

## Cardio Metabolic Syndrome: A Global Epidemic

Heval M Kelli<sup>1</sup>, Ibrahim Kassar<sup>2</sup> and Omar M Lattouf<sup>1\*</sup>

<sup>1</sup>Emory University School of Medicine, USA

<sup>2</sup>University of Massachusetts Medical School, USA

### Abstract

Cardio Metabolic Syndrome (CMS), also known as insulin resistance syndrome or metabolic syndrome X, is a combination of metabolic disorders or risk factors that essentially includes a combination of diabetes mellitus, systemic arterial hypertension, central obesity and hyper-lipidemia. Common to these diseases of metabolism is the associated development of atherosclerotic cardiovascular disease (ASCVD). Studies have shown a strong link between CMS and increased prevalence of peripheral vascular diseases, coronary artery disease and myocardial infarctions as well as cerebro-vascular arterial diseases and stroke.

**Keywords:** Cardio metabolic syndrome; Hyperlipidemia; Obesity; Stroke; Myocardial infarction

**Abbreviations:** AACE: American Association for Clinical Endocrinology; ALLHAT: Antihypertensive Lipid Lowering Treatment to Prevent Heart Attack Trial; ART: Anti-Retroviral Therapy; ASCVD: Atherosclerotic Cardiovascular Disease; ATP III: Adult Treatment Panel III; BMI: Body Mass Index; BP: Blood Pressure; CADISS: Coronary Artery Disease in Saudi Study; CASS: Coronary Artery Surgery Study; CB1: Cannabinoid Receptor-1; CHD: Coronary Heart Disease; CKD: Chronic Kidney Disease; CMRFC: Cardio Metabolic Risk Factors Clusters; CMS: Cardio Metabolic Syndrome; COPD: Chronic Obstructive Pulmonary Disease; CRP: C-reactive protein; CVD: Cardio Vascular Disease; DBP: Diastolic Blood Pressure; DM: Diabetes mellitus; DPP: Diabetes Prevention Program; EGIR: European Group for study of Insulin Resistance; EU: Europe; FDA: Food and Drug Administration; GCC: Gulf Cooperative Council; HDL High Density Lipoprotein; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HIV Human Immunodeficiency Virus; HR Hazard Ratio; IDF: International Diabetes Federation; IOTF International Obesity Task Force; JACC: Journal of American College of Cardiology; LDL: Low Density Lipoprotein; LTSB: Leisure Time Sedentary Behavior; ME: Middle Eastern; MFP: Mediterranean Food Pattern; Me-Can: Metabolic syndrome and Cancer project; NAFLD: Nonalcoholic Fatty Liver Disease; NCEP-ATP III: National Cholesterol Education Program Adult Treatment Panel III; NCEP: National Cholesterol Education Program; NHANES: National Health and Nutrition Examination Studies; NRTIs: Nucleoside Reverse Transcriptase Inhibitors; OR: Odds Ratio; PAMELA: Pressioni Arteriose Monitorate E Loro Associazioni; PIs: Protease Inhibitors; QALY: Quality-Adjusted Life-Year; RF: Risk Factor; RR: Relative Risk; SAH: Systemic Arterial Hypertension; SCD Sudden Cardiac Death; SBP: Systolic Blood Pressure; TG: Triglycerides; TLGS: Tehran Lipid and Glucose Study; US: United States; VLCD: Very Low Calorie Diet; WHO: World Health Organization

### Background and Impact

Cardio Metabolic Syndrome (CMS), also known as insulin resistance syndrome or metabolic syndrome X, is a combination of metabolic disorders or risk factors that essentially includes a combination of diabetes mellitus, systemic arterial hypertension, central obesity and hyper-lipidemia. Common to these diseases of metabolism is the associated development of Atherosclerotic Cardiovascular Disease (ASCVD) [1]. Studies have shown a strong link between CMS and increased prevalence of peripheral vascular diseases, coronary artery

disease and myocardial infarctions as well as cerebro-vascular arterial diseases and stroke [2].

Interest in these diseases is easily justified when cardiovascular disease is the cause of death of 18 million people around the world with diabetes and hypertension being the major risk factors [3]. Cardiovascular diseases are of global concern, rather than a first world concern, as evidenced by a 1999 World Health Report, which disclosed that 85% of CVD came from developing low- and middle-income countries [4]. Diabetes mellitus, a key component of CMS, has been shown by many studies and meta-analysis to create an increased relative risk (RR) for CVD events and death of 1.78 [5]. Alternatively, patients with characteristics consistent with CMS are at a 5-fold risk of developing diabetes [1,6].

With the rise of obesity around the world, CMS has become a global pandemic with estimates of more than 1.1 billion adults being overweight and 312 million being obese. In certain regions of the world such as in the Middle East, the rate of obesity has tripled within the last 20 years making it one of the regions at highest risk for the downstream effects of these diseases [3]. In the United States, obesity has been on the rise. In 1999, there were approximately 50 million Americans with CMS compared to 64 million in 2000. The prevalence of obesity has risen from 22.5% in the 1988-1994 to 30.5% in 1999-2000. Although obesity is a well-recognized risk, a recent study of 30 years follow-up has shown that middle-aged men with CMS were at increased risk for CVD and related death irrespective of BMI status [7], implying that CMS is an independent risk factor regardless of BMI. Aging is also believed to be a contributing factor to the rising prevalence of CMS [5].

According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III), the presence of any 3 of the following clinical abnormalities would meet the criteria for the definition

**\*Corresponding author:** Omar M Lattouf, Professor of Surgery/Cardiothoracic, Emory University School of Medicine, 6th Floor Medical Office Tower, 550 Peachtree Street NE, Atlanta, Georgia 30308, USA, Tel: 1-404-686-2513; E-mail: [olattou@emory.edu](mailto:olattou@emory.edu)

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for CMS: dyslipidemia (elevated triglyceride, high apolipoprotein B and depressed serum levels of High Density Lipoprotein HDL), central obesity, systemic arterial hypertension and hyperglycemia [8]. Other international organizations such as the International Diabetes Federation (IDF), European Group for study of Insulin Resistance (EGIR) and the American Association for Clinical Endocrinology (AACE) use slightly different diagnostic criteria to meet the definition of CMS. However, they all share the commonality of central obesity and insulin resistance, which are considered benchmarks for diagnosis of the syndrome [4,5].

The various internationally recognized definitions are listed below as published in the Scientific Statement of the American Heart Association / National Heart, Lung, and Blood Institute [1].

Of the aforementioned definitions, those of the WHO and ATP III are most widely used. The WHO criteria revolve around the presence of diabetes mellitus and insulin resistance as key requirement plus two other risk factors (obesity, hypertension, high triglycerides, reduced HDL-C level, or micro-albuminuria) [5]. In the ATP III and EGIR definition obesity, as a risk factor, has been further refined to be more specific to central obesity rather than total body obesity and overweight. National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) modified its detection guideline to allow the presence of any three of five risk factors (hyperglycemia, hypertension, central obesity, elevated triglycerides or depressed HDL-C levels) to confirm a diagnosis. By doing so, it is thought that earlier detection of patients at risk is reached earlier and thus efforts would be made to reduce the later stage development of atherosclerotic cardio vascular changes [1].

## Global Impact of Cardio Metabolic Syndrome

The epidemic proportion of Cardio Metabolic Syndrome in the world today and its subsequent downstream impact on the cardiovascular system, renal system, cerebrovascular system, immune system, and on cancer diagnoses collectively herald a catastrophic impact on the world population with anticipated tens of millions of avoidable deaths [9]. Considering the health and economic factors projected to occur due to the effects of this syndrome, the forecast is dismal and bodes poor for individual nations and for humanity as a whole. Unless concerted efforts with clear and concentrated action plans are carried out by the world community to address this silent and little noted epidemic, the cost in lives lost may be in excess of those caused by natural disasters, man-made disasters, accidental deaths and even major conflicts and wars. The ever-growing dimension of this health problem justifies a global "call-to-arms" that should be addressed by international bodies such as the United Nations and senior world leaders.

Proactive strategies that blend preventive therapies, exercise programs, and therapeutic regimens on massive population scales must be carried out to bring this disease process into check. This is a situation where one could justifiably state that massive problems require massive solutions. Alternatively this disease, with its growing rate and secondary end organ dysfunction, could easily strain the rich and poor nation's economies alike leading to unforeseen financial and health difficulties at the micro family level as well as on national and international levels.

Preventive and therapeutic intervention must focus on the reduction of the clinical manifestations of atherosclerotic disease by altering the modifiable risk factors: obesity, physical inactivity, SAH, DM and dyslipidemia [1].

## Incidence of CMS and its Risk Factors

### World

The changing socio-economic conditions in the world has led, it is believed, to an alarming increase in the prevalence of diabetes and obesity and secondarily that of CMS, particularly in the developing nations. The 1988 World Health Report described that 85% of cardiovascular diseases come from parts of the world that are of low- and middle-income countries. One study projected that in 2030 there will be a prevalence of diabetes in 366 million individuals, with 298 million of them in developing nations [3,4]. The changing socio-economics with improved dispensable income, increased urbanization and the associated increased dependence on public and private transportation with decreased obligatory exercise have led to sedentary life style, lesser physical activities and a more positive energy balance magnified by calorie rich and unhealthy diets [4,10]. This phenomenon, newly labelled as "lifestyle syndrome" or "New World syndrome" is considered to be causative in the rise of cardiovascular related morbidity and mortality in developing nations [10].

An even more alarming finding is that CMS is a disease entity that is not limited to adults. In many countries around the world, more pediatric patients are at risk of developing CMS due to reduced exercise and increased food consumption leading to the rise of childhood and teenage obesity. Although the data on young people is rather limited; CMS according to one report was present in 4.2% in adolescents [11].

### USA

In the US, according to the NCEP/ATP III definition, approximately 1 million adolescents or 4% of the American adolescent population have CMS. The 2003-2006 National Health Report states that approximately 34% of the US population over the age of 20 years meets the NCEP/ATP III criteria for CMS. A slight gender difference exists with 35.1% of male and 32.6% of female meeting such criteria. In those patients meeting the criteria the following risks and their incidences are reported: abdominal obesity (53%), hypertension (40%), and hyperglycemia (39%) [12]. Grundy has shown that obesity is critical force behind the progression of CMS 5. Others have affirmed such findings in a report that showed that 65% of obese males and 56.1% of obese females meet the criteria for CMS. Age is an independent factor in increasing the incidence of CMS with adults over 40 years of age are twice as likely to have CMS as those over 20 years of age [12].

In addition to the factors noted above, race and ethnicity play important roles in defining the incidence of CMS as related to gender [13]. According to the National Health and Nutrition Examination Studies (NHANES) the prevalence of CMS in females was higher than males in African American and Mexican American populations but the inverse is true in the non-Hispanic white population [13,14]. It is reported that 37.2% non-Hispanic white males satisfy the definition of CMS and are twice as likely to be diagnosed while 33.2% Mexican Americans and 25.3% non-Hispanic black males meet the criteria. Interestingly, there is no significant racial discrepancy in females. While non-Hispanic white males are at higher risk than females, non-Hispanic females are 1.5 less likely to develop CMS than non-Hispanic black and Mexican American females [12].

Among Americans of Middle Eastern (ME) origin 28% fulfilled the WHO definition and 23% met ATP III criteria. Females were more likely than males to have CMS, with higher prevalence of large waist circumference and low HDL. Hypertriglyceridemia and hyperglycaemia were more common in males [15]. Insulin resistance

in males and low HDL in females were associated with low 25-OH-D level [16]. Further, obesity and smoking were present more than in the general US population [17].

## Europe

It is estimated that one-fourth of the adult European population has CMS. However the prevalence is not uniform across geographic locations or age groups studied [5]. Subcomponents of the syndrome also differ between various EU countries. The prevalence of hypertension with metabolic syndrome was 36% in Germany, 11% in Spain, and 10% in Italy [18].

## Rest of world

The increased urbanization and decreased physical exercise in Africa and other world countries is believed to make major contribution to the rising prevalence of CMS [19] with higher rates of CMS in urban women as compared to rural women (5.9% vs.1.8%) according to WHO criteria.

In India's urban areas 22.9% of men and 39.9% of women ( $p < 0.001$ ) met the ATP-3 criteria for CMS [20].

In the Philippines, the prevalence of metabolic syndrome stands at 11.9% by NCEP/ATP III criteria and 14.5% by International Diabetes Federation (IDF) criteria. In such patients, low HDL-C was the most prevalent component of CMS noted in 60.2% of men and 80.9% of women affected [21].

In the general population of the Seychelles aged 25-64 years, the prevalence of CMS increased markedly with age, with a prevalence of 25.0%, in men and 24.6% in women according to the WHO definition. Diabetes, high blood pressure and adiposity were the criteria most commonly found [22].

In sub-Saharan Africa, an interesting association between Human Immunodeficiency Virus (HIV) infection and its treatment with two classes of Anti-Retroviral Therapy (ART); Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and Protease Inhibitors (PIs), have been made with increased prevalence of metabolic syndrome, diabetes and cardiovascular disease [23].

In Nigeria, a cross sectional adult population based study revealed an overall prevalence of CMS of 18.0% in the semi-urban community versus 10.0% in the rural community increasing to 34.7% and 24.7% respectively in the population with hypertension [24].

## Middle East and North Africa

In the Gulf Cooperative Council (GCC); Bahrain, Kuwait, Oman, Qatar, Saudi Arabia and the United Arab Emirates) the prevalence of CMS among men and women ranged from 20.7% to 37.2% (ATPIII definition) and from 29.6% to 36.2% (IDF definition). Obesity, Type 2 diabetes and related metabolic and cardiovascular diseases are highly prevalent in the GCC.

Socio-demographic status, age, female gender, higher income, lower educational attainment, urban residence in Saudi Arabia, and rural residence in the United Arab Emirates were commonly noted in CMS patients [25].

In Iran, by all definitions, the prevalence of the metabolic syndrome was higher in women, urban areas, and in the 55- to 64-year age-group compared to men, rural areas, and in other age-groups respectively. The metabolic syndrome was estimated to affect 11 million Iranians [26].

In the Tehran Lipid and Glucose Study (TLGS) published recently in *JACC*, 446 out of 6,215 adults with no prior CVD developed first CVD events during 8.1 years of follow up. In this study obese patients without diabetes or the IDF criteria for CMS were at an insignificant increased risk for CVD events as compared to a similar but non-obese cohort group (multivariate adjusted hazard ration of 1.07:1.0). In contrast, patients with diabetes or CMS at the start of study had a hazard ratio for CVD development of 2.1 in normal weights and 2.35 for obese respectively.

This study provides further evidence that BMI alone is a poor predictor of CVD events, while diabetes and CMS are strong predictors [27].

In the North African country of Tunisia, a study involving randomly selected population sample of 863 subjects aged  $\geq 40$  years of age, the prevalence of the metabolic syndrome according to the IDF criteria was 55.8% in women and 30.0% in men ( $P < 0.001$ ) with gender differences attributed primarily to higher rate of central obesity, lower HDL and to a lesser extent, hypertension [27].

In Turkey, the prevalence of CMS syndrome (ATP criteria) did not differ between urban (33.8%) and rural (33.9%) population, while it did between adult males (28%) and females (39.6%) [28].

In another study from Turkey on 15,468 adult Caucasians, age was a strong predictor for the presence of CMS with a prevalence of 15% in 30-39 years old cohort vs. 28% in a 50-59 years old cohort [29].

In a North Jordan study with data collected on a random sample of 1121 local citizens aged 25 years and older, CMS-ATP III criteria was noted 28.7% of men and 40.9% of women, with increasing prevalence in older subjects in both groups. Low HDL cholesterol was most common in men (62.7%) and central obesity most common in women (69.1%) [30].

In the Gulf country of Oman, a study on a random sample of 1,419 adult Omani citizens aged 20 years and older, ATP III defined CMS was present in 19.5% of men and 23.0% of women. Low HDL was present in 75.4% of CMS subjects followed by central obesity at 24.6%, with significant gender difference (women 44.3% and men 4.7%) [31].

In the Emirate National Diabetes Study on 4097 men and women aged  $\geq 20$ , 40% met the ATP III and IDF criteria for CMS. Larger abdominal waist and low HDL level were the two most common features present. In this study, age ( $\geq 40$  years), female gender, family history of diabetes, and rural location positively influenced the diagnosis [32].

In the West Bank of the Jordan River, hypertriglyceridemia, low HDL cholesterol, overall obesity, and smoking were significantly more prevalent in the urban adult population, whereas central obesity was more prevalent in the rural population [33].

In Qatar, the prevalence of CMS was 26.5% and 33.7% according to ATP III and IDF criteria ( $p < 0.001$ ). The prevalence increased with age and body mass index and decreased with higher education and physical activity [34].

In Lebanon, CMS was prevalent in 31.2% of population sample studied. Interestingly, men were significantly more likely to have the syndrome than women (OR=2.31, 95% CI=1.41-3.79). Abdominal obesity and low HDL-C contributed most to diagnosis [35].

In Saudi Arabia, the Coronary Artery Disease in Saudi Study (CADISS) conducted on 17,293 subjects revealed a CMS age-adjusted prevalence in males of 37%. Urban dwellers had significantly higher

syndrome prevalence at 44% compared to rural at 35.6%. Low HDL cholesterol made major contribution to the CMS diagnosis in Saudi Arabia [36].

In another Saudi study, prevalence of CMS among 10-18 year old children and adolescents was high at 9.4% with essentially comparable prevalence among boys (8.1%) and girls (10.3%). In those affected, low HDL was noted in 86% and hypertriglyceridemia in 33% [37].

### Pediatric population

In the US, the prevalence of CMS is 4.2% among adolescents of different ethnicities aged 12-19 years who participated in the NHANES III. Among obese adolescents, the incidence of CMS was greater than 30% [11].

In northern Mexico, the prevalence of CMS among children and adolescents aged 10-18 years (N=965), ranged from 3.8% to 7.8% according to the definition used [38].

In Kuwaiti children and adolescents ages 10-19 years, the IDF criteria put the prevalence at 14.8% while the ATP III criteria puts it at 9.1% [39].

In Iran, 2-14% of children and adolescent met at least one of the internationally accepted criteria for the CMS, with some of those children as young as 6 years of age [10].

Internationally, the overall prevalence of CMS in young people is on the rise. In the South Korean 12-19 year old population, the CMS prevalence increased significantly from 6.8 percent in 1998 to 9.2 percent in 2001 [10].

Jordanian children and adolescents aged 7-18 years, CMS prevalence was reported in 15% in obese subjects versus 3% in overweight ones and 0.3% in normal weights [39,40].

## Cardio Metabolic Syndrome Risk Factors and Associated Health Hazards

### Systemic arterial hypertension

Hypertension is defined as Systolic Blood Pressure (SBP)  $\geq$  140 mm Hg or Diastolic Blood Pressure (DBP)  $\geq$  90 mm Hg [41]. In the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) population study, high normal or frank hypertension was noted in greater than 80% of studied individuals who met the CMS criteria. Less common was visceral obesity, lipid abnormalities, and impaired fasting glucose [41].

The common association between hypertension, obesity and diabetes explains the high incidence of left ventricular dysfunction, arteriolar sclerosis and renal dysfunction in many of these patients afflicted with this syndrome. Common underlying pathophysiology being overly active sympathetic system, renal angiotensin and abnormal renal-sodium handling leads to endothelial cell dysfunction and secondary atherosclerotic changes [42].

Obesity is believed to play a pivotal role in the development and exacerbation of hypertension [43].

Systemic arterial hypertension in patients with CMS is a predictor of accelerated atherosclerosis in the carotid arteries [8]. The WHO puts high blood pressure as the leading cause of cardiovascular related mortality causing more than 7 million deaths every year worldwide.

In a landmark study conducted on 5.4 million subjects (1980-2008) and published in *Lancet*, it was reported that in the early phase

of the study mean systolic blood pressure was higher in high income countries as compared to mid and lower income countries. Toward the end period of the study, mean SBP dropped in high-income countries by 7.3 mmHg and increased by 3.3 mm Hg in lower income countries. It was estimated, with population growth, that the number of people in the world with uncontrolled hypertension has increased from 605 million in 1980 to 978 million in 2008. North America, Australasia, and Western Europe led the world in drop in blood pressure while countries in sub-regions of Oceania, East Africa, South Asia, Southeast Asia, and West Africa led in increased SBP.

The differing prevalence and changing blood pressure levels; with improvement in high income areas and worsening in low income areas are attributed to access to screening and utilization of anti-hypertensive therapy or lack of such [39].

### Disorders of lipid metabolism

According to the 2001 National Cholesterol Education Program/ATP III:

Dyslipidemia in the Cardiac Metabolic Syndrome is defined as:

- Serum triglycerides  $\geq$  150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides

- Serum HDL cholesterol  $<$ 40 mg/dL (1 mmol/L) in men and  $<$ 50 mg/dL (1.3 mmol/L) in women or drug treatment for low HDL-C [44].

Serum dyslipidemia with elevation in serum triglycerides and small LDL particles along with depressed levels of high-density lipoprotein (HDL) are recognized risk factors for atherosclerotic vascular changes, coronary artery diseases and cardiovascular events. It is estimated that this triad of dyslipidemia is cause to an estimated 4.4 million deaths every year worldwide [45].

Stress associated oxidization of lipoprotein is becoming recognized as a risk factor for CVD [46].

The InterHEART study, the largest worldwide epidemiological survey conducted in 50 countries on 50,000 patients showed that apolipoprotein B-100 to A-1 ratio is the strongest determinant of cardiovascular risk. Contributing to the metabolic syndrome risk factors, psychosocial stress, lack of exercise and smoking were major determinants of CHD [47].

The relation between diabetes and lipid disorder was alluded to a metabolic defect that leads to an overproduction of an excess level of very low density lipoprotein (VLDL) particles leading to accumulation of small LDL particles which in turn lead to atherosclerotic change development particularly in the conditions of depressed blood levels of HDL [48]. Recent work has established correlation between higher concentration of oxidized LDL and increased incidence of metabolic syndrome, as well as its sub-components of central obesity, glucose intolerance, and hypertriglyceridemia [49]. Patients who have the lipid triad were more likely to have other aspects of CMS more so than those with isolated elevated LDL-C [50,51].

In another landmark study conducted between 1980 and 2008 on 3 million adult participants in 199 countries the total cholesterol level increased with age and peaked around 50-60 years of age. Globally in 2008, standardized mean total cholesterol level was 4.64 mmol/L for men and 4.74 mmol/L for women. There was only slight decrease in cholesterol levels over the entire follow up period (less than 0.1 mmol/L per decade of follow up) starting in the 1980 and ending in 2008. Fasting total cholesterol concentrations remained highest in high-

income countries between 1980 and 2008 (5.62 and 5.19 mmol/L) as compared to middle-income countries (4.91 and 4.70) and low-income countries (4.46 and 4.20) respectively [52].

Western Europe and New Zealand had the highest cholesterol concentrations (6 mmol/L in men and women in the 1980s) as compared to the lowest level in the world noted in several African countries (4 mmol/L). North America ranked lower than Western Europe in cholesterol levels [52].

### Central obesity

The International Obesity Task Force (IOTF) estimates that globally, at least 1.1 billion adults are overweight, of whom 312 million are obese. In adults, the prevalence of obesity is estimated to have doubled or even tripled in less than two decades. More worrisome is that the rate of obesity in children has risen at an even faster rate. In certain parts of Italy and other countries up to 36% of children are overweight. This unchecked and rapid rise in children's obesity could very likely accentuate and accelerate the prevalence of diabetes and CVD [53].

Central obesity, or more specifically stated intra-abdominal obesity is increasingly believed to be key contributor to, and a major driving force to the elevated risks associated with CMS. This association may be directly linked to increased secretion of adipokines, a group of cytokines and cell to cell signaling proteins secreted by adipose tissue, in abdominally obese individuals, and indirectly, through increased insulin resistance [54]. In the San Antonio Heart Study, high waist-to-hip ratio and fasting insulin levels were significant predictors of developing metabolic syndrome. The odds ratio for developing metabolic syndrome was 2.8 in men and 5.9 in women with waist circumference above "Action Level 2-at 102 cm in men and 88 cm in women," compared with those with waist below "Action Level 1-at 94 cm in men and 80 cm in women" [55].

Abdominal obesity has become an accepted marker for 'dysfunctional adipose tissue' and is of central importance in clinical diagnosis of CMS [56]. Although central obesity is becoming a stronger marker for CMS, higher BMI remains, according to many authorities, a valid indicator of CMS [57]. The development of central obesity, as shown in serial studies conducted in the Mauritius and in Australia, preceded the clinical diagnosis of DM, SAH, and lipid disorder as well as the ultimate diagnosis of CMS [58].

In developing countries, the rising prevalence of obesity and cardio metabolic syndrome is becoming a leading cause for morbidity and mortality due to type 2 diabetes mellitus (T2DM) and cardiovascular disease [4]. The increasing age-related prevalence of CMS may be due in part to or occur in parallels with muscle mass reduction and reduced muscle oxidative capacity [59].

In another landmark study conducted on 9.1 million adults 20 years of age or older in 199 countries, the prevalence of obesity worldwide increased from 4.8% for men and 7.9% for women in 1980 to 9.8% in men and 13.8% in women in 2008. It is estimated that globally one third of the world population has BMI of 25 kg/m<sup>2</sup> or greater and that 205 million men and 297 million women are obese. Obesity was highest in North American men with a prevalence of 29.2%. Globally over the last 3 decades there has been steady increase in BMI in men and women by an average of 0.5 kg/m<sup>2</sup> or more per decade. The world largest BMI increase per decade of follow up occurred in Oceania (1.8 kg/m<sup>2</sup> per decade) followed by rises of 1.3–1.4 kg/m<sup>2</sup> in southern and central Latin America [60].

### Smoking

Although smoking is not part of the CMS, in one study on 4,542 men without metabolic syndrome at baseline and followed for an average of 3 years, the incidence of CMS was 8.0% in nonsmokers, 17.1% in ex-smokers, and 13.9% in sustained smokers (P<0.001) [61]. Heavy smokers (≥ 20 pack-years) were shown to have a significantly increased risk of developing CMS and lipid triad than were non-smokers or former smokers [62]. In a Japanese study on 5,697 men, abdominal CT scans tended to show reduction of Visceral Abdominal Fat (VAF) in ex-smokers the longer periods of smoking cessation were. Smoking cessation (≤14 years) led to reduction of odds ratio of having CMS by 35–55.6% [63]. Smoking more than 20 pack year was associated with a RR of 1.9 for developing CMS as compared to those who did not smoke [64]. During life time of smokers, a dose dependent association seems to exist for the further development of CMS [65].

CMS is more prevalent among current smokers and the two are associated with significantly greater risk of CVD (OR: 3.54). Alternatively, smoking cessation reduces CVD risk by approximately 37% in males with CMS. The OR for stroke was elevated to 2.41 in smokers with CMS [66]. In one study alcohol intake was associated with reduced prevalence of CMS among smokers; 19% in smokers who did not drink vs. 13% in smokers who also drank vs. 12% in drinkers but non-smokers vs. 7% who consumed neither [67].

### Lack of exercise

It has long been established that physical activity and exercise are associated with better overall health, well-being and reduced body fat. In a study on Leisure Time Sedentary Behavior (LTSB), the odds ratio for having CMS was 1.94 in men with 4 hr/day of LTSB as compared to those with one hour/day of LTSB. Four hours of LTSB was associated with 1.88 OR of increased waist dimension, 1.84 OR of reduced HDL and 1.55 OR for SAH. In women greater than four hours of LTSB was associated with an OR of 1.54 for CMS [68].

In the United States, excessive television watching (average 2.2 hrs/day) and non-working time computer use (1.7 hr./day) are accepted to have an association to the rising prevalence of CMS [69,70]. In a population-based study on 6,241, it was reported that with each hour/day of increased TV viewing, there was a 26% increase in CMS prevalence in women, while a total physical activity greater than 2.5 hrs/week was associated with reduction in the prevalence of insulin resistance and dyslipidemia in both genders and improvement in weight and BP control [71].

Early commitment to exercise in children and adolescents has been shown to reduce the future risk for the development of CMS. In a seven year follow up study, it was shown that lack of childhood exercise is associated with 6 times the risk of developing CMS during adolescent years. Thus, it is suggested that a longitudinal relationship exists between exercise and protection from future development of CMS [72].

Physical activity provided protective effects even in patients with CMS. In a study on 10,134 men and women aged 45-79 years at baseline, CHD event rate was lower in men with MS who were active and developed a lower CHD event rate than in men without MS but were inactive (11.5% vs. 12.8%). Similar association was noted for women. In other words inactivity was worse than CMS in causing cardiac events [73]. In another study on 2,920 men and women, age 70–79 years, without mobility limitations at baseline, the prevalence of metabolic syndrome was 38.6%. Those with CMS had an adjusted

Relative Risk (RR) of 1.46 for developing mobility limitations. The risk increased with higher central obesity and worse hyperglycemia [74,75].

## Cancer

In a study on 33,230 men aged 20-88 years and followed for 14 years, CMS was associated with a 56% greater age-adjusted risk in cancer mortality. Each of the components of CMS, central obesity, elevated TG, depressed HDL, DM increased cancer risk by: 28% (P=0.01); 25% (P=0.009); 25% (P=0.007); and 22% respectively. CMS had significant association for increased risk for lung (P<0.0001) and colorectal cancer (P=0.004) [76].

In the Metabolic syndrome and Cancer project (Me-Can) conducted in Norway, Austria, and Sweden with 274,126 men and 275,818 women participating, there was significant increase in risk among men for fatal cancer of the liver, gallbladder, rectal and respiratory tract cancer as well as increased incidence of thyroid cancer and multiple myeloma. Likewise in women, significant associations were found for incident and or fatal cancer secondary to pancreatic, urinary bladder, uterine, cervical, and stomach cancers [77].

In the Risk Factors and Life Expectancy Project conducted in Italy in which nine different large-scale epidemiological studies that were performed between 1978 and 1987 on a total of 62,285 men and women of 20-69 years of age, persons with CMS were found to have a nearly 3-fold increase in risk of dying from colon cancer compared to those without CMS [77]. In another report by Colangelo et al. on a total of 35,582 American men and women, the risk of colorectal cancer mortality was 67% greater in men and 29% greater in women who had 3-4 of the CMS risk factors components as compared with cohorts who did not have CMS [78].

In a 13.5 year follow up study on 163 patients, 29.8% of whom had CMS, the Rate Ratio for developing breast cancer was 1.92 and 2.6 in the presence of 1-2 CMS components and 3-5 components respectively [79]. Likewise in 16,209 men, in another study with 27 years follow-up, any 2 CMS risk factors created a RR of 1.23 (p<0.04) and any three had a RR 1.56 (p<0.00) for developing prostate cancer [80].

In patients diagnosed with hepatocellular carcinoma, CMS was more commonly present (37.1%) than infection with HBV or HCV, alcohol-related liver disease or non-specified cirrhosis (7.3%, 18.3%, 18.9%, and 14.7% respectively). CMS was present in 30% of patients with intra-hepatic cholangiocarcinoma, second only to cholelithiasis (32.3%) in this cancer group [81].

## Kidney disease

As expected, with its established cardiovascular effects, there is strong association between CMS and microalbuminuria and Chronic Kidney Disease (CKD). The Odds Ratio for CKD increases with the presence of greater CMS component numbers. Patients with 2,3,4 or 5 components had multivariate-adjusted odds ratios of 2.21, 3.38, 4.23 and 5.85 for CKD respectively [82].

## Psychosocial disorders

CMS has been associated with increased incidence of psychological and mood disorder such as schizophrenia and depression [83-86].

## Cardio metabolic syndrome and other diseases

CMS was more prevalent in women with polycystic ovarian disease [87], sleep apnea [88], nonalcoholic fatty liver disease (NAFLD) [81,89], in psoriasis [90,91] in patients with elevated serum Iron levels [92], erectile dysfunction [93] and in those with gallstone diseases [94].

## Pathophysiology

Pathophysiology of CMS is predicated upon a complex series of cellular and sub cellular events leading to increased insulin resistance, abnormal release of free fatty acids into the circulation, increased low density lipoproteins and triglycerides and decreased level of high density lipoproteins, reduced liver glucose production and altered muscle handling of glucose and increased non-infectious inflammatory markers; adipokines and cytokines [95,96]. Insulin plays a role in regulation of adipose tissue lipolysis which is main source for plasma free fatty acids. Insulin resistance is associated with obesity and excess visceral fat and it upregulate the rate of lipolysis. The increased release of free fatty acids stimulate further insulin resistance by suppressing cellular glucose uptake and glucose production [97,98]. These series of events lead to increased vasoconstriction, elevated fluid retention, and increased blood pressure in addition to exacerbation of abnormal deposits of fatty material in blood vessels, liver and muscle tissue.

## Genetic and environmental factors

Some of the cardiometabolic risk factors have clear heritability trends such as diabetes and dyslipidemia while obesity may have more environmental and behavior influence [99]. At risk individuals may be co-influenced by combination of inheritance as well as environmental factors that if not appropriately addressed would lead to exacerbation of the disease processes and worsening of the end outcomes of cardiovascular, renal and other effects of the disorder. However, Genetic studies have provided so far only limited evidence for a common genetic background of the cardiometabolic syndrome and there have been conflicting associations of genes and gene variants rather than consistently reproducible associations and linkages [100].

Animal studies showed that cardiometabolic syndrome significantly alters cardiac gene expression profile, which may be involved in development of cardiac pathologies in the presence of metabolic syndrome [101].

Nonetheless, the hope remains that understanding the genetic determinants of cardiometabolic syndrome will lead to early detection of new cases and possible preventive strategies. The crucial role of genetics in cardiometabolic syndrome has been hindered to some degree by the lack of a consistent definition of the syndrome, the varying combination of phenotypes even within a single definition, ethnic disparities, and gender influences. In fact the development of cardiometabolic syndrome represents an intricate interaction between genetic susceptibilities and environmental influences. In addition, epigenetic factors (DNA methylation and histone modification) are likely to play important roles in the pathogenesis of the cardiometabolic syndrome and they might mediate the effects of environmental exposures on the risk of development cardiometabolic syndrome [102].

Then there have been increasing number of reports suggesting that chronic exposure to and accumulation of endocrine disrupting chemicals (EDCs), especially so-called the persistent organic pollutants (POPs) within the body might be associated with metabolic Syndrome caused by mitochondrial dysfunction [103].

Accordingly, life style modification with diet, exercise, weight control, BMI reduction, smoke cessation and controlling pollution and mitochondrial toxins exposure become valuable positive environmental factors that could have positive effects on the long term benefits of patients with familial hyperlipidemia and at risk for developing diabetes.

## The controversy

Despite the above controversy exists on whether CMS is truly a syndrome triggered by insulin resistance leading to series of events causing obesity, hypertension, dyslipidemia and hyperglycemia or is it a cluster of coexisting risk factors that for one reason or another tend to appear in certain patient populations. This controversy is debated at length in the medical literature that goes beyond the scope of this article. For our purpose and from a clinical view point, we feel that the close association and prevalence of cardiovascular diseases, diabetes, hypertension, dyslipidemia, obesity and lack of exercise justify our attention to this problem irrespective of whether ultimately it is defined as a syndrome or as a cluster of risks.

## Non-pharmacological Methods to Prevent, Control or Reverse CMS

### Exercise

Experts agree that moderate exercise with a minimum of 30 minutes of moderate intensity physical activity such as fast walking on daily bases would reduce the incidence or intensity of CMS [104]. Simple measures such as reducing non-physical and sedentary activities; TV watching, video gaming or non-work related computer use to a limit of one hour per day, could potentially reduce the prevalence of CMS in the US adult population by 30-35% [70]. Sedentary living with low or no exercise leads to insulin resistance and secondary hyperinsulinemia, type II diabetes and the associated obesity, hypertension, hyperlipidemia and the ultimate common and undesired clinical outcome of atherosclerosis [105].

Regularly practiced exercise programs, particularly aerobic type training, have been shown to be effective not only in reducing weight but also to address, correct and reverse some of the principle defects of CMS by enhancing endothelial function, improve insulin signalling in fat and skeletal muscle, skeletal muscle biogenesis, and excitation-contraction coupling and in reducing blood glucose and lipogenesis in adipose tissue. Exercise, when regularly performed, reduces body weight and body fat content [106]. Regular exercise with cardio-respiratory fitness programs, in patients with CMS, has been shown to trend toward a reduction in the risks associated with all-cause mortality [107]. Diet and regular exercise have more favourable effects on reducing the development of diabetes mellitus than that of the oral anti-hyperglycemic agent metformin (58% versus 31%) [108].

Three year follow up of patients at risk for developing CMS revealed statistically significant rise in prevalence of the metabolic syndrome in non-exercise group (55% to 61%; $P=0.003$ ) and reduction of CMS prevalence in the exercise group (51% to 43%; $P<0.001$ ) [109].

The Finnish Diabetes Prevention Study performed on 522 middle-aged, overweight subjects with impaired glucose tolerance and followed for 3 years showed similar results of exercise related benefit, with better weight control and reduced manifestations and prevalence of CMS [110].

Absent diabetes, CVD or cancer at baseline, a Finland population-based study on 1069 middle-aged men, showed that those engaging in greater than 3 hours per week were 60% less likely to develop CMS [111].

### Diet-intake of fruits and vegetables

Various dietary regimens have been investigated for their potential roles and level of effectiveness in controlling or reversing CMS.

Mediterranean style diets have generated particular interest due to their intrinsic reliance on balanced use of whole grain, fruits and unsaturated fats. Studies have shown that Mediterranean Food Pattern (MFP) diet which is low in red meat, rich in grains and cereal, high in mono-unsaturated fat, and moderate on alcohol intake is associated with decrease in triglyceride level, better insulin sensitivity, and reduced insulin levels [112]. Mediterranean -style diets that are rich in grains, cereals, fruits, vegetables, and monounsaturated fats and low on red meat have been shown to be negatively associated with features of the metabolic syndrome [113].

The Framingham Offspring Study has shown a 38% reduction in prevalence of CMS among the highest consumers of cereal fiber compared those with lowest consumers [114]. In the SUN prospective cohort conducted on 5,360 participants and followed up for a median of 74 months, adherence to the MFP was associated with lowest incidence of CMS as compared to those with the least adherence who had higher incidence of CMS. Interestingly, higher MFP was more likely to occur in women, older subjects and physically active individuals [115].

The benefits of whole grain intake, common to the MFP may be due to the observed increased insulin sensitivity and reduced insulin level noted in subjects consuming such grains as part of their diet [116]. In a Swedish study (2,040 men and 2,959 women) white type bread intake was associated with a higher risk of hyperinsulinemia and dyslipidemia while the risk of central obesity and dyslipidemia was lowered with the fiber bread food pattern [117].

Increased intake of fruits and vegetables is associated with improved insulin sensitivity [118].

On the other hand, high red meat intake is strongly associated with high likelihood (4.7 fold increase in CMS, as shown in a Japanese-Brazilians men aged 40 -79 years) [119]. Long term follow up of high meat eaters (greater than 80 g/ day) was associated with higher systolic arterial BP than men eating less than 80 g per day [120]. The Oxford-EPIC cohort on more than 11,000 subjects, aged 20-79 years showed higher mean BP in subjects who were regular meat eaters as compared to those who were not [121].

Adherence to a Mediterranean-style dietary pattern was associated with a 20% lower risk of having the metabolic syndrome [122]. In a controlled Italian trial MFP type diet was associated with weight loss, reduction in inflammatory markers; IL-6, IL-7, IL-18, and CRP, and improved insulin sensitivity and endothelial function [123].

### Weight loss

Obesity, whether central or total body, being one of the hallmarks of CMS has been a target for reduction in patients with this syndrome with an aim to reduce total body weight by 7-19% in the first 6 months - year. To do so, participants would have to cut their daily caloric intake by 500-1000 calories<sup>1</sup>. Various diet regimens have become popular in the US for weight control and reduction. Of four studied in a randomized trial, Atkins diet (-4.7 kg) was superior to Zone (-1.6 kg), LEARN (-2.6 kg) and Ornish (-2.2 kg) in weight loss, decrease in BP among non-diabetic, and in premenopausal women with body mass index of 27-40 [124].

When addressing obesity, NCEP-ATP III recommends diet and exercise in order to reduce central obesity, abdominal girth and their associated insulin resistance since they are believed to be the root causes of the increased risks of CMS [44]. In patients with CMS, weight reduction (6.5%) caused by a very low calorie diet (VLCD) resulted in substantial and sustainable reductions of systolic (11.1 mmHg)

and diastolic (5.8 mmHg) blood pressure (BP), glucose (17 mg/dl), triglycerides (94 mg/dl) and total cholesterol (37 mg/dl) at 4 weeks and beyond (all  $p < 0.001$ ) [125].

New drug regimens have been introduced with promising potential for weight loss in overweight and obese patients. Orlistat, an FDA approved drug, binds intestinal fat and reduces its absorption, has been shown to reduce weight, LDL, fasting insulin and leptin and to a lesser extent reduce the level of CRP [126]. In addition to Orlistat, Sibutramine is another drug that has been shown to cause moderate weight loss in CMS patients has also received FDA approval [127,128]. A new generation drug, Rimonabant, a selective cannabinoid receptor-1 (CB1) antagonist, has been shown to reduce weight, improve circumference, increase HDL cholesterol levels, reduce LDL cholesterol, TG and reduce insulin resistance in patients suffering from CMS [129].

### Obesity surgery

In a clinical trial on patients meeting the ATP III criteria for CMS and subjected to two laparoscopic surgical procedures; Vertical Banded Gastroplasty or Gastric Bypass benefited with sustained weight loss one year post procedure. Both groups had significant weight loss of approximately 30% of their body weight, 11 mm Hg drop in systolic BP, 11.4 mm drop in diastolic BP, 46 mg/dL blood glucose drop, 196 mg/dL TG drop and 33 mg/dL total cholesterol drop.

Both procedures were equally effective in resolving CMS in over 95% of patients at one year [130].

### Control of systemic arterial hypertension

Beta blockers and diuretics have been shown to be effective in reducing cardiac event risks in hypertensive CMS patients. Treatment of elevated blood pressure in patients with CMS should take into account that the associated attention to weight loss and reduction in sodium dietary intake may have a direct effect on lowering systemic arterial hypertension and thus watchful attention to anti-hypertensive medication. Careful re-evaluation of the hypertension regimen should take place with weight loss [131].

### Lowering cholesterol

Total cholesterol reduction and improvement of HDL to total Cholesterol ratio have been targets for reducing incidence of CV events and cardiovascular related mortalities. In adult groups' of 40-49, 50-69, and 70-89 years, reduction in total cholesterol by 1 mmol/L reduced the HR for such events to 0.44, 0.66 and 0.83 respectively [132].

Statin therapy has an established value and benefit in the treatment of patients with CMS and type 2 diabetes. They are effective in reducing ASCVD events in such patients. Most trials have shown a CVD risk reduction in the range of 25-30% except the GREACE study showed a 50% CVD risk reduction [133]. Simvastatin, one of the more commonly used statins, has been shown to reduce the ASCVD relative risk by half. Simvastatin increases HDL-C and Apo A-1 level [51].

Statins beneficial role in reducing ASCVD risk may be explained in part on their ability to reduce apo-B-containing lipoproteins. Statins 30-40% reduction of apo-B levels is associated with a similar level of ASCVD risk reduction by 30-40%. These benefits have been noted in CMS and DM-II patients [134]. Non-statin therapy with fibrates and nicotinic acid, both triglyceride-lowering drugs, when added to statins have been reported to reduce ASVCD risks in CMS and type II DM patients by reducing TG levels and further reduction of non-HDL-C [50].

The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) in its 2002 report endorsed, in patients with documented atherogenic dyslipidemia, targeting elevated TG (>200 mg/dL) as part of a comprehensive lipid-lowering therapy after the goal for LDL-C has been attained. In other words, treatment strategy should focus initially on reducing LDL-C and once that is achieved, treatment should focus on bringing TG levels to below 200 mg/dL [135].

The ALLHAT, Antihypertensive Lipid Lowering Treatment to Prevent Heart Attack Trial, conducted on 42,000 patients receiving traditional less expensive diuretic (chlorthalidone) plus beta blocker versus newer generations more expensive, Calcium Channel blocker, ACE inhibitors and alpha adrenergic blockers (amlodipine, lisinopril, and doxazosin) and Pravastatin or "usual" cholesterol lowering therapy found cholesterol lowering benefits in both arms of the lipid lowering regimens. The CVD event reduction demonstrated in study was attributed to the added "safe" blood pressure control of the lesser expensive diuretic [136].

According to guidelines of the Adult Treatment Program III (ATP III) - National Cholesterol Education Program, LDL cholesterol, being the primary target of lipid-lowering therapy, should be reduced to <than 100 mg/dL in patients with demonstrated ASCVD or DM- II, as such without therapy they will have a 10 year >20% CHD risk in accordance with the Framingham Study. Reducing LDL-C to <than 130 mg/dL is an acceptable target for most other patients with CMS [131].

### Smoking cessation

It has long been established that smoking is associated with many negative health effects including atherosclerotic coronary artery disease, peripheral and cerebro-vascular disease in addition to increased risk of COPD, lung and esophageal cancer. Discontinuation of smoking has beneficial effects in reducing relative risk of mortality (36%) in CHD patients who quit compared with those who continued [137]. All-cause mortality was significantly lower in smokers encouraged to discontinue smoking as compared to control group not receiving aggressive and program-specific instructions. Thus, it was concluded that even modest level participation in smoking cessation provided important mortality reduction benefit [138]. Cigarette smoking exacerbates the already elevated risk of death in patients with CMS [139].

A ten-year randomized controlled trial of anti-smoking advice in 1445 male smokers, revealed over the course of the trial an 18% mortality reduction in coronary related death in the treatment group as compared to controls [140]. Active smoking is associated with a HR for risk of SCD of 2.47 as compared to non-smokers. Quitting smoking is associated with 36% RR for cardiac life threatening events (95% confidence interval, 1.46-4.19). Patients who had stopped smoking had no significant increase in the risk of SCD compared with patients who had never smoked (hazard ratio, 1.06; 95% confidence interval, 0.70-1.62) [137,141].

During period of follow up of smokers who had been hospitalized, irrespective of reason, and received intensive anti-smoking education, a 9.2% absolute mortality reduction as compared to those who did not was noted [142]. In the Coronary Artery Surgery Study (CASS), patients who continued smoking had 6 year RR mortality of 1.7 as compared to those with similar clinical conditions but did quit [143].

### Moderate alcohol intake

In a study on 8,125 participants in the Third National Health

and Nutrition Examination Survey, light (1-19 drinks per month) or moderate (20/month) alcohol intake were found to have OR for prevalence of CMS of 0.65 and 0.34 ( $p < 0.05$ ) respectively as compared to non-drinkers. The benefits were lost with greater than 20 alcoholic drinks per month. Alcohol consumption had inverse relations with insulin levels, TG levels and low HDL as well as central obesity [144].

In the 1998 Korean National Health and Nutrition Examination Survey conducted on 7,962 Korean adult men and women, the adjusted OR for CMS was  $< 0.8$  for those consuming  $< 15$  gm/day of alcohol. The benefit was lost with heavy alcohol intake [145]. Likewise in Mediterranean population studies, moderate alcohol consumption was associated with a lower prevalence of CMS and the associated DM, peripheral vascular and coronary disease, while heavy drinking led to loss of those benefits [146].

**Opposite effect:** The 1999–2002 National Health and Nutrition Examination Survey revealed that alcohol intake in excess of accepted dietary guidelines (one per drinking day for women and two for men) was associated with increased incidence of insulin resistance, elevated TG, central obesity and hypertension, thus losing any potential benefits associated with limited intake of alcohol [147,148].

In a Korean prospective cohort study of 3,833 males and females aged 40-69 years, a four year follow up revealed a dose response increase in relative risk of developing CMS. Very light drinkers (0.1-5 g/day) had a low RR of 1.13, while those at the upper end of the scale consuming  $> 30$  g/day had a RR of 1.63150.

### Stress management

The Whitehall II study conducted on 10,308 British civil service men and women, aged 35-55, and followed-up for an average of 14 years revealed that employees under chronic work-related stress had odds ratio of 2.25 to develop CMS than those without work related stress [149]. A Finnish study on a random sample of 3,407 women and men aged 18–78 years revealed stress, including financial related stress, to be associated with insulin resistance, obesity and elevated TG levels [150].

Among women, depressive symptoms, stressful life event(s), intense anger and feeling tense increase the likelihood of developing CMS (1.19-1.66) [151].

### Economics of CMS

The cost of care per individual patient treated for CMS, according to one study varies greatly between one country and another. In the European Community, CMS in German patients with hypertension are estimated to cost €24,427 million per year, €1,900 million in Spain and €4,877 million in Italy. The 2020 forecast for expenditure is an expected rise by 59%, 179% and 157% for the 3 countries respectively. The greater cost in Germany as compared to Spain and Italy is attributed to the differing prevalence of CMS in these 3 sample countries. In Germany, hypertensive patients with CMS account for over 60% of all hypertensive patients, while In Spain and Italy they account for a quarter of the hypertensive populations. Germany has one of the highest prevalence of central obesity in Europe. The treatment of SAH in CMS patients has been estimated to cost 2-3 times of that for non CMS patients [18].

Meta-analysis of 383,420 individuals with one or more components of CMS (hypertension, diabetes, lipid abnormalities, and obesity) revealed that the adjusted total annual health care cost per individual

patient suffering with an individual component of CMS was \$5,564 while those with 4 components incurred a cost of care of \$12,287 [152].

The Chicago Heart Association Detection Project in Industry, a prospective cohort of 6,582 adult participants (40% women), aged 33 to 64 years at study starting points initiated in 1967-1973 and followed until end of life at varying ages of 66 to 99 years revealed significant cost difference during the life-time of patients with and without CMS. In low risk CMS patients the annual cost of CVD care was \$10,367 lower than those with 4 or more components of CMS, while the annual cost of total charges was \$15,318 lower [153].

The increased societal proportion of patients 65 years and older from 12% in 2000 to an anticipated 20% in 2050, including those at high risk for CVD, is expected to significantly escalate the cost of care to new and unprecedented levels [154].

In the Diabetes Prevention Program, it was estimated that at-high-risk program participants in diabetes prevention and life-style modification compared to those at-high-risk but program non-participant had a reduced 30-year chances of getting diabetes from about 72% to 61%, for a serious complication from 38% to 30%, and diabetes-complications related death from 13.5% to 11.2%, respectively. The 30-year cost/quality-adjusted life-year (QALY) of implementing DPP- lifestyle modification program from a health plan perspective was calculated to be about \$143 000 [155]. DPP was superior in delaying the onset of DM-II by 11 years instead of 3 years for metformin group. The cost per QALY was approximately \$1100 for the lifestyle intervention and \$31,300 for the metformin intervention [156].

Obesity increased the annual cost of care for the treatment of SAH from \$3,911 to \$6,197, DM from \$6,006 to \$7,986 and for dyslipidaemia treatment from \$4,760 to \$7,636. In addition, diabetes, dyslipidemia, and hypertension resulted in greater missed work and reduced overall productivity per afflicted individual at \$1,217, \$763, \$622 respectively. The annual cost of care for obese persons rose from \$838 with zero RF to \$5490 with 1 RF, \$9385 with 2 RF and to 14-folds with 3 RF (\$12,190) respectively [157]. The direct medical cost of treating obese individuals in the US, based on 1996 and 1997 National Health Interview Survey, was estimated to have been \$51.5 billion and to have risen to \$74.3 billion in 2007 [158]. Collectively obese individuals were estimated to have missed 39.3 million work days at a 1994 dollar cost of \$4 billion [159].

In the US, CMS risk factored patients were 40–45% less likely to be employed, missed 179% more work days creating \$18.7 billion in lost productivity in 2007) [160,161]. In 2002 dollars both obesity and smoking each had a national medical related cost tag in excess of \$90 billion [162]. National medical expenditures attributable to Cardio Metabolic Risk Factors Clusters (CMRFC) in the U.S. totalled \$80 billion, of which \$27 billion was spent on prescription drugs. On average, individuals with CMRFC spent \$1,668 out-of-pocket, of which \$830 was for prescription drugs [162].

In a report on Framingham Heart Study patients ( $n=1,053$ ) estimated average level of risk for cardiovascular disease in the elderly was reported to be 19% higher than those for persons with no elevated CMS risk. Smoking had 16% higher Medicare costs than non-smoker's', Systolic blood pressure of 160 mmHg is associated with 11% higher Medicare costs, compared with a systolic blood pressure of 140 mmHg and total blood cholesterol level of 260 mg/dL is associated with 6% (95% CI=3%, 9%) higher Medicare costs, compared with a total blood cholesterol of 180 mg/dL [162-164].

## Conclusion

Cardio Metabolic Syndrome, with its increased risk for coronary artery disease, stroke, peripheral vascular disease, renal insufficiency, cancer and other co-morbid factors as well as an estimated world-wide cardiovascular-related mortality of 18 million per year makes it one of the greatest threats facing mankind today.

The wide prevalence of this syndrome and its component disease across all nations throughout the world; large and small, rich and poor, creates a unique opportunity for world leaders to take serious considerations to uniting their resources and collective efforts to create innovative ways to combat this health and economic destructive disease.

CMS, not only does not spare rich or poor nations, more so it does not spare children as it afflicts them just like it does adults.

CMS control may be possible with aggressive attention to the control of blood pressure, blood glucose, elevated blood lipids, weight reduction, exercise, and cessation of smoking.

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