A Review of Metabolic Syndrome Research in Malaysia

Lim Kean Ghee, FRCS1, Cheah Wee Kooi, MRCP2

[1]International Medical University Clinical School, Seremban, [2]Department of Medicine, Taiping Hospital, Taiping

ABSTRACT

Seventy-three articles related to metabolic syndrome were found in a search through databases dedicated to indexing all literature with original data involving the Malaysian population between years 2000 and 2015. Metabolic syndrome affects 25 to 40% of adult population of Malaysia with the risk increasing with age. Obese children are also at risk. Indian ethnicity has the highest rates, followed by Malay and Chinese. It was found that socioeconomics determinants such as living in urban areas, unemployment, lower income, lower education level and shift workers had higher prevalence of metabolic syndrome. Metabolic syndrome is associated with other medical conditions like cardiovascular diseases, psychiatric disorders, erectile dysfunction, polycystic ovarian syndrome and colorectal cancer. Several biomarkers have been determined to be relevant to our local population but their usage in clinical setting needs further research. Literature into effectiveness of management of metabolic syndrome in Malaysia is lacking and the results were only modest. There are several diagnostic criteria available for metabolic syndrome internationally and their individual significant to our local population is not clear. It also makes it difficult to compare results between studies using different criteria. Finally, we could not identify any local study to look at the health economic burden of metabolic syndrome locally.

KEY WORDS:
metabolic syndrome, risk factors, Malaysia, prevalence, biomarkers, obesity

INTRODUCTION

A literature search of articles as detailed in the paper *Bibliography of clinical research in Malaysia: methods and brief results*[1] using the medical subject heading (MeSH) Metabolic Syndrome X, covering period Jan 2000 - Dec 2015 (last search date 2 Feb 2016) was undertaken and 73 articles were identified. Data relevant to metabolic syndrome in Malaysia were reviewed below.

Metabolic syndrome, previously also known as Syndrome X,[2] is a disorder of energy utilization and storage reflecting underlying insulin resistance. It is characterised by the presence of at least three of the following five risk factors: Central obesity, high serum triglycerides, low high density lipoprotein cholesterol (HDL-C), raised blood pressure and raised fasting blood sugar. There are a number of slightly different diagnostic criteria, including the modified World Health Organization (WHO 1998)[3] the International Diabetes Federation/National Heart, Lung and Blood Institute/American Heart Association, (IDF/NHLBI/AHA-2005) criteria,[4] the revised National Cholesterol Education Program (NCEP ATPIII) 2001[5] and 2005[6] and the Joint Interim Statement (JIS 2009) or "harmonized" criteria.[7] Depending on the guidelines used the prevalence of metabolic syndrome can vary.

SECTION 1: REVIEW OF LITERATURE

EPIDEMIOLOGY
Adult prevalence

One of the earliest works done to estimate the prevalence of metabolic syndrome in Malaysia was to look at the prevalence of clustering of hypertension, abnormal glucose tolerance, hypercholesterolemia and obesity among Malaysians. Using the National Health and Morbidity survey (NHMS) 1996, Lim *et al.* reported 27% of their study population above 30 years have two or more of the risk factor clusters.8 Another study that investigated the prevalence of all the components of metabolic syndrome before most of the common definitions were formulated was that by Nawawi *et al.*[9]

Subsequent studies showed that the overall prevalence of metabolic syndrome among adults in Malaysia lies between 25-40%, depending on the criteria one uses. For example based on the WHO, IDF,NCEP ATP III(2001) and Harmonized (JIS) definitions, according to Wan Nazaimoon *et al.*, the overall crude prevalence of metabolic syndrome was found to be 32.1%, 37.1%, 34.3%, and 42.5% respectively, in a nationwide, cross-sectional study using a two-stage stratified sampling design of 4,341 subjects across Peninsular and East Malaysia in 2008.[10] The largest study, Rampal *et al.*, carried out in 2004, found that the overall prevalence for metabolic syndrome was 27.5% among those >15years old using the IDFcriteria.[11] The prevalence of metabolic syndrome in Malaysia is high relative to Asian countries.[10,11] Table I gives the rates recorded in various studies.

In the Malaysian context, there was stronger correlation between Harmonised (JIS) and IDF definitions (Kappa index, 0.87-0.99),[15,19] moderate correlation between Harmonised (JIS) and NCEP ATP III (2001) definitions (Kappa index 0.86)15 and IDF and NCEP ATP III definitions (Kappa index, 0.58-0.68)[12,17,19] but a poor correlation between the IDF and modified WHO criteria (Kappa index, 0.26-0.31).[12,17]

Cheong et al. have explored whether waist circumference (WC), body-mass index (BMI) or waist-to-hip ratio (WHC) was better at predicting the presence other metabolic

Corresponding Author: keanghee_lim@imu.edu.my

Table I: Prevalence of metabolic syndrome in Malaysia by different diagnostic criteria according to various investigators.

Author (Year of study)	Sample Size	Characteristics	Prevalence of Metabolic Syndrome by different criteria (%)				
			WHO	IDF	NCEP ATP III 2001	NCEP ATP III 2005	Harmonized (JIS)
Rampal et al.[11] (2004)	18,805	>15yrs Pen Malaysia and Sarawak		27.5			
Tan et al.[12] (2005-06)	2,366	25-64 yrs		30.1		36.1	
Mohamud et al.[10] (2006)	4,341	>18 yrs Pen Malaysia and Sabah	32.1	37.1	34.3		42.5
Moy & Bulgiba[13] (2008-09)	1,494	University staff >35 yrs Malays		38.2		41.4	
Chu & Moy[14] (2010-11)	686	University staff >35 yrs Malays				31.9	
Heng et al.[15] (2012)	227	University staff 20-65 yrs Malays		38.8	33.5		38.3
Bee et al.[16]	109	Opportunistic contact 30-65 yrs KL and Selangor	6.4	22.9	16.5		
Zainuddin et al.[17]	298	Villagers 18-59 yrs Kelantan		32.2	28.5		
Tan et al.[18]	1,046	Men >40 yrs Subang Jaya		31.6			
Ramli et al.[19]	8,836	Urban and Rural >30 yrs Pen Malaysia and Sabah		37.4	26.5		43.4
Chee et al.[20]	675	Government employees >20 yrs Putrajaya		46.3	27.9		48.9

Table II: Prevalence of Metabolic Syndrome by age, gender and ethnicity among Malaysians ≥15 years by IDF criteria, 2004.[11]

	Prevalence (%)		
	Female	Male	Total
Age 15-40 years			
Malays	15.7	14.7	15.2
Chinese	13.9	13.4	13.7
Indians	23.3	21.8	22.5
Indigenous Sarawakians	26.3	22.1	24.2
Age >40 years			
Malays	51.5	38.5	45.0
Chinese	45.4	36.3	40.8
Indians	64.9	51.3	58.3
Indigenous Sarawakians	47.2	34.4	40.6

syndrome factors in the Malaysian population and found that BMI and WC were better than WHR with WC slightly superior.[21]

Age
The prevalence of metabolic syndrome increases with age.[8,10,11,15,18] Under the age of 40 years, the prevalence rate does not exceed 25% but above the age of 40years, it rises to over 40% (Table II). Mohamud et al. and Chee et al. estimated that the risk of metabolic syndrome increased by 3% for every year increase in age.[10,20]

Sex
Table II from Rampal et al. shows that females have a higher prevalence of metabolic syndrome. Overall the prevalence was 30.1% among females and 24.1% among males.[11] Mahamud et al. also found metabolic syndrome more prevalent among women (43.7%) than men (40.2%).[10] Ramli et al. found females had a higher age-adjusted prevalence according to the NCEP-ATP III 2001 (24.1% vs 28.9% and IDF

(36.1% vs 39.3%) criteria but not according to the Harmonised (JIS) definition (43.8% vs 43.9%).[19] In another report from rural Kelantan[22] of the same study by Zainuddin et al.[17] it was noted women had a higher prevalence of metabolic syndrome. This was true by either the Harmonised (JIS) (29.8%vs42.9%) IDF (26.6%vs36.6%) or NCEP ATPIII 2001 (20.2%vs34.3%) definitions.[16]

In contrast, among urban Malays, Heng et al. found the prevalence higher among men, in all age groups by all three criteria they investigated, especially those below 40 years[15] as did Moy and Bulgiba.[13] The prevalence Moy and Bulgiba noted their study of Malay men and women was (52.9% and 47.1% by IDF criteria). The gap was even wider (men 54.7%, women 45.3%) by the NCEP ATPIII 2005 criteria.[13] Chu and Moy recorded similar findings (men 37.1%, women 24.2%).[14] Heng et al. noted a steeper rise in the prevalence of metabolic syndrome with age among women.[15] All three studies however involved urban populations specifically. Similarly Chee et al. found a higher prevalence of metabolic syndrome

among men (57.1%) than women (46.3%) government servants in Putrajaya, by the Harmonized criteria.[20] Abdominal obesity was more prevalent among women and hypertension more prevalent among men.

Tan *et al.* found the prevalence was about equal between men and women.[12] It would appear that the differences in the prevalence of metabolic syndrome seen between genders depended on where the study subjects were recruited. Our local data suggests that in urban areas, men have a higher prevalence of metabolic syndrome, while in rural areas women exceed men. In addition, the differences are also dependent on the metabolic syndrome criteria used. For example, Tan *et al.* found that the prevalence was higher in men than women (37.2% vs 35.3%) by the NCEP ATP III 2005 guidelines, but was the reverse (28.5% vs 31.2%) using the IDF guidelines.[12] The IDF criteria gives more weight to central obesity and females in Malaysia were more likely to suffer from central obesity[19,23] and have higher hip circumference compared to men.[24] In contrast, waist circumference and waist-hip ratio were higher in men, in a study by Azwany *et al.* to determine which factors contributes most to having metabolic syndrome.[24]

Ethnic Differences
Indians, both men and women, have the highest rates of metabolic syndrome compared to other ethnic groups in Malaysia.[10,12,13,16,18,19] Malays were shown to have higher incidence compared to Chinese in some studies[8,10,11,16,19] while data from the Malaysia Non-Communicable Disease Surveillance 2005/2006 did not showed significant difference.[12]

Interestingly, within the Indigenous Sarawakians, there appears to be a marked variation in the incidence between the young and the older generation, with people below age of 40 having a higher rate at 40.6% compared to their older counterparts at 24.2%. Further study is needed to answer this difference. No data was available for the Sabah state.[11] The Indigenous women in four Temuan villages in Selangor showed an incidence rate of 22.7%.[25]

It is noteworthy that studies using different criteria of metabolic syndrome may yield different results even in the same cohort subjects. For example, in one study by Tan, Chinese males were more likely to exhibit metabolic syndrome if NCEP ATP III criteria was used instead of IDF criteria. While like others, they found Indian males (42.3%) had a higher prevalence of metabolic syndrome than Chinese (31.3%), by the IDF criteria, the difference was much smaller (44.2% vs 42.4%) by the NCEP ATP III.[12]

Nevertheless, Tan *et al.* attempted to explain the ethnic disparities of metabolic syndrome in Malaysia. It was shown that Indians were less likely to engage in physical activity and to consume less fruit and vegetable.[12] Although education and family history of chronic disease are associated with metabolic syndrome status, differences in socioeconomic attributes do not explain ethnic disparities in metabolic syndrome incidence.

Geographical and Socio-economic Factors
Mohamud *et al.* noted that, regardless of the criteria used, metabolic syndrome was higher in urban areas.[10] Abdominal obesity was most prevalent (57.4%), was higher in females (64.2%) and was highest in Indians (68.8%). Hypertension was higher in males (56.5%) and highest among Malays (52.2%). In contrast, the Chinese had the highest prevalence of hypertriglyceridemia (47.4%). Lim *et al.* also found that urban residents, individuals with higher income and physical inactivity were associated with increased prevalence.[8] Shariff *et al.* on the other hand, found that metabolic syndrome was higher among women in low income rural communities (32%) compared to low income urban communities (19%) in a sample of 625 reproductive-age women from across Malaysia.[26] They also found metabolic syndrome higher among low income Malays (25%) than Indians (19%). It did not vary with food security status. In rural Kelantan, being a housewife or unemployed, having less income and education was significantly correlated with having metabolic syndrome.[21]

Mohd Nazri et al. found a trend of increasing prevalence of the markers of metabolic syndrome among shift workers compared to day workers which reached statistical significance for those with three of more markers.[27] Moy *et al.* also reported higher rates of metabolic syndrome factors among health care shift workers.[28]

Obesity
Termizy and Mafauzy found that only 40.2% of 102 of their mainly Malay (94%) patients at their obesity clinic (BMI>30) fulfilled the IDF guidelines for metabolic syndrome.[29] The co-morbidity prevalence for raised fasting blood glucose was 17%, followed by 36% for high triglyceride, 40% for reduced HDL and 42% for raised blood pressure. There was no linear correlation for obesity and metabolic syndrome. Class II obese (BMI 35-39.9) patients had a 1.43 higher risk compared to Class I obese (BMI 30-34.9) but Class III obese (BMI >40) had only a 1.23 higher risk. The prevalence in obese females (43.7%) was higher than for males (32.3%).

Diabetes
Tan et al. found that 96.1%, 95.8%, 84.8% and 97.7% of 313 of their diabetic patients aged ≥30 years had metabolic syndrome using NCEP ATP III, WHO, IDF and Harmonized definitions, respectively.[17]

Physical Activity
Chu and Moy found that subjects who sat for ≥9.3 hours a day had a 3.8-fold risk of having metabolic syndrome compared to those who sat ≤6 hours a day.[14] Chee *et al.* found that those in the 'maintenance' stage of doing regular exercise were 17 times less likely to have metabolic syndrome compared to those who have not even contemplated exercising.[20]

Children and Adolescents
It is very unlikely to find metabolic syndrome among non-obese children.

In a small sample of 78 involving children of 8-10-year olds, of whom 43.6% (34/78) were obese, Quah et al. found only one obese child with metabolic syndrome by the IDF criteria.[30] Metabolic syndrome was found in 5.3% of the overweight/obese children but none of the normal-weight children, in a case-control study of 402 normal weight compared with overweight/obese 9-12 year old children in Kuala Lumpur in 2008 using the IDF criteria.[31] They were sampled from a 2,770 school children of whom 30.9% were overweight and 3.3% obese. Indians again were found to have highest odds ratio (OR = 5.5) for metabolic syndrome. Overweight/obese girls had a 2.5 times higher risk of metabolic syndrome compared to boys.

Fadzlina et al. found a 10% prevalence of metabolic syndrome among the 280 (25.4%) overweight 13-yr old school children, out of a sample of 1,104, in the West coast of Peninsula Malaysia using the IDF criteria.[32] The overall prevalence was 2.6% (males=3.4%, females=2.1%). None of the normal weight had metabolic syndrome. Those who had a habit of sleeping 7-9 hours had a lower risk of having metabolic syndrome compared to those who slept either more or less.

By the NCEP ATP III criteria, metabolic syndrome was diagnosed in 30.4% of 335 obese adolescent boys and girls aged 12–18 years from 10 randomly selected schools in Penang.[33] More than 90% of obese adolescents had at least one metabolic abnormality. Metabolic syndrome was more prevalent among obese boys (40.2%) compared to obese girls (17%). Boys had significantly higher mean waist circumference and triglycerides and lower HDL-C. Indians had the highest prevalence of metabolic syndrome (36.4%), followed by Chinese (33.8%) and Malays (27.4%). Elevated triglyceride levels were more prevalent among Chinese, hypertension more prevalent among Malays, and the other three abnormalities among Indians.

Elderly
The prevalence of metabolic syndrome was 43.4% in a sample of 343 elderly (>60 yrs) residing low cost flats in an urban area in the central of Malaysia according to the IDF criteria.[34] More women (48.1%) were affected than men (36.3%). Being obese or overweight was the strongest predictor. High carbohydrate intake increased risk of metabolic syndrome in men 2.8 fold. In women, higher fat free mass index (3.9), physical inactivity (2.1) and good appetite (2.3) increased the risk of having metabolic syndrome.

ASSOCIATED DISEASES
Cardiovascular Diseases
Metabolic syndrome is of course known for its nature to increase cardiovascular disease risks. Yeow et al. have shown that it significantly increases other markers of cardiovascular risks such as HbA1c, albumin:creatinine ratio and highly sensitive C-reactive protein.[35] Said et al. reported that metabolic syndrome increased the score of the Framingham Risk Score for cardiovascular disease among Malaysian patients with schizophrenia.[36] Aminuddin et al. determined that the carotid femoral pulse wave velocity (PWVCF), a measure of arterial stiffness, and high-sensitivity C-reactive protein (hs-CRP),was significantly higher among metabolic

syndrome vs healthy participants in study of volunteers recruited via advertisement. The Augmentation index(AI), a measure of wave reflection that arrives back to the aorta after the forward wave and another measure of arterial stiffness, was not significantly different. There was a significantly higher AI value for metabolic syndrome individuals by the Harmonized criteria, but that disappeared when adjusted for race. The AI was significantly higher in Malays compared with Chinese.[37]

Psychiatric Disorders
Even before metabolic syndrome was recognized as an entity, it had been noticed that psychotic patients had high rates of obesity and type 2 diabetes. This was thought on account of several reasons, including an inactive lifestyle, poor dietary choices and side effects of antipsychotic medications.[38] Not surprisingly when schizophrenics are surveyed they have been found to have a higher than normal prevalence rates of metabolic syndrome, as by Said et al. (46.7%, 126/270, by NCEP ATP III (2001) criteria).[36] In a further report these investigators noted that for patients on monotherapy, the average prevalence of metabolic syndrome was higher for patients on the seven different types of first generation antipsychotics studied compared to the seven different types of second generation antipsychotics.[39] Elevated fasting blood glucose was the least common metabolic syndrome component encountered. Atypical antipsychotics differ markedly in their risk to cause metabolic disturbance and caution is needed when prescribing these agents to patients with psychosis.[40]

Roffeei et al. found that the A allele of the FTOrs9939609 T>A gene, the G allele of the LEPRrs1137101A>G gene and the T allele of the MTHFRrs1801133C>G gene were associated with metabolic syndrome in a sample of 206 outpatient schizophrenic patients of whom 59.7% (123/206) had metabolic syndrome. They found no association for polymorphisms of the ADIPOQ, ADRA2A, BDNF, DRD2, HTR2A. HTR2C, LEP, MC4R and PMCH genes.[41]

On the other hand, in a very small study, Abdul Hamid et al. found that 13/31 (41.9%) of their mood disorder patients had metabolic syndrome by the IDF criteria compared to only 3/20 (15%) of their schizophrenic patients.[42] They noted having antipsychotic therapy was not associated with prevalence of metabolic syndrome. Hat et al. observed that 37.5% of their sample of patients with major depressive disorders had metabolic syndrome by the IDF criteria.[43] Neither severity of depression nor any type of medication was significantly associated with metabolic syndrome.

Erectile Dysfunction/Testosterone Deficiency
Tan et al. found 20.8% prevalence of self-reported erectile dysfunction and 16.0% of biochemical testosterone deficiency among a sampled population of men from Subang Jaya. All the components of metabolic syndrome were significantly associated with both erectile dysfunction and testosterone deficiency.[18] Chin et al. also showed testosterone and sex hormone-binding globulin levels were significantly reduced in metabolic syndrome male subjects compared to non-metabolic syndrome subjects.[44]

Polycystic Ovarian Syndrome

Arumugam and Majeed have also shown a strong correlation between polycystic ovarian syndrome and glucose intolerance, obesity and dyslipidaemia, in a cross-sectional case-control study of Malaysian women, although they did not apply all the factors of the various definitions of metabolic syndrome.[45] They note that he association between insulin resistance and polycystic ovarian syndrome is well-established, although its pathogenesis is still elusive.

Gestational Diabetes

Shyam et al. screened 77 (out of 304) women aged between 20-40 years (mean 30.5years) with gestational diabetes, who had either a family history of diabetes, dysglycemia and/or central obesity 2-6 months after delivery for metabolic syndrome. They found 22% (17/77) had metabolic syndrome by the Harmonized criteria.[46]

Colorectal cancer

Ulaganathan et al. have observed that having metabolic syndrome was associated with a 2.25 times risk of having colorectal cancer in a case control study in Malaysia.[47] Colorectal cancer patient had a 70.7% prevalence of metabolic syndrome compared to a 39.3% prevalence among controls. The more components of metabolic syndrome an individual had the high the risk for colorectal cancer.

MANAGEMENT

Nutrition

Shahar et al. tested a nutrition education intervention programme among elderly (>60yrs) rural Malays with metabolic syndrome delivered via group counselling sessions, talks, and cooking and exercise demonstrations. Assessed at 3 and 6 months, the only significant finding was a decrease in WC among women (from a mean 104cm to 100cm) in the intervention group (n=14) versus the control group (n=12). Mean values of the parameters of metabolic syndrome did improve in the intervention group, but only marginally.[48]

Teng et al. observed that both amount and type of dietary fats alter thrombogenic factors, but only the amount of dietary fatty acids affects postprandial lipemia among subjects with metabolic syndrome.[49]

Physical activity

There is growing evidence that regular physical activity favourably affects component factors of metabolic syndrome. Chee et al. conducted an interventional trial among employees of government agencies in Putrajaya, with metabolic syndrome, who regularly logged in to Facebook. 120 participants completed the programme after they were randomised into two groups. One group received weekly posts to promote physical activity. Each member of both groups received a pedometer and both groups had fortnightly meetings. The Facebook group increased their number of steps per day by 3,295 (84.5%) from baseline, while the control group showed an increase of 520 (13.2%) steps after four months. The Facebook page was then deactivated. After two months the Facebook groups was still recording 2,264 (58.1%) steps above baseline while the control group recorded 379 (9.6%) extra steps daily. A correlation was seen between the change in the number of steps taken daily and improvement in all measurements of metabolic syndrome. There was a 94.3% reduction in metabolic syndrome in the Facebook group after four months compared to 21.2% in the control group. After two more months the prevalence of metabolic syndrome rose 5.7% in the Facebook group and 9.4% in the control group.[50]

BIOMARKERS

Adiponectin, an adipocyte-secreted cytokine, which possesses insulin-sensitizing properties, is thought to play a role in the metabolic syndrome. Adiponectin levels decrease with obesity. Low et al. found a significantly lower adiponectin levels in overweight/obese compared to normal/underweight pregnant mothers in their first trimester in a small study of 104 subjects in Selangor.[51] Lau and Muniandy have found low adiponectin levels (hypoadiponectinemia) strongly associated with metabolic syndrome and also with type 2 diabetes.[52] The mean value of serum adiponectin was 9.13 µg/ml among controls compared with 7.22µg/ml among subjects with metabolic syndrome and 6.51µg/ml among subject with both metabolic syndrome and type 2 diabetes. Another case-control study by Aris et al. also found significantly different mean adiponection levels among healthy respondents (13.21±3.88 mmol/l) and subjects with metabolic syndrome (11.64±4.26 mmol/l).[53]

The adiponectinpolypeptide, with 244 amino acids, is encoded by the ADIPOQ gene on chromosome 3q27.3. More than 30-70% of the variability of the blood levels of adiponectin are thought to be explained by genetics.[54] Several single nucleotide polymorphisms(SNP) are associated with hypoadiponectinemia in some populations. Lau and Sekaran found that none of the single nucleotide polymorphisms ADIPOQ SNP+45T>G, SNP+276G>T, SNP+639T>C and SNP+1212A>G influence circulating levels of adiponectin in Malaysian men.[55] When examining the allelic variants, they found variants of certain alleles associated with elevated LDL levels, blood pressure, plasma glucose or waist circumference. However, there was no conclusive link between SNP+45T>G and SNP+276G>T with traits related to metabolic syndrome. However, the C allele of SNP+639T>C and the G allele of SNP+1212A>G were associated with increased risk of dyslipidemia, hyperinsulinemia and obesity among Malay men.[56]

Resistin, a macrophage-derived polypeptide, conversely, has been shown to be up-regulated in subjects with insulin resistance. Lau and Muniandy found high levels of resistin (hyperresistinemia) strongly associated with metabolic syndrome and with type 2 diabetes.[52] The mean value of serum resistin was 14.39 ng/ml among controls compared with 15.78 ng/ml among subjects with metabolic syndrome and 27.05 ng/ml among subjects with both metabolic syndrome and type 2 diabetes. They derived an apidonectin-resistin (AR) index that was more strongly associated with increased risk of type 2 diabetes and metabolic syndrome than neither hypoadiponectinemia or hyperresistinemia alone.[52]

The resistin polypeptide, with 108 amino acids, is encoded by the RETN gene on encoded on chromosome 19p13.2. It is estimated that up to 70%of the variation in circulating resistin levels can be explained by genetic factors.[57] Lau and Muniandy found that the SNP variants SNP-420C>G and SNP+299G>A of the resistin gene were strongly associated with serum resistin levels. For the SNP-420C>G variants, the G/G genotype had the highest serum resistant levels. For the SNP+299G>A it was the A/A genotype who had the highest levels.[55] They also showed that the G allele of SNP-420C>G and the A allele of SNP+299G>A were associated with increased risk of hyperglycaemia among Chinese, and impaired beta-cell function and insulin sensitivity among Indians.[56]

Plasma plasminogen activator inhibitor-1 (PAI-1) the primary physiological inhibitor of endogenous fibrinolysis acts via inhibition of **tissue plasminogen activator** (tPA) and **urokinase type activator** (uPA), often leading to fibrin accumulation in basement membranes and interstitial tissues. Increased PAI-1 and decreased tPA promotes thrombosis and is associated with metabolic syndrome. However, the cardiovascular risks of raised PA-1 disappear when adjustments for the markers of metabolic syndrome are made, suggesting raised PA-1 is a consequence of metabolic syndrome rather than its cause. Al-Hamodi et al. have found PA-1 activity high in metabolic syndrome subjects, with or without type 2 diabetes in a case-controlled study compared with non-metabolic syndrome subjects, with and without type 2 diabetes respectively.[58] tPA activity negatively correlated with its antigen.

Several SNPs in the PAI-1 gene have been identified, among which is the 4G/5G polymorphism (in the 4G allele at 3' end the 5th G is replaced by A). Al-Hamodi et al. have found in a study of 126 Malaysian subjects that carriers of the 4G/4G allele have the highest PA-1 activity and carriers of the G5/G5 allele the lowest.[59] Heterozygous 4G/5G have values closer to 4G/4G. 4G/4G individuals were most prone to metabolic syndrome.

Hepatocyte nuclear factor 4 (HNF4) alpha
Polymorphism of the hepatocyte nuclear factor 4 (HNF4) alpha gene is thought to be associated with insulin resistance and metabolic syndrome. Saif-Ali et al. have found the single nucleotide polymorphisms (SNP) rs1885088 of the HNF4 alpha gene to be associated with type 2 diabetes with metabolic syndrome in Malaysians, while other SNPs were associated with diabetes without metabolic syndrome.[60]

Vitamin D
Moy and Bulgiba noted vitamin D insufficiency was associated with metabolic syndrome in a sample of 380 Malay employees of a public university (OR=1.73).[61] The oxidative stress of metabolic syndrome is postulated to have the potential to damage bone-forming osteoblasts. Mixed results have been observed in bone mass measured by dual-energy x-ray absorptiometry (DEXA) and calcaneal quantitative ultrasonometry (QUS) in men. Chin et al. found no difference in calcaneal speed of sound between those with metabolic syndrome and healthy respondents in a cross-sectional study of 309 men in the Klang valley.[62]

Osteocalcin
Shyam et al. found that low osteocalcin was associated with diabetes but not adiposity in subjects with metabolic syndrome and central obesity.[46]

SECTION 2: RELEVANCE OF FINDINGS FOR CLINICAL PRACTICE
Metabolic syndrome may be viewed as part of a spectrum of cardiovascular disease from normality to overt diseases such as diabetes mellitus, hypertension, coronary artery disease and stroke. It is interesting to know that there are many genetic and advance biomarkers that are associated with metabolic syndrome. The increasing knowledge of these biomarkers enables us to understand the basic science of the condition better. However, in clinical practice, the ultimate aim in managing cardiovascular disease is to prevent end organs involvement, to improve survival and to improve quality of life. The clinical relevance of biomarkers in this context is not evident. The metabolic syndrome is a syndrome developed to help in predicting cardiovascular diseases that uses easily measurable clinical parameters and a simple blood triglyceride level and our focus should be as such.

However, the existence of several metabolic syndrome definition makes it difficult for us to compare and communicate between research data. For example, different criteria give us different prevalence of metabolic syndrome amongst different ethnicity even in the same cohort. There are differences in waist cut-offs measurements between the Caucasians and Asians. However, we do not know whether this difference is presence between our ethnic groups and if so, how significant it is. In fact, the mismatch of incidence between metabolic syndrome and diabetes among different ethnic groups in Malaysia may be partially explained by the current metabolic syndrome definition used. Lower central obesity cut-off for Malays would improve the match between the incidence of metabolic syndrome and diabetes between Malays and Chinese in this country.

We do not know about our population awareness of metabolic syndrome and its risk factors. Like any non-communicable disease, we need to understand the healthcare providers and public perception and knowledge of the condition before any successful interventional programme could be planned. In addition, any successful intervention would probably need multidimensional approach. Therefore, it is not surprising that a unilateral approach management in the available literatures were only able to show very modest results.

SECTION 3: FUTURE RESEARCH DIRECTION
Clinically relevant research in the field of metabolic syndrome is much lacking comparing to magnitude of burden of this condition in this country. We need consensus on the criteria of metabolic syndrome that is best suited for our population in order to allow better comparison and merging of data. Validation of waist cut-offs measurement in our population may improve definition of metabolic syndrome for local use better. Studies should be done to look into our population awareness of metabolic syndrome and its

risk factors. More research into effective management programme will help us to tackle the metabolic syndrome problem better. However, multidisciplinary management approach would probably gather more useful knowledge than a unidisciplinary approach. Finally, research into the health economic burden of metabolic syndrome in this country will help the policy makers plan health resource better.

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APPENDIX 1: Definition of Metabolic Syndrome by different criteria

Risk factors (RF)	Modified WHO	NCEP-ATP III (2001)	IDF (2005)	NCEP-ATP III (2005)	Harmonised JIS (2009)
Obesity	BMI >30kg/m2 or Waist-hip ratio M>0.9 F>0.85	Waist Circumference M ≥102 cm F ≥88 cm	Waist Circumference M ≥90 cm F ≥80 cm	Waist Circumference M ≥90 cm F ≥80 cm	Waist Circumference M ≥90 cm F ≥80 cm
Blood Pressure	Systolic BP ≥140 and/or diastolic BP ≥90 mmHg or on treatment for HPT	Systolic BP ≥130 and/or diastolic BP ≥85 mmHg or on treatment for HPT	Systolic BP ≥130 and/or diastolic BP ≥85 mmHg or on treatment for HPT	Systolic BP ≥130 and/or diastolic BP ≥85 mmHg or on treatment for HPT	Systolic BP ≥130 and/or diastolic BP ≥85 mmHg or on treatment for HPT
Fasting plasma glucose	≥6.1 mmol/L or previously diagnosed T2DM	≥6.1 mmol/Lor previously diagnosed T2DM	≥5.6 mmol/L or previously diagnosed T2DM	≥5.6 mmol/L or on treatment for T2DM	≥5.6 mmol/L or on treatment for T2DM
Triglycerides	>1.69mmol/L	≥1.7 mmol/L	≥1.7 mmol/L or on treatment for TG	≥1.7 mmol/L or on treatment for TG	≥1.7 mmol/L or on treatment for TG
HDL-C	M<0.90 mmol/L F<1.0 mmol/L	M <1.03 mmol/L F <1.29 mmol/L	M <1.03 mmol/L F <1.29 mmol/L L or on treatment for HDL-C	M <1.03 mmol/L F <1.29 mmol/L L or on treatment for HDL-C	M <1.0 mmol/L F <1.3 mmol/L L or on treatment for HDL-C
Metabolic syndrome definitions	Fasting plasma glucose ≥6.1 mmol/L+ 2 or more RF	At least 3 RF	Waist Circumference + 2 or more RF	At least 3 RF	At least 3 RF