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Metabolic Syndrome In Light Of Five Different Definitions.

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ABSTRACT

Metabolic syndrome (MetS) is a worldwide epidemic, It is known for its complex etiology. MetS is a syndrome and its definition includes a cluster of etiologically related factors that have a direct effect to increase the risk of coronary heart disease (CHD), other atherosclerotic cardiovascular diseases (CVD), and type II diabetes mellitus (DM Type-II). Core manifestations of the syndrome are abdominal obesity and/or insulin resistance (IR). Recently, many additional factors besides those traditionally used to define MetS have been identified to be associated with MetS. Currently, Several different definitions of MetS exist at present, which cause a significant confusion as to whether they identify the same individuals or not. There are substantial confusions related to the prevalence trend, relation with age, sex, obesity, hypertension. In this review, we critically compared the existing definitions and discussed the trends related to prevalence, relation with age, sex, obesity and hypertension. We conclude that there is still a need to develop uniform criteria to define MetS, and further work to understand association of MetS with obesity to better identify patients at risk and there is a need of early marker to diagnose and treat MetS before the complications develop fully.

Keywords: MetS, metabolic syndrome, epidemic.

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INTRODUCTION

Metabolic syndrome (MetS) is a worldwide epidemic, It is known for its complex etiology. It produced a huge socioeconomic burden on the society. MetS is a syndrome and its definition includes a cluster of etiologically related metabolic abnormalities that have a direct effect to increase the risk of coronary heart disease (CHD), other atherosclerotic cardiovascular diseases (CVD), and type II diabetes mellitus (DM Type-II) and cerebrovascular disease[1]. Core manifestations of the syndrome are abdominal obesity and/or insulin resistance (IR). Obesity is rampant worldwide. The increasing trend in obesity is due to two important factors, availability of plentiful inexpensive food supplies and sedentary and stressful jobs.

Other main components of MetS include Atherogenic dyslipidemia (hypertriglyceridemia and elevated apolipoprotein B (apoB), low HDL cholesterol(dyslipidemia) and increased LDL), elevated glucose associated with insulin resistance, elevated blood pressure (BP), prothrombotic state and proinflammatory state.

HISTORY OF METABOLIC SYNDROME

The risk factors linked to DM were known as early on as the 1920s, but its only 1950s that term "metabolic syndrome" came to use. [2]. It became common in the 1970s. In 1947, Jean Vague a French physician noticed that people with upper body obesity seemed to have an increased risk for conditions like atherosclerosis, diabetes, gout and kidney stones[3]. In 1977 Herman Haller in his studied risk factors associated with atherosclerosis. He used the term "metabolic syndrome" for his observation of the link between obesity, diabetes mellitus, high blood lipids, a high uric acid level and fatty liver disease with atherosclerosis development. According to Gerald Phillips's hypothesis the underlying factor for all is one and that could be linked to the combined presence of these risk factors. If that one factor is identified by research it will help to prevent cardiovascular disease. In his view that common factor could involve the sex hormones.As continuation of above hypothesis, in 1988, Gerald Reaven based on his research said that insulin resistance could be that one underlying factor producing this constellation of abnormalities, he named it "syndrome X" which he later renamed metabolic syndrome (MetS)[5].

DIFFERENT DEFINITIONS OF METS : Since then, many expert groups and international organizations, came up with different definitions of metabolic syndrome.

It is the WHO who made the first attempt in 1998 to propose that MetS can be defined by putting all these parameters together which include insulin resistance (IR) in the form of hyperglycemia or frank diabetes mellitus type 2(DMT2), as the very important components of the metabolic syndrome, along with the any two of the following parameters(Reffer Table -3): 1.Raised BP, 2.Hypertriglyceridemia and/or low HDL-cholesterol, 3.Obesity (as measured by waist/hip ratio or body mass index (BMI), 4.Microalbuminuria[5]

EGIR came with some modification shortly after that and excluded microalbuminuria from the syndrome, while it added hyperinsulinemia newly[6]. Other changes done were replacement of BMI with waist circumference as the main indicator to assess obesity, and introduced new cut-offs for the other components of the syndrome(Reffer Table -3).

NCEP: ATPIII came up with a new set of criteria in 2001. It included following parameters 1. Waist circumference, 2.Blood lipids, 3.BP, 4.Fasting glucose[7]

The difference between NCEP:ATPIII definition and WHO, EGIR definitions is absence of IR (Reffer Table -3).. The International Diabetes Federation (IDF) published a new criteria in 2005 to define the metabolic syndrome with further more clearity[8].

The IDF added abdominal obesity to the list of diagnostic parameters of MetS and gave a special emphasis on waist circumference measurement as a simple screening tool of obesity that was also included by AHA/NHLBI[9] (Reffer Table -3).

Apart from waist circumference remaining all other components of MetS remain the same in the AHA/NHLBI and IDF definitions. But the IDF recommended a lower cut-off points for waist circumference in Europeans (94 cm for men, 80 cm for women), while the AHA/NHLBI recommended higher cut-off points of 102cm in men and 88cm in women(**Table -1**).

Table - 1 : American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) criteria (2004)[9].

Any three of the following:
• Waist circumference 102 cm or greater in men, 88 cm or greater in women.
• Triglycerides 150 mg/dl or greater.
• HDL-cholesterol < 40 mg/dl in men and < 50 mg/ dl in women.
• BP 130/85 mmHg or greater.
• Fasting glucose 100 mg/dl or greater.

IDF and NCEP:ATP III are currently widely used definitions. They stress mostly upon waist circumference, a measure of central obesity, making them obesity-centric. Where as WHO, AACE[10] and the EGIR definitions focus mainly on insulin resistance, making them glucocentric (Reffer Table -3).

When compared to white Europeans of the same BMI, Asians have 3 to 5 percent higher total body fat[11].Because of this Asians develop risk of DMT2, at much lower levels of obesity compared to Europeans. These findings lead to lowering of the cut points for overweight and obesity for Asians[12].

To address these issues of total body fat differences the IDF, has proposed a new set of criteria with ethnic/racial specific cut-offs[13].

Finally all these practical difficulties in MetS definitions lead to the formulation of consensus definition, which says, there should not be any component that is obligatory for MetS instead of this each components should be considered important for risk prediction, is currently popularly accepted(**Table -2**).

Table -2 : Consensus definition (incorporating IDF and AHA/NHLBI definitions)[13]

Any three of the following:
• Elevated waist circumference (according to population and country-specific definitions).
• Triglycerides 150 mg/dl or greater.
• HDL-cholesterol < 40 mg/dl in men and < 50 mg/ dl in women.
• BP 130/85 mmHg or greater.
• Fasting glucose 100 mg/dl or greater.

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Table – 3 : Different definitions of MetS

C/F	WHO (1998)	EGIR(1999)	ATPIII(2001)	AACE(2003)	IDF(2005)
Insulin resistance	IGT, IFG, T2DM, or lowered insulin Sensitivitya plus any 2 of the following	Plasma insulin >75th percentile plus any 2 of the following	None, but any 3 of the following 5 features	IGT or IFG plus any of thefollowing based on the clinical judgment	None
Body weight	Men: waist-to-hip ratio >0.90; women: waist-to-hip ratio >0.85 and/or BMI > 30 kg/m2	WC ≥94 cm in men or ≥80 cm in women	WC ≥102cm in men or ≥88 cm in women	BMI ≥ 25 kg/m2	IncreasedWC (population specific) plus any 2 of the following
Lipids	TGs ≥150mg/dL and/or HDL-C <35 mg/dL in men or <39 mg/dL in women	TGs ≥150mg/dL and/or HDL-C <39 mg/dL in men or women	TGs ≥150mg/dL HDL-C <40mg/dL in men or <50mg/ dL in women	TGs ≥150mg/ dL and HDL-C <40mg/dL in men or <50mg/dL in women	TGs ≥150mg/dL or on TGs Rx. HDL-C <40mg/dL in men or <50mg/dL in women or on HDL-C Rx
Blood pressure	≥140/90mmHg	≥140/90mmHg or on hypertension Rx	≥130/85mmHg	≥130/85mmHg	≥130mmHg systolic or ≥85 mmHgdiastolic or on hypertension Rx
Glucose	IGT, IFG, or T2DM	IGT or IFG (but not diabetes)	>110mg/dL (includes diabetes)	IGT or IFG (but not diabetes)	≥100mg/dL (includes diabetes)[b]
Other	Microalbuminuria: Urinary excretion rate of >20mg/min or albumin:creatinin ratio of >30mg/g.			Other features of insulin resistancec	

Epidemiology of MetS according to the various definitions used : Approximately 20 – 25% of the world's total adult population has the cluster of risk factors that is metabolic syndrome**.** Cornier MA et al in 2008 showed prevalence of metabolic syndrome (MetS) depends on many factors like the MetS criteria used in different definitions, the composition (sex, age), the ethnicity and race of the population studied**.** Though the prevalence varies depending on the diagnostic criteria used, according to Hollman G (2008), Hillier TA et al (2006) and Do Carmo I et al (2008) MetS is more and on further rise in all Western countries, as well as Asian and European countries probably due to its direct relation with rising obesity in the world. Its prevalance extends froma range of 9.8% in male urban population of north India to 42% in female urban population of Iran[14]**.**

There are three NHANES cohorts (1988-1994, 1999-2002 and 2003-2006). There is a 5% increase in the MetS patients using the NCEP ATP III revised criteria, during the last 15 years, But there is no such change when WHO criteria is used though this criteria is more restrictive. Prevalance of MetS is more when IDF definition is used. It may be because of lower cut-off point for waist circumference[15].

According to a West African study the prevalence of MetS in mexico was 69.14%, 63.58%, 43.83%, , and using the IDF, the WHO and the NCEP-ATP III critaria, respectively.

A Nigerian report showed the prevalence rate of MetS over 80% among DM patients[16]. The rising MetS in African populations is largelythe result of "adoption of western lifestyle which is nothing but reduced physical activity, replacement of the fruit rich typical African diet with the more energy laden foods"[16].

According to one study prevalence of MetS affected 60% of the Atlantic European Mainland, 68% of Central Europe, 50% of Northwest Europe and 52% of the Mediterranean regions[17]. Turkey has a prevalence of 33.9% for MetS, it is higher in women (39.6%) and lower in men (28%)[18]. Saudi Arabia has a prevalence of 16.1% according to the IDF. In Tunisia, MetS incidence was 45.5% according to the IDF criteria[18].

A study done on Iranians of all 30 provinces of Iran in the age range of 25-64yrs showed a prevalence of 37.4%, based on the IDF definition. Same population showed a prevalence of 41.6% based on the ATPIII/AHA/NHLBI definitions. The prevalence of MetS has increased over the past decades in Iranian population as other ethnics[19].

Relation With age and sex : There are two aspects as far as the relation of MetS with age is concerned.

1. Prevalence of MetS with age
2. Prevalance of different components of MetS with age

According to Cornier MA et al (2008), Alkerwi A et al (2011), Hildrum B (2007) Prevalence of MetS increases with age, according to NHANES 2003-2006 cohort, the prevalence of MetS was found to increase with age: approximately 20% of males and 16% of females under 40 years of age, 41% of males and 37% of females between 40-59 years, and 52% of males and 54% of females 60 years and over. There is similar trend of rise in prevalence of MetS with advancing age is observed in other populations as well[20,21,22]. The possible reasons for increasing MetS prevalence with age can be age-related rise of BP, blood glucose and abdominal obesity.

It is observed that rise in the prevalence of MetS continues till sixth decade of life, but after sixth decade the prevalence is variable by different studies. According to some studies, metabolic syndrome prevalence drops off after the sixth or seventh decade of age in both sexes[23,24], and in some studies only in men[25,26,27].

Reason for this might be a bias in taking part, those individuals who developed obesity-related complications have already died or decline to take part in a study[28]. Possible reason for this variability of prevalence could be different complications which are directly related to obesity or independent of obesity leading to higher mortality rate[29,30]. 2.Definition used for metabolic syndrome may also be a reason[31].

Even with the use of same definition, observations are different in different countries [32,33,34]. This focusses on the importance of country wise estimation of MetS prevalance.

As per some studies prevalance is higher in men than in women [35,36,37], But as per NHANES III (1988–1994) data prevalence of MetS in women is higher than that of men in individuals older than 50 years[].

The variation in prevalence of metabolic syndrome in men and women may be due to 1. Differences in body fat distribution, men have more visceral and hepatic fat, and women have more total body fat [38]. 2.Higher prevalence of smoking, tobacco chewing and alcohol use in men may be another factor for higher incidence of MetS in males, these both substances are linked with the development of metabolic syndrome[39]. 3.Menopause with its cardiometabolic effects may have the explaination to the decreased sex difference seen in metabolic syndrome prevalence with older age [30,38].

Coming to the prevalance of components of MetS with age. Different studies have shown different phenotypes of MetS among different age groups.

According to Gharipour M et all[40] Low HDL-cholesterol was the most common component, followed by raised triglycerides, central obesity (ABO), increased blood pressure (HTN), and fasting hyperglycemia in descending order of prevalence.

The combination of MetS components which was found to be most prevalent was raised triglycerides, low HDL-cholesterol and abdominal obesity (50.7%) in all age groups and especially in younger group (63.2%).In old age group subjects, the most prevalent combination of components of MetS was low HDL-cholesterol ,raised triglycerides and hypertension (43.9%).

Relation of MetS with BMI: The prevalence of MetS is directly proportional to BMI, MetS increase dramatically as BMI increases.Overweight males and females were found to be more than 6 and 5.5 times respectively, likely to meet the criteria for MetS compared to underweight and normal weight individuals according to NHANES 2003-2006[15].

Increase in MetS reflects the transition from a traditional to a Western-like lifestyle.

The dramatic rise of obesity and MetS in developing countries is a result of a number of factors. LikeOn one side shift to low fertility, low mortality, higher life expectancy, transition from infectious diseases to a high prevalence of lifestyle related diseases are there on the other hand economically more resourcefulness leading to shifts in dietary and physical activity patterns. These all factors produce significant effects on body composition and its metabolism which ultimately results in abdominal obesity with higher BMI, and an increase in different body lipids and Type II diabetes mellitus[41].

Surprisingly, some researchers (Ruderman NB et al (1981,1998), Zavaroni I et al (1989), Dvorak RV et al (1999), St-Onge MP et al (2004)) found that even some lean individuals developed features of MetS raising the questions on the present explanation of pathogenesis of MetS [42].

They called them metabolically obese normal-weight (MONW) individuals. They despite having their weight and BMI in normal range, showed metabolic abnormalities typical of obese individuals.

These metabolic abnormalities include increased levels of central adiposity, insulin resistance, raised TG's, low levels of HDL-cholesterol, impaired fasting glucose, and hypertension. This clustering of risk factors has been called the metabolic syndrome (MetS) [43].

On the other hand some researchers(Ferrannini E et al (1997), Bonora E et al (1998), Brochu M et al (2001), Karelis AD et al) came across the individuals whom they called metabolically healthy obese (MHO) individuals. They despite having a higher BMI exceeding 30 kg/m^2, are insulin sensitive and lack most of the typical metabolic abnormalities of obese individuals.

Elevated' blood pressure and MetS: Prevalence of raised blood pressure was remarkably high in comparison to the other MetS components. Ina study The MetS component 'elevated blood pressure' showed the most pronounced increase with age[44]. A cut off value of <130/85 mmHg BP is used in R ATP-III and IDF definitions. It

seems strict for the aged subjects where age related natural rise of BP is not taken into consideration [45]. Early screening to diagnose hypertension is important because approximately 50% of the deaths from stroke or CVD result from hypertension [46]. The optimal BP threshold value in elderly for intervention is still debatable, especially in the old[47,48]. The hypertension treatment guideline of JNC 8(James PA et al 2014) advised to aim for a BP <140/90 mmHg in non-diabetic adults (<60 years), and a BP values <150/90 mmHg were advised for ≥60 years old, elderly patients.

When we apply the age-adjusted threshold value of BP, it results in a reduction of subjects fulfilling the BP criteria. This leaves behind a possibility of missing those patients who had a BP of 130– 140 systolic and 85–90 diastolic, Whether they face severe long-term implications needs to be investigated.

REFERENCES

[1] Kaur J. A comprehensive review on metabolic syndrome Cardiology Research and Practice 2014; 1–21.

[2] Kylin E. Studien ueber das Hypertonie-Hyperglyca “mieHyperurika” miesyndrom,” Zentralblatt fuer Innere Medizin 1923;44:105–127,.

[3] Vague J. Sexual diferentiation. A factor afecting the forms of obesity. Presse Medicale 1947;30:39–40.

[4] Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37:1595-1607.

[5] Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15:539-553.

[6] Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). Diabet Med 1999;16;442-443.

[7] Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486-2497.

[8] International Diabetes Federation: The IDF consensus worldwide defnition of the metabolic syndrome, http://www.idf.org/metabolic-syndrome.

[9] Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Arterioscler Thromb Vasc Biol 2004;24:e13-e18.

[10] Einhorn D, Reaven GM, Cobin RH, Ford E, Ganda OP, Handelsman Y et al. American College of Endocrinology position statement on the insulin resistance syndrome. Endocr Pract 2003;9:237-252.

[11] Deurenberg P, Deurenberg-Yap M, Guricci S. Asians are different from Caucasians and from each other in their body mass index/body fat percent relationship. Obes Rev. 2002; 3: 141-6.

[12] Low S, Chin MC, Ma S, Heng D, Deurenberg-Yap M. Rationale for redefining obesity in Asians. Ann Acad Med Singapore. 2009; 38: 66-69.

[13] Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA et all. International Diabetes Federation Task Force on Epidemiology and Prevention, National Heart, Lung, and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society, International Association for the Study of Obesity: Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009; 120: 1640-1645.

[14] Misra A, Khurana L. Obesity and the metabolic syndrome in developing countries. J Clin Endocrinol Metab 2008; 93:S9-30.

[15] Ford ES, Li C, Zhao G. Prevalence and correlates of metabolic syndrome based on a harmonious definition among adults in the US. J Diabetes 2010; 2:180-193.

[16] Okafor CI. The metabolic syndrome in Africa: Current trends. Indian J Endocrinol Metab 2012;16(1): 56–66.

[17] Farsang C, Naditch-Brule L, Perlini S, Zidek W, Kjeldsen SE. Inter-regional comparisons of the prevalence of cardiometabolic risk factors in patients with hypertension in Europe: the GOOD survey. J Hum Hypertens2009; 23 (5): 316 -324.
[18] Sliem HA, Ahmed S, Nemr N, El-Sherif I. Metabolic syndrome in the Middle East. Indian J Endocrinol Metab 2012; 16 (1): 67–71.
[19] Tavassoli AA, Gharipour M, Khosravi A, Kelishadi R, Siadat ZD, Bahonar A, et al. Gender differences in obesogenic behaviour, socioeconomic and metabolic factors in a population-based sample of Iranians: The IHHP study. J Health PopulNutr. 2010;28:602–9.
[20] Cameron AJ, Shaw JE, Zimmet PZ. The metabolic syndrome: prevalence in worldwide populations. Endocrinol Metab Clin North Am 2004; 33: 351-75,table.
[21] Azizi F, Salehi P, Etemadi A, Zahedi-Asl S. Prevalence of metabolic syndrome in an urban population: Tehran Lipid and Glucose Study. Diabetes Res Clin Pract 2003; 61: 29-37.
[22] Aguilar-Salinas CA, Rojas R, Gomez-Perez FJ, Valles V, Rios-Torres JM, Franco A et al. High prevalence of metabolic syndrome in Mexico. Arch Med Res 2004; 35: 76-81.
[23] Cameron AJ, Magliano DJ, Zimmet PZ, Welborn T, Shaw JE. The metabolic syndrome in Australia: prevalence using four definitions. Diabetes Research and Clinical Practice 2007;77:471–478.
[24] Deepa M, Farooq S, Datta M, Deepa R, Mohan V. Prevalence of metabolic syndrome using WHO, ATPIII and IDF definitions in Asian Indians: the Chennai Urban Rural Epidemiology Study (CURES- 34). Diabetes/Metabolism Research and Reviews 2000;23: 127–134.
[25] Adams RJ, Appleton S, Wilson DH, Taylor AW, Dal Grande E, Chittleborough C, et al. Population comparison of two clinical approaches to the metabolic syndrome: implications of the new International Diabetes Federation consensus definition. Diabetes Care 2005;28: 2777 –2779.
[26] Gavrila D, Salmeron D, Egea-Caparros JM, Huerta JM, Perez-Martinez A, Navarro C, et al. Prevalence of metabolic syndrome in Murcia Region, a southern European Mediterranean area with low cardiovascular risk and high obesity. BMC Public Health 2011;11:562.
[27] Park YW, Zhu S, Palaniappan L, Heshka S, Carnethon MR, Heymsfield SB. The metabolic syndrome: prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988–1994. Archives of Internal Medicine 2003;163:427–436.
[28] Zamboni M, Mazzali G, Zoico E, Harris TB, Meigs JB, Di Francesco V, et al. Health consequences of obesity in the elderly: a review of four unresolved questions. International Journal of Obesity 2005;29:1011–1029.
[29] Fiuza M, Cortez-Dias N, Martins S, Belo A. Metabolic syndrome in Portugal: prevalence and implications for cardiovascular risk–results from the VALSIM Study. Rev Port Cardiol 2008; 27:1495-1529.
[30] Cameron AJ, Magliano DJ, Zimmet PZ, Welborn T, Shaw JE. The metabolic syndrome in Australia: prevalence using four definitions. Diabetes Res Clin Pract 2007;77:471-478.
[31] Cornier MA, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, Stob NR, et al. The metabolic syndrome. Endocrine Reviews 2008;29:777–822.
[32] van Vliet-Ostaptchouk JV, Nuotio ML, Slagter SN, Doiron D, Fischer K, Foco L, et al. The prevalence of metabolic syndrome and metabolically healthy obesity in Europe: a collaborative analysis of ten large cohort studies. BMC Endocrine Disorders 2014;14: 9.
[33] Hildrum B, Mykletun A, Hole T, Midthjell K, Dahl AA. Age-specific prevalence of the metabolic syndrome defined by the International Diabetes Federation and the National Cholesterol Education Program: the Norwegian HUNT 2 study. BMC Public Health 2007;7:220.
[34] Gavrila D, Salmeron D, Egea-Caparros JM, Huerta JM, Perez-Martinez A, Navarro C, et al. Prevalence of metabolic syndrome in Murcia Region, a southern European Mediterranean area with low cardiovascular risk and high obesity. BMC Public Health 2011;11:562.
[35] Scuteri A, Laurent S, Cucca F, Cockcroft J, Cunha PG, Manas LR, et al. Metabolic syndrome across Europe: different clusters of risk factors.European Journal of Preventive Cardiology 2015;22:486–491.
[36] Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 2002;287:356–359.
[37] Kuk JL, Ardern CI. Age and sex differences in the clustering of metabolic syndrome factors: association with mortality risk. Diabetes Care 2010 33 2457–2461.
[38] Pradhan AD. Sex differences in the metabolic syndrome: implications for cardiovascular health in women. Clinical Chemistry 2014:60:44–52.

[39] Slagter SN, van Vliet-Ostaptchouk JV, Vonk JM, Boezen HM, Dullaart RP, Kobold AC, et al. Combined effects of smoking and alcohol on metabolic syndrome: the LifeLines cohort study. PLoS ONE 2014;9: e96406.

[40] Gharipour M, Sadeghi M, Hosseini M, Andalib E, Boroujeni MB, Sarrafzadegan N. Effect of age on the phenotype of metabolic syndrome in developing country. Adv Biomed Res 2015;4:103.

[41] Misra A, Khurana L. Obesity and the metabolic syndrome in developing countries. J Clin Endocrinol Metab 2008;93:S9-30.4.

[42] Diamanti-Kandarakis E, Papavassiliou AG, Kandarakis SA and Chrousos GP. Pathophysiology and types of dyslipidemia in PCOS. Trends Endocrinol Metab 2007;18:280-285.

[43] Grundy SM, Brewer HB, Cleeman JI, Smith SC, Lenfant C. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004;109:433–438.

[44] Slagter SN, van Waateringe RP, van Beek AP, van der Klauw MM, Wolffenbuttel BHR, van Vliet-Ostaptchouk JV. Sex, BMI and age differences in metabolic syndrome: the Dutch Lifelines Cohort Study. Endocrine connections 2016;6:278-88.

[45] Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, et al. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. Hypertension 2004;43:1239–1245.

[46] Laslett LJ, Alagona P, Clark BA, Drozda JP, Saldivar F, Wilson SR, et al. The worldwide environment of cardiovascular disease: prevalence, diagnosis, therapy, and policy issues: a report from the American College of Cardiology. Journal of the American College of Cardiology 2012;60(Supplement 25): S1–S49.

[47] Andersson C, Vasan RS. Lower is not always better? Blood pressure treatment targets revisited. Journal of the American College of Cardiology 2014;64:598–600.

[48] Schwartz CL, McManus RJ. What is the evidence base for diagnosing hypertension and for subsequent blood pressure treatment targets in the prevention of cardiovascular disease? BMC Medicine 2015;13:256.