Singh et al. 2014) and increased prevalence of obesity (Liu et al. 2013; Ganz et al. 2014; Nandimath et al. 2016; Awasthi et al. 2017) observed earlier in T2DM patients when compared to controls is also apparent in the present study. It was observed that while T2DM patients show higher BMI than the controls of the same ethnic group, normal BMI was observed in Japanese T2DM patients and the difference was attributed to the difference in insulin secretion and action between two ethnic groups (Sone et al. 2003). Higher insulin secretion and lower insulin sensitivity was reported in obese than leanT2DM patients (Sone et al. 2003). In the male and female patients with T2DM, significantly higher BMI is observed in the present study as against the gender specific controls, which is in contrast to the study in which no significant difference was observed in Japan (Mano et al. 2015). Weight gain and consequent increase in BMI and obesity in patients with T2DM may be due to aging associated increase in fat mass, decreased physical activity, poor diet, usage of antidiabetic drugs such as sulphonylurea, thiazolidinediones and insulin and weight loss was shown to improve glycemic control (Daousi et al. 2006; Hills et al. 2010; Kamath et al. 2011). Association of obesity and T2DM has been observed in both cross-sectional and longitudinal studies and a number of factors such as duration of obesity, body fat distribution, physical activity, diet, genetics and ethnicity were

shown to increase the risk of T2DM in obese people (Al-Quwaidhi et al. 2013).

The BMI cut-off values of 24.80kg/m^2 (sensitivity: 68.90% and specificity: 50.16%), 23.30 kg/m^2 (sensitivity:77.32% and specificity:38.89%) and 24.70 kg/m^2 (sensitivity: 80.38% and specificity: 45.54%) obtained, respectively, for pooled, male and female T2DM samples of the present case control study from Hyderabad are somewhat higher than those obtained in a recent case-control study from Manipal, Karnataka (Awasthi et al. 2017), where the BMI cut off values were observed to be 21.85 kg/m^2 (sensitivity: 82% and specificity: 65%), 22.07 kg/m^2 (sensitivity:76% and specificity: 66%) and 22.28 kg/m^2 (sensitivity: 80% and specificity: 68%) for pooled, male and female T2DM samples, respectively, and similar to that obtained by Snehalatha et al.(2003) in the population of Tamil Nadu (23 kg/m^2: sensitivity/specificity: 67.1/62.7% for men and 66.8 /52.9% for women). The foregoing observations suggest the higher sensitivity of the gender specific cut off values of BMI, underlines the importance of using such cut offs in the prediction of T2DM and other complex disorders. In terms of contribution of BMI in explaining the variation in the dependent variable, T2DM, the cut-off values obtained through ROC analysis and the quantitative trait BMI explained relatively greater proportion of variation (5.1% and 6.2%), when compared to that based on 95 percentile value of the control sample (1.2%). Although these results are qualitatively similar to that of PCOS, the amount of variation in T2DM explained by BMI is much smaller in proportion. The AUC of >0.6 for these cut-off values of BMI indicates that BMI might be useful in predicting the risk of T2DM in our population albeit not to the extent that it can do with reference to PCOS.

Coronary Artery Disease

Lower mean BMI and lower prevalence of obesity in CAD patients against controls suggest the possibility of the effect of life style modifications such as diet control and enhanced physical activity usually recommended by the physicians and practised by the CAD patients. Lower prevalence of obesity in CAD patients against controls in the present study is in agreement with the similar findings of Panwar et al (2011). CAD patients with obesity are referred to cardiac rehabilitation and those who were enrolled in cardiac rehabilitation programme showed decreased weight and BMI (Sadeghiet et al. 2013). However, while most earlier case-control studies showed significantly higher mean BMI (Kosuge et al. 2006; Amani et al. 2010; Singh et al. 2013; Zhou et al. 2013), Panwar et al. (2011) could not find significant difference in BMI between patients and controls. There were also studies that showed higher prevalence of obesity in CAD patients than controls (Amani et al. 2010; Singh et al. 2013). Prevalence of obesity was found to be lower in CAD patients than controls up to the sixth decade after which the reverse trend was observed, concurrent to the increased prevalence of obesity in the older age observed by us in the present study and earlier by Chapman (Chapman 2008). This may suggest that BMI based obesity plays a dual and age dependent role in CAD, implying that the risk of CAD may increase after the age of 60 years in the obese people.

Although obesity is presumed to increase the risk of cardiovascular diseases such as hypertension, CAD, heart failure and arryhythmias, dyslipidemia and type 2 diabetes, obese people were shown to have better survival rate after acute myocardial infarction (MI) (Won et al. 2017). Further, the CAD patients who were obese had better outcome after percutaneous coronary intervention than the non-obese CAD patients (Akin and Nienaber 2015). These contrasting observations are termed as obesity paradox. The proposed mechanisms for obesity paradox include increased size of the coronary arteries, greater remodelling of heart after MI, high calorie reserve, likely life style changes, altered cytokine and hormone profile, quenching of high levels of TNF-α by high density TNF-α receptors, low levels of circulating natriuretic peptides and high levels of free lipoproteins (Akin and Nienaber 2015). Unfortunately, no cut-off values of BMI are available for predicting the risk of CAD in the Indian context. The ROC analysis of our sample suggests AUC to be 0.55, which suggests that BMI is not useful in predicting the risk of CAD in the population of Hyderabad. BMI cut-off value obtained by calculating 95 percentile based value of controls was not found to be associated with CAD while BMI cut-off value obtained by using ROC was found to explain only a small proportion of its variation (3.3%).

CONCLUSION

The results of our study suggest that BMI cut-off value may be disease and sex-specific and therefore it is necessary to determine BMI

cut-off values specific to different diseases as well as gender. Further, our study suggests that the BMI may not be a useful obesity measure in predicting the risk of CAD and the other measures of obesity can be explored for their usefulness as predictors. It would be also prudent to verify our results in other Indian cohorts to verify if these cut offs are also population specific. However, BMI cut-off values were found to have greater ability in predicting the risk of PCOS than T2DM and sex-specific cut-off values showed higher sensitivity than the pooled cut-off values. Cut-off values obtained from ROC curve explained higher variation in these diseases and showed significant association with higher odds ratio suggesting that ROC based cut offs rather than 95 percentile value of the control cohort is a better approach in establishing the cut-off value.

RECOMMENDATIONS

In order to establish if the cut off values obtained based on our study of the three NCDs are universal and can be for Indian populations in general, it is necessary to obtain cut off values for different ethnic or geographic populations of India and test the universality. Like for many other risk factors of complex genetic disorders/NCDs, obesity also seems to have its own independent genetic architecture. It may be worthwhile to explore the possible role of some of the obesity related genetic variants that may interact with those of NCDs/ and or their risk factors and act as proxy to obesity in the manifestation of the NCDs.

ACKNOWLEDGEMENTS

BMR thanks Director General, ICMR, for granting Emeritus Medical Scientist position to BMR, facilitating my post-retirement research activity. The data analysed for this paper were collected as part of three plan projects of the Indian Statistical Institute (ISI) on PCOS, T2DM and CAD undertaken by BMR during 2008-2013 as Professor of ISI and he thanks the successive Directors for logistic support. BMR also thanks Drs. Shilpi Dasgupta, Uma Jyothi and Pranav Chand for their assistance in collecting the data when they were Ph.D. students working in the respective projects.

REFERENCES

Akin I, Nienaber CA 2015. Obesity paradox in coronary artery disease. *World J Cardiol*, 7: 603-608.

Al-Quwaidhi AJ, Pearce MS, Critchley JA, O'Flaherty M 2013. Obesity and type 2 diabetes mellitus: A complex association. *Saudi J Obesity*, 1: 49-56.

Amani R, Noorizadeh M, Rahmanian S, Afzali N, Haghighizadeh MH 2010. Nutritional related cardiovascular risk factors in patients with coronary artery disease in Iran: A case-control study. *Nutr J*, 9: 70.

Awasthi A, Rao CR, Hegde DS, Rao KN 2017. Association between type 2 diabetes mellitus and anthropometric measurements: A case control study in south India. *J Prev Med Hyg*, 58: E56-E62.

Babu GR, Murthy GVS, Ana Y, Patel P, Deepa R, Neelon SEB, Kinra S, Reddy KS 2018. Association of obesity with hypertension and type 2 diabetes mellitus in India: A meta-analysis of observational studies. *World J Diabetes*, 9: 40-52.

Banjare JB, Bhalerao S 2016. Obesity associated noncommunicable disease burden. *Int J Health Allied Sci*, 5: 81-87.

Beydoun HA, Stadtmauer L, Beydoun MA, Russell H, Zhao Y, Oehninger S 2009. Polycystic ovary syndrome, body mass index and outcomes of assisted reproductive technologies. *Reprod Biomed Online*, 18: 856-863.

Brothers KJ, Wu S, DiVall SA, Messmer MR, Kahn CR, Miller RS et al. 2010. Rescue of obesity-induced infertility in female mice due to a pituitary-specific knockout of the insulin receptor. *Cell Metab*, 12:295-305.

Chapman IM 2008. Obesity in old age. *Front Horm Res*,36: 97-106.

Chitme HR, Al Azawi EAK, Al Abri AM, Al Busaidi BM, Salam ZKA, Al Taie MM et al. 2017. Anthropometric and body composition analysis of infertile women with polycystic ovary syndrome. *J Taibah University Medical Sciences*,12: 139-145.

Dasgupta S, Sirisha P, Neelaveni K, Anuradha K, Sudhakar G, Reddy BM 2012. Polymorphisms in the IRS-1 and PPAR-α genes and their association with polycystic ovary syndrome among South Indian women. *Gene*, 503: 140-146.

Dasgupta S, Reddy BM 2013. The role of epistasis in the etiology of polycystic ovary syndrome among Indian women: SNP-SNP and SNP-environment interactions. *Ann Hum Genet*, 77(4): 288-298.

Daousi C, Casson IF, Gill GV, MacFarlane IA, Wilding JPH, Pinkney JH 2006. Prevalence of obesity with type 2 diabetes in secondary care: Association with cardiovascular risk actors. *Postgrad Med J*, 82: 280-284.

Ganz ML, Wintfeld N, Li Q, Alas V, Langer J, Hammer M 2014. The association of body mass index with the risk of type 2 diabetes: A case-control study nested in an electronic health records system in the United States. *Diabetology and Metabolic Syndrome*, 6: 50.

Garg N, Dharmalingam M, Prabhu V, Murthy N S 2016. Carotid intimo-medial thickness: A predictor for cardiovascular disorder in patients with polycystic ovarian syndrome in the South Indian population. *Indian J Endocr Metab*, 20: 662-666.

Hills AP, Shultz SP, Soares MJ, Byrne NM, Hunter GR, King NA, Misra A 2010. Resistance training or obese, type 2 diabetic adults: A review of the evidence. *Obesity Reviews*, 11: 740-749.

Kaaks R, Lukanova A, Kurzer MS 2002. Obesity, endogenous hormones, and endometrial cancer risk: A synthetic review. *Cancer Epidemiol Biomarkers Prev,* 11: 1531-1543.

Kamath A, Shivaprakash G, Adhikari P 2011. Body mass index and waist circumference in type 2 diabetes mellitus patients attending a diabetic clinic. *Int J Biol Med Res,* 2: 636-638.

Kosuge K, Sasaki H, Ikarashi T, Toyabe S, Akazawa K, Kobayashi C et al. 2006. Risk factors for severe coronary artery disease-a case-control study of patients who have undergone coronary artery bypass grafting. *J AtherosclerThromb,* 13: 62-67.

Lavie CJ, Milani RV, Ventura HO 2009. Obesity and cardiovascular disease: Risk Factor, paradox, and impact of weight loss. *JACC,* 53: 1925-1932.

Legro RS 2012. Obesity and PCOS: Implications for diagnosis and treatment. *Semin Reprod Med,* 30: 496-506.

Liu L, Chen L, Dai J, Chen J, Liang Y, Pei T et al. 2013. Case-control study on the risk factors of type 2 diabetes of Dong nationality in Western Hunan. *Zhong Nan Da XueXueBao Yi Xue Ban,* 38: 1057-1064.

Manning K, Senekal M, Harbron J 2016. Non-communicable disease risk factors and treatment preference of obese patients in Cape Town. *African Journal of Primary Health Care and Family Medicine,* 8: 913.

Mano Y, Yokomichi H, Suzuki K, Takahashi A, Yoda Y, Tsuji M et al. 2015. Do bodymass index trajectories affect the risk of type 2 diabetes? A case-control study. *BMC Public Health,* 15: 718.

Misra A, Chowbey P, Makkar BM, Vikram NK, Wasir JS, Chadha D et al. 2009. Consensus statement for diagnosis of obesity, abdominal obesity and the metabolic syndrome for Asian Indians and recommendations for physical activity, medical and surgical management. *J Assoc Physicians India,* 57: 163-170.

Nandimath VA, Swamy CS, Nandimath SA, Jatti G, Jadhav S 2016. Evaluation of certain risk factors of type 2 diabetes mellitus: A case–control study. *Int J Med Sci Public Health,* 5: 1334-1339.

Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C et al. 2014. Global, regional and national prevalence of overweight and obesity in children and adults 1980-2013: A systematic analysis. *Lancet (London, England),* 384: 766-781.

Ofei F 2005. Obesity - a preventable disease. *Ghana Medical Journal,* 39(3): 98-101.

Okafor CI, Fasanmade O, Ofoegbu E, Ohwovoriole AE 2011. Comparison of the performance of two measures of central adiposity among apparently healthy Nigerians using the receiver operating characteristic analysis. *Indian J Endocrinol Metab,* 15: 320-326.

Panwar RB, Gupta R, Gupta BK, Raja S, Vaishnav J, Khatri M et al. 2011. Atherothrombotic risk factors and premature coronary heart disease in India: A case-control study. *Indian J Med Res* 134: 26-32.

Pradeepa R, Anjana RM, Joshi SR, Bhansali A, Deepa M, Joshi PP et al. 2015. Prevalence of generalized and abdominal obesity in urban and rural India- the ICMR - INDIAB Study (Phase-I) [ICMR - INDIAB-3]. *The Indian J Med Res,* 142(2): 139-150.

Pranavchand R, Kumar AS, Anuj K,Vishnupriya S, Mohan Reddy B 2016. Distinct patterns of association of variants at 11q23.3 chromosomal region with coronary artery disease and dyslipidemia in the population of Andhra Pradesh, India. *PLoS ONE* 11(6): e0153720.doi:10.1371/journal.pone.0153720.

Pranavchand R, Reddy B 2016. Genomics era and complex disorders: Implications of GWAS with special reference to coronary artery disease, type 2 diabetes mellitus, and cancers. *J Postgrad Med,* 62: 188-198.

Pranavchand R, Kumar AS, Reddy BM 2017. Genetic determinants of clinical heterogeneity of the coronary artery disease in the population of Hyderabad, India. *Human Genomics,* 11: 3.

Sadeghi M, Ghashghaei FE, Rabiei K, Golabchi A, Noori F, Baboli MT et al. 2013. Does significant weight reduction in men with coronary artery disease manage risk factors after cardiac rehabilitation program? *J Res Med Sci,* 18: 956-960.

Sharma S, Majumdar A 2015. Prevalence of metabolic syndrome in relation to body mass index and polycystic ovarian syndrome in Indian women. *J Hum Reprod Sci,* 8: 202-208

Singh R, Prakash M, Dubey R, Roy K, Kotwal A, Mahen A 2013. Body composition parameters as correlates of coronary artery disease. *Indian J Med Res,* 138: 1016-1069.

Singh S, Singh AP, Multani MK, Purohit A 2014. Clinical and biochemical profile of Indians with type 2 diabetes mellitus: A problem lurking for India. *Trop J Med Res,* 17: 91-98.

Snehalatha C, Viswanathan V, Ramachandran A 2003. Cut-off values for normal anthropometric variables in Asian Indian adults. *Diabetes Care,* 26: 1380-1384.

Sone H, Ito H, Ohashi Y, Akanuma Y, Yamada N 2003. Obesity and type 2 diabetes in Japanese patients. *The Lancet,* 361: 85.

Thangavelu M, Godla1 UR,Godi S, Paul SFD, Maddaly RA 2017. Case-controlled comparative hospital-based Study on the clinical, biochemical, hormonal, and gynecological parameters in Polycystic ovary syndrome. *Indian J Pharm Sci,* 79: 608-616.

Uma Jyothi K, Jayaraj M, Subburaj KS, Prasad KJ, Kumuda I, Lakshmi V et al. 2013. Association of TCF7L2 Gene Polymorphisms with T2DM in the Population of Hyderabad, India. *PLoS ONE,* 8: e60212. doi: 10.1371/journal.pone.0060212.

Uma Jyothi K, Reddy BM 2015. Gene–gene and gene–environment interactions in the etiology of type 2 diabetes mellitus in the population of Hyderabad, India. *Meta Gene,* 5: 9-20.

Won KB, Hur SH, Nam CW, Ann SH, Park GM, Lee SG et al. 2017. KAMIR (Korea acute myocardial infarction registry) Investigators. Evaluation of the impact of statin therapy on the obesity paradox in patients with acute myocardial infarction: A propensity score matching analysis from the Korea Acute Myocardial Infarction Registry. *Medicine (Baltimore),* 96: e7180.

Welt CK, Chan JL, Bullen J, Murphy R, Smith P, DePaoli AM et al. 2004. Recombinant human leptin in women with hypothalamic amenorrhea. *N Engl J Med,* 351: 987-997.

Yang Y, Liu B, Xia W, Yan J, Liu HY, Hu L et al. 2017. *FTO* genotype and type 2 diabetes mellitus: spatial analysis and meta-analysis of 62 case-control studies from different regions. *Genes,* 8: 70.

Zhou Y, Liu T, Jia C 2013. Joint effects of serum ferritin and body mass index on the risk of coronary artery disease: A case-control study. *BMJ Open,* 3: eoo3695.

Paper received for publication on February 2019
Paper accepted for publication on February 2019