Clarifying and Revealing the Gender Differences in the Relationships of Lean and Fat Mass with Metabolic Syndrome Risk Factors in Asian Men and Women

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Abstract: *Objectives*: To clarify the relationships of fat and lean mass with the metabolic syndrome risk factors in Asian men and women. *Methods*: This is a cross sectional study of 530 and 1326 Singaporean men and women. The lean mass index (LMI), fat mass index (FMI) and abdominal fat index (AbFI) were computed with height adjustments as with BMI, and were categorized into four groups to evaluated for their relationships with the various metabolic syndrome risk factors. *Results*: Men have 35% more LMI, 57% less FMI and 30% less of AbFI than in women. Lean and fat mass have independent and gender-specific relationships with the various metabolic syndrome risk factors. Varying amounts of LMI in men have no bearing on the MetS risk factors. While in women, high LMI is associated with risk factors for metabolic health. High FMI in men is cardio-protective, while high FMI in women is associated with higher insulin resistance markers. High AbFI in both men and women is a predictor, possibly, of poorer metabolic health. BMI reflects the combined association of LMI, FMI and AbFI. *Conclusions*: The results clarify and reveal the clear gender differences in the relationships of LMI, FMI, AbFI and BMI with the various MetS risk factors. These news findings, together with known predicators of MetS such as age, physical exercise, male and female hormones, should form the basis to establish different and gender-specific management modalities for MetS.

Keywords: Fat Mass Index (FMI), Lean Mass Index (LMI), Abdominal Fat Mass Index (AbFI), Body Mass Index (BMI),
Metabolic Syndrome (MetS), Metabolic Syndrome Risk Factors, Cardio-protection

1. Introduction

Metabolic syndrome (MetS) is linked to increased risk of multiple chronic diseases such as cardiovascular disease, diabetes, arthritis, chronic kidney disease, schizophrenia, and several types of cancer and of early death [1–3]. With the growing affluence, MetS is becoming a major health problem, not only in more advanced but also in developing countries [4]. In the US, the prevalence of MetS has reached an epidemic proportion of more than 30% among all adults [5]. With the increasing prevalence of MetS, there is a need to better understand the public health burden and to establish prevention strategies for its management. Metabolic syndrome is known to be associated with insulin resistance, dyslipidemia, hypertension, type-2 diabetes and obesity [6]. The efforts to better understand MetS have been confounded by the lack of consistent associations with some of the clinical components of MetS, especially that of obesity. The association of obesity with MetS has been equivocal, and it may be abdominal obesity rather than general obesity that predicates the higher risks for MetS [7, 8]. A main reason for the ambiguity in the relationship between obesity and MetS is the inherent inaccuracy of the anthropometric indices used to define obesity. Body mass index (BMI), defined as total body mass divided by m2, has long been used as an index of obesity [9]. However, studies have shown that BMI is not an accurate index of obesity, principally because it neither differentiates between lean and fat mass. More correctly, BMI should be viewed as a body mass index including lean and fat mass that is

adjusted for height [10, 11].

More recently, most of the anthropometric indices have been replaced by adiposity derived from dual X-ray energy absorptiometry (DXA), ultrasound and others scanners. However, even the DXA-derived percent body fat has its limitations. In general, women have about 10% more body fat than men, therefore expressing fat mass, as a percent does not reflect the actual amount of fat. A 20% body fat in a 200 pound-man is definitely more than a 20% body fat in a 100-pound woman. As suggested earlier, the association with MetS may not be related to fat expressed in percent, but rather to the absolute amount of fat mass [7, 12].

It has long been assumed that only fat mass is associated with the increased risk of MetS. The question remains, does the amount of lean mass have any relationship with metabolic syndrome, if there is, what is it? The current study made use of the fat mass index (FMI), lean mass index (LMI) and abdominal fat index (AbFI) of a large cohort of Asian men and women and sought to clarify some of the above-mentioned unresolved questions.

2. Materials and Methods

2.1. Subjects

The Institutional Review Board of the National University Hospital of Singapore approved this study. Each volunteer gave his/her written informed consent. Five hundred and thirty Singaporean men and 1320 Singaporean women, aged between 29y and 72y, living in the community were recruited through advertisements in the media and through word of mouth. As the primary objective of the overall study was to evaluate the determinants of the natural aging process, only individuals without a history of major medical illnesses such as cancer, hypertension, thyroid dysfunction, diabetes, osteoporotic fracture, cardiovascular events, major sleep disorders, or major joint surgery were included in the study. Subjects were not paid for their participation. The cohorts of men and women represented the diverse spectrum of people in Singapore, ranging from those with low to high levels of education, working and non-working, and those in various types of vocation. Their profiles were typical of people in Singapore, which is a highly urbanized city-state with no rural population. The methodology used was previously reported [13].

2.2. General Questionnaire

Each subject answered a self-administered and investigator-guided questionnaire. Questions asked included their medical, social, sex, physical exercise, and family history.

2.3. Biochemical and Hormone Measurements

An overnight 12h fasting blood sample was collected in the morning on any day between 9.00am and 11.00am for all men and postmenopausal women. For premenopausal women,

the fasting blood sample was collected between Day 3-5 of their menstrual cycle. The sera were stored at -80°C until analysis. Serum levels of total cholesterol (TC) and triglycerides (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and fasting glucose level (GLU) were measured by methods reported earlier [13]. Serum concentrations of insulin (INS) were measured in-house using the Axsym platform from Abbott Laboratories (Irving, TX).

2.4. Whole Body DXA Scan

Each volunteer had a whole body scan using the dual-energy X-ray absorptiometry (DXA) (Hologic, Bedford, MA, USA). The DXA machine calibrated the total fat and lean mass (TFM, TLM) and fat and lean mass in the various regional areas such as the limps, the abdomen and the trunk.

2.5. Blood Pressures and Anthropometric Measures

Trained clinical researchers, using a standardized manual sphygmomanometer, measured the brachial systolic (Sys) and diastolic (Dia) blood pressures, after subjects had rested for five minutes. Height in centimeter, and body weight in kilograms were measured for each volunteer.

2.6. Intensity of Exercise (METmin)

The intensity of exercise, expressed as metabolic equivalent of task-minutes (METmin) and its computation was reported earlier [14]. This score took into account the type, duration and frequency/week of exercise for each participant. The relevant data were gathered from the self-administered and investigator-guided questionnaire.

2.7. Definitions of Fat Mass Index (FMI) Lean Mass Index (LMI) and Abdominal Fat Index (AbFI)

As with the BMI, height in meter-square (m^2) was used to adjust for differences in body size. Fat mass index (FMI) was calculated as total fat mass divided by m^2 [15]. Likewise, lean mass index (LMI) and abdominal fat index (AbFI) were calculated with similar adjustment for height.

2.8 Indices of Insulin Resistance

Triglyceride/HDL ratio has been considered as a cardiovascular risk factor and has also been used as an index of insulin-resistant individuals.[16] As suggested by McLaughlin et al [16], a TG/HDL of >1.80 was used as an indication that an individual is insulin resistant.

Homeostasis model assessment (HOMA) was also used as a measure of insulin resistance. The product of fasting insulin and glucose levels and dividing it by 22.5 gives the value for HOMA [17]. A HOMA value of >2.8 computed from a single fasting blood sample correlated well with other measures of insulin resistance. The data in the present study showed that TG/HDL and HOMA were positively and significantly correlated.

2.9. Body Mass Index (BMI)-, Fat Mass Index (FMI)-, Lean Mass Index (LMI)- and Abdominal Fat Index (AbFI)-groups

Based on the normal distribution for the Singaporean men and women, four groups each for the FMI, LMI, AbFI and BMI were categorized: Group#1: Low (< 5%), Group#2: Normal (>5% to 85%), Group#3: High (>85% to 95%) and Group#4: Excess (>95 percentile). These different groups were used solely to evaluate their associations with the various MetS risk factors.

2.10. Statistical Analysis

Statistical analyses were performed using SPSS for windows version 27.0 (Armond, NY). Basic descriptive statistics and multivariate analyses coupled with the Bonferroni correction for multiple comparisons were used on continuous measurements. Age and the intensity of exercise (METmin) were shown in our earlier studies to correlate with different body composition, and with various metabolic factors [18]. The estimated marginal means with the Bonferroni correction for multiple comparisons allows for the independent associations of LMI, FMI, AbFI and BMI with the various MetS risk factors. The four levels allow for evaluating the relationships, not only of the high and excess but also the low amount of body composition with the various MetS risk factors.

3. Results

Table 1 shows the 5th, 50th, 85th and 95th percentiles to categorise the four groups of LMI, FMI, AbFI and BMI. These body composition profiles reveal the quantitative differences of these indices between Singaporean men and women. Using the values at the 50th percentile, the BMI and LMI in men, respectively, are 7.8% and 35.9% higher than corresponding values in women (Table 1). On the other hand, men have 57.2% less fat mass than women (Table 1). What is interesting is when the amount of abdominal fat was height-adjusted, Singaporean men have 33.8% less of abdominal fat than in women, which is contrary to the prevailing assertion that men have more abdominal fat than women [19].

Table 1. Percentile values of various body indices in men and women.

Men (n=530)	5.0%	50%	85%	95%
BMI (kg/m^2)	19.7	23.5 (7.8%)	26.8	28.5
LMI (kg/m^2)	14.7	17.4 (35.9%)	19.3	20.6
FMI (kg/m^2)	2.89	5.16 (-57.2%)	7.00	7.94
AbFI (kg/m^2)	0.66	1.42 (-33.8%)	2.02	2.30
Women (n=1326)	5%	50%	85%	95%
BMI (kg/m^2)	18.1	21.8	25.2	28.2
LMI (kg/m^2)	10.7	12.8	14.5	15.9
FMI (kg/m^2)	5.33	8.11	10.3	11.9
AbFI (kg/m^2)	1.04	1.90	2.50	2.99

* Percent in brackets denote the differences between the values at the 50th percentile in men and corresponding values in women.

The most significant finding of the present study is that LMI, FMI and AbFI are independently and differentially associated with the various MetS risk factors, and in several instances, with very clear gender differences (Tables 2 – 4).

This, perhaps is the first report showing that lean mass, independent of FMI and AbFI, is associated with some MetS risk factors in women but not in men (Table 2). Varying levels of LMI in men are not associated with any significant differences in any of the MetS risk factors (Table 2). In women, on the other hand, high levels of LMI are associated with poorer MetS risk factors when compared to those in women with normal levels of LMI (LMI#2). The increasing levels of LMI are associated with a progressive decrease in HDL and increases in TC/HDL, glucose, insulin and HOMA levels (Table 2). In addition, the levels of TG and TG/HDL, though not statistically different, tend to be higher in women with higher LMI when compared with those with normal levels of LMI (Table 2).

Another clear gender difference is the association of FMI with the MetS risk factors. In men, after adjusting for AbFI and LMI, higher FMI appears to be cardio-protective. At excess levels (FMI#4), diastolic blood pressure, TC, TG, TG/HDL, and the atherogenic index (TC/HDL) are significantly lower than in men with normal FMI (FMI#2) (Table 3). However, glucose, insulin and HOMA levels are not significantly different when compared those with normal levels of FMI (Table 3). These observations are noted in men who have more then 50% less FMI than in women.

In women, on the other hand, high FMI (FMI#4) appears to be adverse to metabolic health, especially for the glucose metabolism. Women with excess FMI have significantly higher INS and HOMA levels when compared to those in women with lower FMI levels (FMI#2 & FMI#3) (Table 3). As in men, excess FMI (FMI#4) appears to the cardio-protective; though not statistically significant, levels of TG, and TG/HDL are trending lower and HDL levels trending higher when compared to corresponding levels in women with normal FMI (FMI#2) (Table 3).

Table 2. *Comparisons of various metabolic risk factors among the 4 LMI groups in both men and women with Age, METmin, FMI, and AbFI as covariates.*

Men	LMI#1 (n=24)	LMI#2 (n=374)	LMI#3 (n=45)	LMI#4 (n=24)	P values
LMI (kg/m^2)	13.9+0.22	17.2+1.10	20.0+0.41	21.8+0.34	1v2,3,4 (<0.001, <0.001, <0.001), 2v3,4 (<0.001, <0.001), 3v4 (<0.001)
Sys B/P (mm Hg)	121+2.93	128+0.74	129+2.16	131+2.99	NS
Dia B/P (mm Hg)	76+1.90	80+0.48	81+1.40	81+1.93	NS
TC (mg/dl)	5.88+0.21	5.74+0.05	5.80+0.15	5.60+0.21	NS
TG (mmol/l)	1.24+0.14	1.48+0.03	1.59+0.10	1.39+0.14	NS
TG/HDL	0.94+0.14	1.21+0.04	1.33+0.11	1.08+0.15	NS
HDL (mg/dl)	1.41+0.06	1.34+0.02	1.36+0.04	1.39+0.06	NS
LDL (mg/dl)	3.92+0.19	3.74+0.05	3.74+0.14	3.62+0.19	NS
TC/HDL	4.29+0.21	4.48+0.05	4.47+0.16	4.17+0.22	NS
GLU (mmol/l)	4.73+0.14	4.94+0.04	4.91+0.11	5.03+0.15	NS
INS (mIU/L)	6.00+0.72	7.31+0.18	8.26+0.53	8.26+0.74	NS
HOMA	1.28+0.19	1.65+0.05	1.85+0.14	1.89+0.19	NS

Women	LMI#1 (n=67)	LMI#2 (n=1063)	LMI#3 (n=130)	LMI#4 (n=66)	P values
LMI (kg/m^2)	10.3+0.06	12.7+0.03	15.1+0.03	16.6+0.10	1v3,4 (<0.001, <0.001), 2v3,4 (<0.001, <0.001), 3v4 (<0.001)
Sys B/P (mm Hg)	123+2.00	121+0.54	123+1.01	123+2.07	NS
Dia B/P (mm Hg)	78+1.19	77+0.32	78+0.61	77+1.24	NS
TC (mg/dl)	5.66+0.11	5.65+0.03	5.68+0.06	5.60+0.11	NS
TG (mmol/l)	1.00+0.29	1.16+0.08	1.27+0.15	1.38+0.30	NS
TG/HDL	0.60+0.22	0.76+0.06	0.92+0.11	1.14+0.23	NS
HDL (mg/dl)	1.80+0.04	1.68+0.01	1.36+0.04	1.39+0.06	1v2,3,4 (0.045, <0.001, <0.001), 2v3,4 (0.006, <0.001), 3v4 (0.023)
LDL (mg/dl)	3.42+0.10	3.49+0.03	3.53+0.05	3.56+0.10	NS
TC/HDL	3.26+0.11	3.50+0.03	3.75+0.06	4.19+0.22	1v3,4 (0.001, <0.001), 2v3,4 (<0.001, <0.001), 3v4 (0.002)
GLU (mmol/l)	4.73+0.06	4.73+0.02	4.81+0.03	4.99+0.07	1,2v4 (0.038, 0.001)
INS (mIU/L)	5.39+0.41	6.21+0.11	7.41+0.21	9.73+0.43	1v3,4 (<0.001, <0.001), 2v3,4 (<0.001, <0.001), 3v4 (<0.001)
HOMA	1.14+0.11	1.33+0.03	1.61+0.05	2.31+0.11	1v3,4 (0.001, <0.001), 2v3,4 (<0.001, <0.001), 3v4 (<0.001)

* Values are reported as mean+SE

Table 3. *Comparisons of various metabolic risk factors among the 4 FMI groups in both men and women with Age, METmin, LMI, and AbFI as covariates.*

Men	FMI#1 (n=24)	FMI#2 (n=372)	FMI#3 (n=47)	FMI#4 (n=24)	P values
FMI (kg/m^2)	2.36+0.08	5.00+0.05	7.44+0.04	8.81+0.37	1v2,3,4 (<0.001, <0.001, <0.001), 2v3,4 (<0.001, <0.001), 3v4 (<0.001)
Sys B/P (mm Hg)	133+3.52	128+0.76	126+2.48	124+3.47	NS
Dia B/P (mm Hg)	82+2.25	80+0.49	78+1.59	73+2.22	2v4 (0.010)
TC (mg/dl)	5.57+0.24	5.84+0.05	5.36+0.17	5.13+0.21	2v4 (0.029)
TG (mmol/l)	1.52+0.16	1.55+0.04	1.08+0.12	1.07+0.16	2v3,4 (0.001, 0.030)
TG/HDL	1.22+0.17	1.28+0.04	0.80+0.12	0.80+0.17	2v3,4 (0.002, 0.043)
HDL (mg/dl)	1.37+0.07	1.33+0.02	1.40+0.05	1.44+0.07	NS
LDL (mg/dl)	3.54+0.22	3.82+0.05	3.49+0.16	3.24+0.22	NS
TC/HDL	4.21+0.25	4.58+0.05	3.93+0.18	3.75+0.25	2v3,4 (0.004, 0.009)
GLU (mmol/l)	4.97+0.17	4.91+0.04	4.95+0.12	5.22+0.17	NS
INS (mIU/L)	8.09+0.86	7.31+0.19	8.10+0.61	7.57+0.85	NS
HOMA	1.85+0.22	1.62+0.05	1.86+0.16	1.80+0.22	NS

Women	FMI#1 (n=69)	FMI#2 (n=1058)	FMI#3 (n=133)	FMI#4 (n=66)	P values
FMI (kg/m^2)	4.79+0.05	7.88+0.04	11.00+0.04	12.98+0.12	1v2,3,4 (<0.001, <0.001, <0.001), 2v3,4 (<0.001, <0.001), 3v4 (<0.001)
Sys B/P (mm Hg)	121+2.31	121+0.57	122+1.23	122+2.47	NS
Dia B/P (mm Hg)	76+1.38	77+0.34	77+0.73	77+1.48	NS
TC (mg/dl)	5.62+0.13	5.67+0.03	5.61+0.07	5.59+0.14	NS
TG (mmol/l)	1.33+0.34	1.27+0.08	0.94+0.18	1.39+0.14	NS
TG/HDL	0.86+0.25	0.87+0.06	0.62+0.13	0.51+0.27	NS
HDL (mg/dl)	1.69+0.05	1.64+0.01	1.70+0.03	1.77+0.05	NS
LDL (mg/dl)	3.38+0.11	3.53+0.03	3.46+0.06	3.40+0.12	NS
TC/HDL	3.44+0.13	3.62+0.03	3.49+0.07	3.35+0.13	NS
GLU (mmol/l)	4.77+0.07	4.75+0.02	4.72+0.04	4.90+0.08	NS
INS (mIU/L)	7.15+0.47	6.58+0.12	6.04+0.25	8.33+0.50	2,3v4 (0.007, <0.001)
HOMA	1.58+0.12	1.42+0.03	1.27+0.06	1.95+0.13	2,3v4 (0.001, <0.001)

* Values are reported as mean+SE

Table 4. *Comparisons of various metabolic risk factors among the 4 AbFI groups in both men and women with Age, METmin, FMI, and LMI as covariates.*

Men	AbFI#1 (n=25)	AbFI#2 (n=372)	AbFI#3 (n=47)	AbFI#4 (n=23)	P values
AbFI (kg/m^2)	0.46+0.03	1.36+0.02	2.16+0.01	2.57+0.04	1v2,3,4 (<0.001, <0.001, <0.001), 2v3,4 (<0.001, <0.001), 3v4 (<0.001)
Sys B/P (mm Hg)	126+3.40	127+0.76	131+2.50	132+3.60	NS
Dia B/P (mm Hg)	75+2.20	80+0.49	81+1.60	80+2.31	NS
TC (mg/dl)	5.24+0.24	5.78+0.05	5.66+0.18	5.93+0.25	NS
TG (mmol/l)	1.05+0.16	1.46+0.04	1.75+0.12	1.54+0.17	1v3 (0.014)
TG/HDL	0.70+0.17	1.21+0.04	1.48+0.13	1.19+0.18	1v2,3 (0.018, 0.007)
HDL (mg/dl)	1.61+0.07	1.34+0.02	1.22+0.05	1.34+0.07	1v2,3 (0.001, <0.001)
LDL (mg/dl)	3.24+0.22	3.78+0.05	3.67+0.16	3.91+0.19	NS
TC/HDL	3.39+0.25	4.48+0.06	4.76+0.18	4.57+0.22	1v2,3,4 (<0.001, 0.001, 0.024)
GLU (mmol/l)	4.82+0.16	4.90+0.04	4.97+0.12	5.58+0.15	1v2,3,4 (0.030, 0.030, 0.001)
INS (mIU/L)	6.41+0.86	7.17+0.19	8.84+0.63	10.18+0.90	1,2v4 (0.047, 0.009)
HOMA	1.38+0.22	1.57+0.05	2.01+0.16	2.67+0.19	1,2,3v4 (0.002, <0.001, 0.032)

Women	AbFI#1 (n=66)	AbFI#2 (n=1061)	AbFI#3 (n=134)	AbFI#4 (n=65)	P values
AbFI (kg/m^2)	0.86+0.02	1.82+0.01	2.71+0.01	3.27+0.05	1v2,3,4 (<0.001, <0.001, <0.001), 2v3,4 (<0.001, <0.001), 3v4 (<0.001)
Sys B/P (mm Hg)	121+2.33	121+0.58	122+1.23	125+2.52	NS
Dia B/P (mm Hg)	75+1.40	77+0.35	78+0.74	79+1.51	NS
TC (mg/dl)	5.68+0.13	5.64+0.03	5.70+0.07	5.65+0.14	NS
TG (mmol/l)	1.03+0.34	1.20+0.08	1.15+0.18	1.16+0.37	NS
TG/HDL	0.63+0.26	0.82+0.06	0.78+0.14	0.78+0.28	NS
HDL (mg/dl)	1.89+0.05	1.66+0.01	1.61+0.03	1.65+0.06	1v2,3,4 (<0.001, <0.001, 0.027)
LDL (mg/dl)	3.39+0.12	3.50+0.03	3.55+0.06	3.41+0.12	NS
TC/HDL	3.13+0.13	3.55+0.03	3.73+0.07	3.65+0.14	1v2,3 (0.006, 0.001)
GLU (mmol/l)	4.80+0.07	4.74+0.02	4.76+0.04	4.99+0.08	2,3v4 (0.021, 0.017)
INS (mIU/L)	6.47+0.48	6.38+0.12	6.79+0.26	8.78+0.52	1,2,3v4 (0.026, <0.001, <0.001)
HOMA	1.41+0.12	1.37+0.03	1.45+0.07	2.08+0.13	1,2,3v4 (<0.001, <0.001, <0.001)

* Values are reported as mean+SE

Table 5. *Comparisons of various metabolic risk factors among the 4 BMI groups in both men and women with Age and METmin as covariates.*

Men	BMI#1 (n=21)	BMI#2 (n=375)	BMI#3 (n=41)	BMII#4 (n=24)	P values
BMI (kg/m^2)	19.1+0.12	23.3+0.09	27.6+0.07	30.9+0.59	1v2,3,4 (<0.001, <0.001, <0.001), 2v3,4 (<0.001, <0.001), 3v4 (<0.001)
Sys B/P (mm Hg)	125+2.80	127+0.75	130+2.27	133+3.00	NS
Dia B/P (mm Hg)	78+1.81	79+0.48	82+1.50	82+1.90	NS
TC (mg/dl)	5.68+0.19	5.74+0.05	5.84+0.16	5.70+0.21	NS
TG (mmol/l)	1.17+0.13	1.47+0.04	1.70+0.11	1.49+0.14	1v3 (0.013)
TG/HDL	0.80+0.14	1.21+0.04	1.43+0.11	1.27+0.15	1v2,3 (0.32, 0.004)
HDL (mg/dl)	1.57+0.06	1.34+0.02	1.29+0.05	1.25+0.06	1v2,3,4 (0.001, 0.001, 0.001)
LDL (mg/dl)	3.60+0.18	3.75+0.05	3.78+0.14	3.78+0.19	NS
TC/HDL	3.73+0.21	4.47+0.06	4.66+0.17	4.68+0.22	1v2,3,4 (0.004, 0.003, 0.012)
GLU (mmol/l)	4.82+0.14	4.91+0.04	5.03+0.11	5.18+0.14	NS
INS (mIU/L)	4.75+0.77	7.00+0.21	11.34+0.62	10.69+0.81	1v2,3,4 (0.029, <0.001, <0.001), 2v3,4 (<0.001, <0.001)
HOMA	1.01+0.19	1.55+0.05	2.64+0.16	2.48+0.21	1v2,3,4 (0.044, <0.001, <0.001), 2v3,4 (<0.001, <0.001)

Women	BMI#1 (n=66)	BMI#2 (n=1062)	BMI#3 (n=133)	BMII#4 (n=65)	P values
BMI (kg/m^2)	17.2+0.09	21.6+0.06	26.5+0.08	29.8+0.18	1v2,3,4 (<0.001, <0.001, <0.001), 2v3,4 (<0.001, <0.001), 3v4 (<0.001)
Sys B/P (mm Hg)	117+1.04	122+0.54	124+1.50	129+2.17	1v2,3,4 (0.001, 0.001, <0.001), 2v4 (0.004)
Dia B/P (mm Hg)	75+0.63	77+0.32	80+0.90	80+1.30	1v2,3,4 (0.002, <0.001, <0.001), 2v3 (0.009)
TC (mg/dl)	5.51+0.06	5.68+0.03	5.73+0.08	5.68+0.12	1v2 (0.035)
TG (mmol/l)	0.91+0.15	1.22+0.08	1.37+0.22	1.44+0.31	NS
TG/HDL	0.53+0.12	0.82+0.06	1.04+0.17	1.15+0.24	NS
HDL (mg/dl)	1.83+0.02	1.66+0.01	1.44+0.03	1.40+0.05	1v2,3,4 (<0.001, <0.001, <0.001), 2v3,4 (<0.001, <0.001)
LDL (mg/dl)	3.27+0.05	3.53+0.03	3.68+0.07	3.64+0.11	1v2,3,4 (<0.001, <0.001, 0.011)
TC/HDL	3.11+0.06	3.57+0.03	4.18+0.08	4.28+0.12	1v2,3,4 (<0.001, <0.001, <0.001), 2v3,4 (<0.001, <0.001)
GLU (mmol/l)	4.64+0.03	4.74+0.02	4.91+0.05	5.20+0.07	1v2,3,4 (0.032, <0.001, <0.001) 2v3,4 (0.003, <0.001), 3v4 (0.003)
INS (mIU/L)	4.51+0.22	6.34+0.11	10.07+0.32	12.40+0.46	1v2,3,4 (<0.001, <0.001, <0.001), 2v3,4 (<0.001, <0.001), 3v4 (<0.001)
HOMA	0.94+0.06	1.36+0.03	2.22+0.08	3.02+0.12	1v2,3,4 (<0.001, <0.001, <0.001), 2v3,4 (<0.001, <0.001), 3v4 (<0.001)

* Values are reported as mean+SE

After adjusting for the effects of FMI and LMI, AbFI is associated variably with the different MetS risk factors in both men and women. High levels of AbFI (AbFI#4) in both men and women are associated with significantly higher levels of GLU, INS and HOMA when compared with those with normal levels of AbFI (AbFI#2) (Table 4). On the other hand, in both gender, very lower levels of AbFI (AbFI#1), are associated with significantly lower levels of GLU, INS, HOMA, TC/HDL as well as higher levels of HDL when compared to those with normal AbFI (AbFI#2) (Table 4). In men only, low AbFI (AbFI#1) is associated with significantly lower TG and TG/HDL levels when compared to those with normal levels of AbFI (Table 4).

The BMI represents the total body mass including those of LMI, FMI, AbFI and bone mass. Therefore, after adjusting only for age and METmin, the associations of BMI with the various MetS risk factors represent the combined effects those of LMI, FMI and AbFI. In men, high BMI (BMI#4) is associated with significantly higher INS and HOMA levels when compared to men with normal BMI (BMI#2), which appears to be similar to those of high AbFI alone (Table 4 & 5). Similarly, as with low AbFI (AbFI#1), low BMI (BMI#1) is significantly associated with lower TG, TG/HDL, TC/HDL, INS and HOMA as well as higher HDL levels than in men with normal BMI (BMI#2) (Table 5). These observations are not unexpected as it was shown that high LMI levels in men are not associated with any significant differences in the various MetS risk factors as compared to those with (Table 2 & 3). While high FMI in men are cardio-protective (Table 3).

Unlike in men, high BMI (BMI#3 & BMI#4) in women are associated with more adverse levels of the MetS risk factors (Table 5). As shown earlier, high levels of LMI, FMI and AbFI in women are independently associated with more adverse levels of the MetS risk factors (Tables 2-4). The combined effects of these three indices, as in the high BMI group, further intensify the increases in INS, GLU and HOMA than by the independent associations of LMI, FMI and AbFI (Tables 2-5). In addition, the combined effects have led to significantly higher systolic and diastolic blood pressures, TC/HDL and significantly lower levels of HDL when compared to women with normal BMI (BMI#2) (Table 5). As with men, low BMI (BMI#1) was associated with significantly lower levels of systolic and diastolic blood pressure, TC, LDL, TC/HDL, GLU, INS and HOMA and higher levels of HDL, and at the same time, although not statistically significant, lower levels of TG and TG/HDL when compared to those with normal BMI levels (Table 5).

4. Discussion

The degree of adiposity appears to be one of the key risk factors of the metabolic syndrome [5, 20], but its precise relationship with MetS has been equivocal [10, 21, 22]. The present study made use of the height-adjusted indices, which provide more accurate and equitable determinations of both lean and fat mass in men and women. Their use has provided clarity in the relationships of the LMI, FMI, AbFI and BMI with the various MetS risk factors, and revealed the gender differences in these relationships.

This is the first study that shows the gender-based relationships between LMI and the various MetS risk factors. While in men, LMI appears to have no bearing on any of the MetS risk factors, in women high LMI is associated with worsening of risk factors related to both cardiovascular health and insulin resistance. These observations occur in spite of women having more than 35% less of LMI than in men, imply that lean mass in woman is not only quantitatively but may also be qualitatively different from those in men. If a qualitative difference exists, what might it be? Most adipose tissues are stored subcutaneously, especially in the gluteal-femoral region. However, there are adipose tissues in ectopic regions outside the subcutaneous sites including the muscles, liver, and the abdomen [23]. Intermascular adipose tissue (IMAT) is found beneath the fascia and within the muscle. It might be possible that lean mass in women may be infiltrated with more IMAT than those in men. Previous research has indicated that excess IMAT can lead to increase in insulin resistance [24, 25]. Therefore, if lean mass in women have excess amount of IMAT, it may then explain that the high lean mass in women is associated with higher levels of the insulin resistance markers.

Another interesting an important gender difference is how FMI relates to the various MetS risk factors. In men, high FMI appears to be cardio-protective and is not a predicator of the other aspects of the MetS. In women, on the other hand, high FMI is associated with higher levels of the insulin resistance markers, while not showing any difference in risk factors for cardiovascular health. The cardio-protection of FMI in men cannot be accounted for merely by the quantum of FMI, as similar or higher levels of FMI in women, did not show any degree of the cardio-protection seen in men. Therefore, it would appear that cardio-protection of FMI is gender specific and not dose dependent. On the other hand, adverse relationship of FMI with insulin resistance occurs in women with excess FMI and may thus be a dose-dependent phenomenon. This suggestion is supported by the observation that in women with high levels of FMI, much higher than those present in men, are not associated with higher levels of the insulin resistance markers until the level reaches the excess level. The gender difference in FMI relationship with the MetS risk factors contrast with the earlier suggestion that subcutaneous adipose tissue (SAT) is a negative predicator of MetS and is cardio-protective [26, 27].

The present study also confirms that it is the high accumulation of abdominal fat and not general subcutaneous fat (SAT) that is adverse to metabolic health, as suggested earlier [28]. In both men and women, high AbFI is associated higher levels of glucose, insulin and HOMA implying that its effect is directed at the carbohydrate metabolism. It is also clear that the lower the abdominal fat is, the better it is for metabolic health. The limitation of the AbFI is the lack of

clarity on the differential amount of abdominal subcutaneous from the visceral adipose tissue (VAT). The VAT has been shown to be more adverse to the metabolic health than the subcutaneous fat [29]. Therefore, modality to reduce adiposity in both men and women must be directed towards reducing abdominal fat so as to mitigate its risk on MetS, especially that for type 2 diabetes.

The associations of BMI with the MetS risk factors represent the combined result of the LMI, FMI and AbFI. As shown earlier, in men, LMI has no, while FMI has a countering effect on that of AbFI. Thus depending on the strength of these opposing components, the resulting association will be reflected by the high BMI groups. In the present study, it appears that men with high BMI reflect the adverse association of high AbFI on the MetS risk factors, and overwhelming the cardio-protective association of high FMI. In women, on the other hand, the combined negative associations of FMI, LMI and AbFI as represented by BMI appear to have an additive effect on the risk factors. Taken together, the gender differences shown in the present study can, perhaps explain why some studies appear to show an obesity paradox on MetS [14, 26].

5. Conclusion

The present study shows that LMI, FMI, and AbFI have independent relationship and BMI reflect the resultant relationship of these three indices with the various MetS risk factors. In addition, apart from AbFI, the independent relationships between LMI, FMI and BMI and the MetS risk factors are distinctly different between men and women. Besides the degree and location of adiposity, and amount of lean mass, other known predicators of the MetS include age, diet, and engagement in physical activities, and in women whether they are premenopausal, postmenopausal and whether they are on and what type of hormone replacement therapy (HRT) [18, 19]. In men, higher testosterone levels are cardio-protective being associated with lower TG, TG/HDL and TC/HDL and higher HDL levels than men with lower levels of testosterone [Goh, unpublished data]. The new findings from the present study provide additional prognostic information to assess the individual risk for MetS and hopefully help in designing effective management plans specific for men and women.

Declaration of Interest

The author does not have any possible conflicts of interest.

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