Metabolic Syndrome in Coronary Artery and Occlusive Vascular Diseases: A Systematic Review

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Abstract

Nowadays, the metabolic syndrome (MS) is highly prevalent and is associated with risk factors for non-transmissible chronic diseases, such as type 2 diabetes mellitus, and coronary atherosclerotic disease. The objective of this systematic review is to describe the results of studies that investigated the association of MS with coronary artery disease and occlusive vascular diseases. We conducted a systematic review of data from original studies published between 1999 and 2008, written in English or Portuguese, using the databases Medline, Pubmed, Science Direct and HighWire Press. We included articles in which the diagnosis of MS was made by the criteria of the National Cholesterol Education Program - Adult Treatment Panel III (NCEP ATP III, 2001). We excluded studies with animals, supplementation studies, and those with oral or intravenous administration of any substance, as well as those of low methodological quality and those which had a heterogeneous initial sample. Despite the heterogeneity among studies, we observed that individuals with MS had a higher probability (risk = 2.13) of developing occlusive vascular diseases, coronary disease, diabetes and stroke. Lifestyle changes such as healthy eating habits, regular physical activity and cessation of smoking should be encouraged by health professionals to minimize the complications and morbidity associated with MS.

Introduction

The metabolic syndrome (MS) is characterized by metabolic changes related to abdominal obesity and insulin resistance. According to the NCEP ATP III[1] the diagnosis is made when there is occurrence of three or more of the following conditions: abdominal obesity (waist circumference above 102 cm in men and 88 cm in women), hypertriglyceridemia (greater than or equal to 150mg/dl); low concentrations of HDL cholesterol (less than 40mg/dl in males and less than 50mg/dl in females); systolic blood pressure above or equal to 130 mmHg, and diastolic blood pressure above 85 mmHg; and fasting hyperglycemia (greater than or equal to 110mg/dl).

There are other proposed criteria for this diagnosis, such as: the World Health Organization[2] (WHO) criteria, which use microalbuminuria and insulin resistance values; the European Group for the Study of Insulin Resistance[3] (EGIR) criteria, which consider insulin resistance as a mandatory risk factor associated with two or more risk factors; the American Heart Association/National Heart, Lung and Blood Institute[4] (AHA/NHLBI) criteria, which require the presence of three or more risk factors associated with coronary artery disease (CAD); and the International Diabetes Federation[5] (IDF) criteria, which use different values for waist circumference according to ethnicity. Despite the many similarities among the criteria, it is observed that the NCEP ATP III[1] criteria are the most used in the literature[4].

The global prevalence of MS is high—between 20% and 25%—and varies according to the diagnostic criteria used[6-9]. Regardless of the diagnostic criteria used, its prevalence is high in individuals with cardiovascular diseases (CVDs)[10]. There are no epidemiological studies to define its prevalence among Brazilians. However, in a regional study with 530 Japanese-Brazilians, a prevalence of 21%[11] was observed, and in a study conducted among the Spanish population of migrants and their descendants in Brazil, a prevalence of 35.6%[12] was observed.

MS is considered a risk factor as important as smoking habit for the development of occlusive vascular diseases and atherosclerotic diseases[1,9,13]. Therefore, the diagnosis and treatment of MS are extremely important because its prevalence is increasing worldwide.

Objective

To describe the results of clinical studies that investigated the impact of MS, diagnosed by the NCEP ATP III criteria[1], on the occurrence of CAD and occlusive vascular disease in individuals aged over 18 years.

Methods

The bibliographic research was conducted in 2008, and the following electronic databases were reviewed: Medline, Scielo, Pubmed, Science Direct and HighWire Press. A retrospective search was limited to indexed original scientific articles, such as clinical, randomized and non-randomized, transversal, prospective, cohort and population-based studies, involving humans aged 18 years or over, published between 2004 and 2008, written in English or Portuguese, with a combination of the following keywords: metabolic syndrome and coronary artery disease, metabolic syndrome and vascular

Key words

Metabolic syndrome; coronary artery disease; vascular diseases; meta-analysis.

diseases. Another strategy we used was the manual selection of references in the articles found.

The articles, originally identified by three different researchers, were selected by the initial search strategy using the following eligibility criteria: (1) articles published in the last four years; (2) articles written in English or Portuguese; (3) Clinical observational studies; (4) randomized or non-randomized studies; (5) studies with adult or elderly human subjects with MS; (6) clinical diagnosis of coronary artery disease and/or occlusive vascular diseases; and (7) studies showing as the main outcome the association of metabolic syndrome abnormalities with these diseases. We included articles that used the NCEP ATP III[1] criteria for the diagnosis of MS and those which used the NCEP ATP III[2] with another criteria for the diagnosis of MS, such as the WHO[2], the EGIR[3], the AHA/NHLBI[4], the IDF[5], or the American College of Endocrinology (ACE)[14] criteria. According to a criterion defined before the search, we excluded studies with animals, supplementation studies, studies with oral or intravenous administration of any substance, studies of low methodological quality and with heterogeneous sample, as well as studies whose information was available in more recent articles.

The selected studies had as the primary outcome the association of metabolic abnormalities of individuals with MS in the presence of coronary artery disease and/or occlusive vascular diseases[15]. The methodological quality of the studies was evaluated considering several aspects: specification of the inclusion and exclusion criteria for the study; random allocation of participants in the study; similarities between the study groups and control groups in the initial phase of the study; and statistical analysis report. Finally, these articles were reviewed to avoid inclusion of duplicated data.

Data Analysis

We used the program RevMan version 5.0 (The Cochrane Collaboration, Copenhagen) to analyze the data[16]. To assess the heterogeneity among studies, we used the Chi[2] test, with n - 1 degrees of freedom, in which "n" is the number of studies. We calculated the significant heterogeneity using the fixed-effects model. The inconsistency (I[2]) was calculated so as to verify the differences between studies that included groups of subjects with and without MS who had CAD or occlusive vascular disease, and an inconsistency rate of 25% was considered low, 50% was considered moderate, and greater than 75% was considered high[17].

Results

A total of 42 studies have been identified, of which 30 used the NCEP ATP III criterion (2001)[1] as the sole diagnostic criteron for MS, and 12 articles used other criteria for the diagnosis of MS besides the NCEP ATP III[1]. A total of 42 articles have been selected, as follows: 14 cohort studies[13,15-27], 12 cross-sectional studies[10,30-40], 8 prospective cohort studies[41-48], 2 observational studies[49,50], 2 prospective studies[51,52], 1 prospective observational study[53], 1 cross-sectional and population cohort study[54], 1 case-control study[55], and 1 longitudinal community-based study[56].

The largest number of publications were from the United States (n = 17), of which only 12 articles used the NCEP ATP III criterion (2001), followed by Italy (n = 6) and Holland (n = 3). Two articles were selected from each of the following countries: England, Greece, France, Canada, Finland, Turkey. From Japan, Argentina, Norway and Austria, only 1 article was selected from each.

The methodological characteristics, year of publication, country of origin, study population, study group, sample age range, criterion used for diagnosis of MS, type, duration and main results of these studies are presented in table 1.

Time duration of some studies was not mentioned. Among the studies in which these data were obtained we observed that no less than 6 months duration[28], was the largest follow-up time of 20 years[53].

The form of recruitment of participants was specified in all studies. The sample size ranged from 83 to 15,922 individuals; of the 42 studies selected, only 2 had lower total sample of 100 individuals; 83 and 87 individuals respectively[32,37].

Most studies included individuals of both genders (n = 36), with the exception of 5 studies that included only women[28,34,37,48,50], and 1 study that included only men in its sample[43]. Of the studies selected, 50% did not mention the sample age range, but 31 (73.8%) selected articles mentioned the mean age and the standard deviation of the study groups. Of the articles which did not mention the standard deviation of the study groups' age, 3 reported only the mean age of the groups, 3 mentioned only the age range of the groups, and 5 mentioned the mean age and the age range of the groups.

Discussion

MS stands out due to its high prevalence and because it represents an important set of cardiovascular risk factors, often associated with central fat deposition and insulin resistance[57]. From the epidemiological point of view, MS is responsible for an estimated increase in overall mortality by 1.5 times, and in mortality from CAD and occlusive vascular disease by 2.5 times[58]. Despite its relevance, in Brazil there is still a lack of data on its characteristics and no epidemiological studies to assess its relationship with increased morbidity from occlusive vascular disease and CAD. The study of MS has also been hampered by the lack of consensus on the criterion for its diagnosis and the cut-off points for its risk factors, with important implications in clinical practice and public health measures. In this review, we selected articles that used the NCEP ATP III[1] criterion for the diagnosis of MS, not only because this is a criterion that has easy applicability in clinical practice, but it is also widely used in scientific publications.

Individually, the components of MS are independent risk factors for the development of atherosclerotic cardiovascular disease[10,13,20,23,24,40,42]. The different criteria used for the diagnosis of MS are based on the principle that its risk factors may interact synergistically, or may increase the risk for CAD and atherosclerotic disease. Some studies have shown that the higher the number of components of MS in an individual,

Table 1 - Characteristics of studies which had metabolic syndrome, vascular occlusive disease and coronary artery disease as the main variables.

Bibliographical Reference / (Country)	Population / Gender	Study Groups	Age Range (years) / Mean and SD (years)	Criteria used for the diagnosis of MS	Type of Study / Duration	Main Results
Carminiti et al., (2008)[30].	Total (n = 286)	1- with MS	Total NM	NCEP ATP III (2001)	Cross-sectional	The prevalence of MS in the study was 48%, with no significant difference in prevalence between genders.
Italy	187 men	2- without MS	66.2 ± 10.6 anos		6 months	Patients with MS showed significant differences in BMI, which was greater in the group with MS, and a reduction in the concentration of HDL-c and in exercise time measured in minutes, which were more pronounced when compared to those of the group without MS.
	99 women		group 1: 67 ± 7 years			Patients with CAD and without MS achieved a higher rate of work during training, when compared to patients with MS. Patients with CAD and MS had lower functional recovery and lower recovery heart rate when compared to those without MS.
			group 2: 66 ± 8.6 years			The maximum exercise capacity achieved during the test effort was significantly lower in the group with MS when compared to the group without MS (7.6 ± 1.8 vs. 9.3 ± 1.2). MS was an independent predictor of a decrease in functional recovery only in female patients with CAD and MS (OR 1.31, 95% CI 1.20 to 1.62).
Hamburg et al., (2008)[15]	Total (n = 2123)	1- with MS (n = 762)	NM	NCEP ATP III (2001)	Cohort	The prevalence of MS was higher than 33% and showed association with increased thickness of the brachial artery and hyperemia. A relationship between MS and vasodilator dysfunction was observed. The HOMA
United States	917 men	2 without MS (n = 1361)	Total 59 ± 9 years		NM	index was significantly higher in the MS group when compared to the group without MS (p <0.0001), in similarity with the prevalence of insulin resistance, classified in the highest quartile of the HOMA index, was 51%
	1206 women		group 1: 61 ± 9 years			and 10% in the groups with and without MS, respectively.
			group 2: 58 ± 9 years			The higher the number of risk factors that characterize MS, the greater the vasodilator dysfunction in patients with MS (p <0.0001). These findings corroborate the hypothesis that MS and insulin resistance act upon the vascular function in order to influence the risk factors that characterize MS.

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Holvoet et al., (2008)[53]. United States	Total (n = 1889) 1058 women 831 men	5 quintiles according to oxidized LDL-c (U/L) and LDL-c (mg/dL) 1: (< 55.4 U/L e < 86 mg/dL) 2: (55.4 – 69.1 U/L e 86 -101 mg/dL) 3: (69.2-81.2 U/L e 102 - 118 mg/dL) 4: (81.3-97.3 U/L e 119-138mg/dL) 5: (≥ 97.4UL e ≥ 139mg/dL)	Total: NM group 1: 1° quintil LDL- oxidada: 40.1 years (NM) 1° quintil LDL-c: 40.2 years (NM) group 2: 2° quintil LDL- oxidada: 40.2 years (NM) - 2° quintil LDL-c: 40 years (NM) group 3: 3° quintil LDL- oxidada: 40.2 years (NM) - 3° quintil LDL-c: 40.3 years (NM) group 4: 4°quintil LDL- oxidada: 40.2 years (NM) 4° quintil LDL-c: 40.1 years (NM) group 5: 5° quintil LDL- oxidada: 40.4 years (NM) 5° quintil LDL-c: 40.5 years (NM)	NCEP ATP III (2001)	Population based prospective observational 20-year follow-up by CARDIA	MS was diagnosed in a 20-year follow-up in 12.9% of the participants. Among the study participants, oxidized LDL was positively associated with male gender, black ethnicity, higher BMI and obesity, C-reactive protein, and MS components. The OR for the dichotomous effect of the risk factors that characterize MS of the largest quintile versus the lowest quintile of oxidized LDL were 2.1 (95% CI, 1.2-3.6) for abdominal obesity; 2.4 (95% CI, 1.5-3.8) for fasting hyperglycemia.; and 2.1 (95% CI, 1.1-4.0) for hypertriglyceridemia. This study shows that an important marker of oxidative stress, measured by the highest quintile of oxidized LDL, was significantly associated with the incidence of MS, as well as abdominal obesity, hyperglycemia and hypertriglyceridemia. However, oxidized LDL showed no association with BP and HDL-c increase.

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Kasai et al., (2008)[31] Japan	Total (n = 656) 496 men 160 women	1- Men 2- Women	Total NM 64.8 ± 10.6 years group 1: 63.9 ± 10.1 years group 2: 67.6 ± 11.5 years	NCEP ATP III (2001) IDF (2006) AHA/ NHLBI (2005)	Cross-sectional 1 year	The prevalence of MS according to NCEP ATP III (2001) was 25.5%. There was no difference in the prevalence of MS between males and females. The Gensini score was used to assess the extent of coronary atherosclerosis, and a higher score was observed only in patients with MS diagnosed by the AHA/NHLBI (2005) criterion. There was no elevation of the Gensini score in patients with MS diagnosed by the NCEP ATP III (2001) and the IDF (2006) criterion; however, female patients with MS showed significant increase in the extent of CAD by all criteria for the diagnosis of MS. When assessing the risk of CAD progression, the association between MS and increased risk CAD progression was observed in both genders (OR 1.39, 95% CI 0.93 to 2.09, p = 0.111 in men and OR 2.32, 95% CI 1.11 to 4.86, p = 0.0256 in women) according to the NCEP ATP III (2001) criterion. Among the individual components of MS, increased BP, reduced concentration of HDL-c, and fasting hyperglycaemia showed association with CAD progression in males. The greater the number of risk factors of MS in an individual, the greater the risk of CAD progression according to coronary angiography.
Noto et al., (2008)[41] Italy	Total (n = 685) 307 men 378 women	1- with MS (n = 157) 2- without MS (n = 528)	Total 35 a 75 years NM 57 ± 11 years group 1: 59 ± 10 years group 2: 56 ± 11 years	NCEP ATP III (2001) IDF (2006)	Prospective Cohort 15-year follow-up by DCV	MS was significantly more prevalent in women (p <0.00001) (31.5%) than in men (12.4%). The clinical and biochemical data of the study groups have shown that patients with MS had higher concentrations of triglycerides, glucose, uric acid, fibrinogen; lower concentration of HDL-c; and higher BMI and WC. As for lifestyle, we observed that alcohol consumption was significantly higher in the MS group when compared to the group without MS. There were no differences between groups as to smoking habit. MS increased the risk for cardiovascular events by up to 1.9 (95% CI, 1.46-2.46). The risk rate for cardiovascular events among patients with and without MS was higher in patients with MS diagnosed by the NCEP ATP III (2001) criterion, when compared to the IDF (2006) criterion. According to the Cox model for risk assessment, the survival curves of patients with MS without glucose intolerance were not statistically different from those with DM and glucose intolerance. MS was a predictive factor for cardiovascular events, independently of the presence of glucose intolerance.

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Gomez Rosso et al., (2008)[32]. Argentina	Total (n = 87)	1- control without MS (n = 56) 2- with MS (n = 31) men (NM) women (NM)	Total: NM group 1: 43 ± 13 years group 2: 48 ± 9 years	NCEP ATP III (2001)	Cross-sectional NM	Patients with MS showed hypoadiponectinemia, increased activity of cell adhesion molecules (CETP), atherogenic lipoprotein and lipid profile, increased BMI, higher concentrations of insulin and higher HOMA index when compared to individuals in the control group. An important finding of this study was the observation of higher molecular leukocyte and endothelial adherence in patients with MS. The increase in CETP in patients with MS, which is crucial for the interaction of leukocytes with the endothelium, with subsequent migration of cells in the artery wall. These inflammatory changes are associated with hypoadiponectinemia, atherogenic lipid and lipoprotein profiles and chemical changes in the composition of HDL-C, accompanied by high concentrations of cholesterol and triglycerides — metabolic conditions present in patients with MS. These results indicate that the atherosclerotic plaque formation is stimulated and the cardiovascular risk is increased in patients with MS.
Ryan et al., (2008)[33]. United States	Total (n = 402 ancestors of Europeans) 227 men 175 women	1 - with abdominal obesity 2- non obese (by WC)	Total: NM group 1: 52 ± 9 years group 2: 50 ± 9 years	NCEP ATP III (2001) IDF (2006)	Cross-sectional NM	The results have shown a significant correlation between WC and BMI (p <0.001). The prevalence of MS was similar regardless of the WC classification used by the IDF criterion (2006) and the NCEP ATP III (2001) criterion. According to the NCEP ATP III (2001) criterion, the prevalence of MS was 40% in the general population, with 24% in individuals aged over 50 years, and 15% in those aged below 50 years. The risk factor for CVDs status was not significant when the volunteers were divided according to BMI and WC. The prevalence of MS or risk factors for CVDs did not vary according to the criteria used. However, BMI and WC effectively identified individuals at risk for CVDs.

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Wierzbicki, et al., (2008)[18]. England	Total (n= 400) individuals from Pakistan. Men and Women from Pakistan (NM)	1 - With CAD defined by 50% stenosis in one or more coronary artery by angiography. 2 - Control: the presence of symptoms similar to group 1 but without evidence of CAD by angiography.	Total: NM group 1: 51.2 ± 9.5 years group 2: 48.2 ± 9.5 years	NCEP ATP III (2001) IDF (2006)	Cohort With recruitment from 1998 to 2001.	The presence of MS as defined by the NCEP ATP III (2001) criterion was 44%. The incidence of CAD (65% vs. 34%, OR: 1.88, p <0.001) differed significantly between the groups with and without MS according to the IDF (2006) criterion, whereas little difference was observed when using the diagnostic criterion of the NCEP ATP III (2001) for the incidence of CAD (53 vs. 48%, p = 0.31). According to this criterion there was no relationship between MS and atheromatous plaque. In contrast, the presence of MS, by the IDF (2006) criteria, was associated with CAD and occlusive vascular disease.
Athyros et al., (2007)[10] Greece	Total (n = 9669) 4738 men 4931 women	1- with MS by NCEP ATP III criterion 2- with MS by IDF criterion 3- with MS by AHA/NHLBI criterion	Total: Over 18 years NM Total 46 ± 18 years group 1: 57 ± 13 years group 2: 56 ± 12 years group 3: 54 ± 16 years	NCEP ATP III (2001) IDF (2006) AHA/ NHLBI (2005)	Cross-sectional 1 year	There was a high prevalence of CVDs in subjects with MS, regardless of the diagnostic criterion used. However, this increase was pronounced when the NCEP ATP III criterion and the AHA/NHLBI criterion were applied. The diagnosis of MS and its treatment, either by LC or drugs, are vital to reduce mortality from CVDs in these individuals.

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Bellia et al., (2007)[49]. Italy	Total (n = 181) without DM 2. men e women NM	1 - with CVDs according to angiography (50% stenosis in at 1.2 or 3 coronary arteries) (60 men and 66 women) 2 - healthy subjects	Total: NM group 1: men aged 34 to 72 years women aged 36 to 70 years group 2: NM	NCEP ATP III (2001)	Observational NM	In most patients with heart disease the presence of MS and Hhcy has been observed. The prevalence of MS and Hhcy was 17.4% and 25.4% respectively. MS and Hhcy were present in 67.2% of patients. Hhcy and MS showed an association with CVDs (OR 2:53, 95% CI, 1.95-12.43 and OR 5.74, 95% CI, 2.67-12.34, respectively). According to data on prevalence, when Hhcy and MS were present in the same individual, there was an increased risk for the development of CVDs (13.11 CI 95% 5.27-32.06). These results suggest that Hhcy and MS may act synergistically in increasing the risk for CVDs. The study also suggests that MS and Hhcy work together in increasing the risk for CVDs more than the presence of two metabolic conditions that characterize MS. The study also suggests that a lifestyle change with emphasis on reducing body weight should be the therapy of choice for MS.
Empana et al., (2007)[42]. France	Total (n = 5585) without DM 2. 2124 men 3461 women	1 - with MS (n = 674) 2 - without MS (n = 4911)	Total: 65 a 85 years 73.5 ± 4.9 years group 1: 73.9 ± 4.9 years group 2: 73.5 ± 4.9 years	NCEP ATP III (2001)	Prospective cohort 3 years	The prevalence of MS was 12.1% among study participants. The most common components of MS in the study population were the elevation of BP (87%), increased WC (26.8%), hypertriglyceridemia (16%), reduced HDL-c (10.3%), and fasting hyperglycemia (3.8%). Patients with MS had higher risk for plaques in the carotid (33%), increased common carotid artery intima-media thickness (46%), and increased thickness of the lumen, (62%) even after adjustment for age, study center, gender, smoking habit, treatment for reduction of atherogenic lipid profile and history of CVDs. Individuals with MS had higher frequency of carotid atheromatous plaques (OR 1.30, 95% CI, 1.09 to 1.55), higher common carotid artery intima-media thickness (OR 1.81, 95% CI, 1.37 to 2.41), and increased thickness of the lumen (OR 2.17, 95% CI, 1.61 to 2.94) (top quintile) after adjustment for other cardiovascular risk factors. This association was observed in both genders and in subjects without prevalent CVDs. The elevation of BP was the main determinant of relationship between MS and the parameters measured in the carotid, especially the thickness of the lumen.

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Hajer et al., (2007)[19]. Norway	Total (n = 2169) 1692 men 477 women	1- First Tertile of hcy (9.8 ± 1.3 μmol/L) 2- Second Tertile of hcy (13.3 ± 1.0 μmol/L) 3- Third Tertile of hcy (20.4 ± 8.5 μmol/L)	Total: NM group 1: 56.8 ± 9.8 years group 2: 59.3 ± 9.8 years group 3: 62.8 ± 10.4 years	NCEP ATP III (2001)	Cohort 2.8-year follow-up of patients with vascular diseases	After adjustment for age, gender and creatinine clearance, the concentration of plasma Hcy was significantly higher in the group with MS (14.9 mmol/l, 95% CI, 14.5 - 15.3 mmol/l v 14.1 mmol/l, 95% CI: 13.8 to 14.5 mmol/l, p = 0.002). Its concentration increased according to the number of risk factors for MS. From 0 to 5 risk factors for MS, the concentration of plasma Hcy increased from 12.7 to 15.9 mmol/L, p = 0.001). In the study general population, it was observed that patients with plasma concentrations of Hcy in the highest tertile showed a 40% increase in risk of new cardiovascular events when compared to those in the lowest concentrations of Hcy tertile (OR 1.4, 95% CI, 0.9 - 2.2). For patients in the intermediate tertile, the increased risk was 10% (OR 1.1, 95% CI, 0.7 to 1.7). Although we observed that individuals with MS had high concentrations of plasma Hcy, these concentrations showed no association with increased risk for the development of new cardiovascular events. In contrast, Hhcy was associated with increased risk for the development of CVDs in patients without MS.
Lapointe et al., (2007)[34]. Canada	Total (n = 124 postmenopausal women)	1 - without MS (n = 78) 2 - with MS (n = 37)	Total: 46 to 68 years NM group 1: 56.4 ± 4.5 years group 2: 57.6 ± 4.0 years	NCEP ATP III (2001)	Cross-sectional NM	The concentration of circulating oxidized LDL had a significant association with some risk factors that characterize MS, such as hypertriglyceridemia (r = 0.48, p <0.0001), low concentration of HDL-c (r = -0.34, p = 0.0001). and fasting hyperglycemia (r = 0.21, p = 0.02). The duration of menopause was also positively associated with the concentration of oxidized LDL. The concentrations of LDL-c, triglycerides and apolipoprotein B showed a positive association with oxidized LDL, whereas there was a negative association with the concentration of HDL-c. The concentrations of LDL-apolipoprotein B (p <0.0001) and triglycerides (p = 0.0006) are the strongest predictors of the concentration of oxidized LDL after multivariate analysis. These predictors are significantly higher in women with MS. Women with MS had significantly increased concentrations of circulating oxidized LDL (79.5 ± 28.3 U / L) when compared to women without DM (64.2 ± 19.9 U / L). As for the number of MS components, women who had 5 MS components had significantly increased concentrations of oxidized LDL (99.5 ± 31.3) when compared to women with 3 MS components(72.9 ± 28 . 1) (p = 0.004).

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Lorenzo et al., (2007)[20].	Total (n = 2559)	1- non Hispanic white men	Total: 25 to 64 years NM	IDF (2006)	Population based cohort	The prevalence of MS was higher by the IDF (2006) criterion, followed by the NCEP ATP III criterion (2001), and the WHO (1999) criterion, respectively. According to the NCEP ATP III (2001) criterion, the prevalence of MS was 24% (from 20.2 to 28.4%) and 29.6% (26.6 -32.8%) in non-Hispanic men and in Mexican-American whites, respectively, and 16.8% (13.8 - 20, 4%) and 30.9% (28.3 - 33.6%) in non-Hispanic white women and in Mexican-American women, respectively. In men and women aged 45 or 55 years, respectively, MS had a higher predictive value for CVDs. The risk for DM 2 in patients with MS was high (OR 6.90, 95% CI, 4.97 to 9.58). In men aged 45 years or over the risk of CVDs from MS was comparable to the multiple risk factor (two or more) in 10 years of CAD (10 to 20%) in women. MS showed increased risk for CVDs, independently of age, gender, ethnicity, history of CVDs and relatives with cardiovascular events, DM 2, non-HDL cholesterol and smoking habit (OR 2.00, 95% CI, 1.33 to 3.01). However, MS increases the CVD risk in individuals who do not have diabetes 2 and CVDs.
United States	1088 men	2- Mexican-American men	group 1: 44 ± 11 years	NCEP ATP III (2001)	7.4-year follow-up	
	1471 women	3- non Hispanic white women	group 2: 43 ± 12 years	WHO (1999)		
		4 - Mexican-American women	group 3: 44 ± 11 years			
			group 4: 43 ± 11 years			

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Skoumas et al., (2007)[54]. Greece	Total (n = 706) Caucasian subjects with familial combined hyperlipidemia) 463 men 243 women + 2282 Volunteers of Attica, a Greek population-based study consisting of: 1128 men 1154 women	1- with MS 2- with DM 2 (gly/cemia higher than 125mg/dL) 3- without MS	Total: Over 20 years NM group 1: 50.3 ± 10.9 years group 2: 52.2 ± 10.8 years group 3: 46.6 ± 9.2 years Participants in the Attica study NM	NCEP ATP III (2001)	Cross-sectional and Population based cohort NM	MS had a higher prevalence in the group with familial combined hyperlipidemia (41.8% — 63% in men and 37% in women) when compared to volunteers in the Attica study (19.8% — 62.69% in men and 37.3% in women). A prevalence of CAD was observed as follows: 15.2% in the group with MS, 11.1% in the group without DM, and 26.5% in the group with DM 2. We found higher concentrations of apolipoprotein B, the main component of the LDL-c particle, in the group with MS (178mg/dL) when compared to the group without MS (170.8 mg/dL); and lower concentrations of apolipoprotein A, the main protein component of the HDL-c particle, in the group with MS (139.8 mg/dL) when compared to the group without MS (146 mg/dL). However, we only found an association of CAD with DM 2.
Stein et al., (2007)[21]. United States	Total (n = 185) Non diabetic African Americans 61 men 124 women	1- Men 2- Women	Total: 28 to 51 years Total: 39.8 ± 3.7 years group 1: 39.7 ± 3.9 years group 2: 39.8 ± 3.6 years	NCEP ATP III (2001)	Cohort 5.3 years	The prevalence of MS was 19%. Of all volunteers in the study, 55% were obese, and 38% had high BP. Men and women had similar mean general characteristics, except BMI and body fat percentage, which were higher in women. Even with higher BMI, the mean concentrations of triglycerides and HDL-c were similar between groups. Although there were no statistical differences between the groups, insulin sensitivity was lower in women. There were significant associations of these concentrations with all other MS components, as well as a positive correlation of HDL-c with insulin sensitivity. The diagnosis of MS may be clinically useful to detect patients with probable insulin resistance and reduction of risks for CVDs.

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Bibliographical Reference /(Country)	Population / Gender	Study Groups	Age Range (years) / Mean and SD (years)	Criteria used for the diagnosis of MS	Type of Study / Duration	Main Results
Wang et al., (2007)[51]. Finland	Total (n = 1025 non diabetic Finnish subjectswith MS)	Divided according to 6 different criteria for the diagnosis of MS	Total: 65 to 74 years NM	IDF (2006) AHA/ NHLBI (2005) ACE (2003) NCEP ATP III (2001) WHO (1999) EGIR (1999)	Population based prospective 13 years	The prevalence of MS is highly variable according to different criteria, ranging from 22.5% by the EGIR (1999) criterion, to 66.4% by the ACE (2003) criterion. According to the NCEP ATP III (2001) criterion, the prevalence of MS was 42.7%, and it was a predictive factor for mortality from CVDs. The MS risk rate for CVDs was 1.43, 95% CI: 1.12-1.84. After using the Cox model for multivariate analysis, male gender, older age, previous AMI, current smoking habit, physical inactivity, HBP, and the urinary albumin to creatinine ratio showed association with CAD, CVDs and all causes of mortality. The hypercholesterolemia was associated with mortality from CAD, and fasting insulin was associated with mortality from CVDs. None of the methods for the diagnosis of MS used in the study was able to predict the overall mortality after adjustment for confounding factors, however, MS should be considered a marker for CVD risk, but no higher than its components evaluated individually.
Brevetti et al., (2006)[35]. Italy	Total (n = 154) 115 men 39 women	1 - with MS (n = 79) 2 - without MS (n = 75)	Total: NM group 1: 67.1 ± 9.0 years group 2: 67.5 ± 10.0 years	NCEP ATP III (2001)	Cross-sectional 1.3 years	The prevalence of MS was 51.9% — 42.7% in men, and 74.3% in women (p <0.01). Individuals with median ankle/brachial index lower than of 0.64 were more susceptible to MS when compared to those with less severe PAD (63.9% versus 42.8%, p <0.02). The association between low ankle/ brachial index was maintained after adjustment for age and gender (OR 2.19, 95% CI, 1.03 to 4.68). When patients with PAD with and without MS were compared we found a higher BMI in subjects with MS (28.2 [25.6 to 29.8 kg/m2] versus 26.1 [24.2 to 27.7 kg / m2], p <0.01) and higher concentrations of C-reactive protein (3.9 [1.6 to 7.6] mg / L versus 2.0 [1.1 to 3.7] mg / L, p <0.02). The occurrence of an AMI was documented in 58.2% of patients with MS and in 37.5% of patients without MS (p <0.01). In multivariate analysis, MS was significantly associated with anterior AMI as well as with the ankle/ brachial index (OR 2.15, 95% CI, 1.06 to 4.38).

Bibliographical Reference / (Country)	Population / Gender	Study Groups	Age Range (years) / Mean and SD (years)	Criteria used for the diagnosis of MS	Type of Study / Duration	Main Results
Eberly et al., (2006)[22]. United States	Total (n = 10950) 4588 men with MS 6362 men without MS	1- with MS 2- without MS	Total: 35 to 57 years (recruitment) NM group 1: 53 ± 5.9 years (6th annual visit) group 2: 53 ± 5.9 years (6th annual visit)	NCEP ATP III (2001)	Population based cohort 18.4-year follow-up of patients with CVDs.	The prevalence of MS was 41.8% among the study participants. In the group with MS 57.9% had 3 criteria for diagnosis of MS, 32.3% had 4 criteria, and 9.9% had all 5 criteria. The most frequent MS components were high BP, hypertriglyceridemia, and low HDL-c concentration. In the MS group hyperglycaemia and lower concentration of HDL-c were predictive of CVD mortality, followed by increased BMI, increased BP and hypertriglyceridemia. In contrast, HDL-c was not a predictive factor in men without MS. The risk of CVD mortality was three times higher in individuals who had all 5 risk factors for the diagnosis of MS when compared to individuals who did not have any of the components for the diagnosis of MS.
Iribarren et al., (2006)[55]. United States	Total (n = 786) 308 men 478 women	1 - with CAD (AMI, angina with ≥ 50% stenosis of the artery or coronary revascularization) 2 - without CAD	Total: NM Men aged over 46 years Women aged over 56 years group 1: 45.8 ± 6.5 years Group 2: 45.2 ± 5.6 years	NCEP ATP III (2001) AHA/ NHLBI (2005)	Control case 4-year period of diagnostic verification.	In the group with CAD, 59% had a AMI, 26% underwent a revascularization procedure, and 16% were diagnosed with angina. The presence of MS was significantly higher in patients with CAD. According to the NCEP ATP III (2001) criterion, the prevalence of MS in the group with CAD and without DM 2 was 32%, and in those with DM 2 it was 26%. The CAD patients had greater elevation of SBP, higher prevalence of hypertension, hypertriglyceridemia, hyperglycemia, hyperinsulinemia, increased C-reactive protein and HOMA index. MS resulted in high risk of early onset of CAD, but the prognosis was not different when the patient had MS or one or more of its risk factors.

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Bibliographical Reference /(Country)	Population / Gender	Study Groups	Age Range (years) / Mean and SD (years)	Criteria used for the diagnosis of MS	Type of Study / Duration	Main Results
Kurl et al., (2006)[43]. Finland	Total (n = 1131 men with no history of DM 2 and CVDs at baseline)	1- with MS (n = 114) 2- without MS (n = 1017)	Total: NM group 1: 51.8 ± 5.8 years group 2: 51.6 ± 5.8 years	NCEP ATP III (2001) WHO (1999)	Population based prospective cohort 14.3-year follow-up	At the beginning of the monitoring only 9% of men had MS according to the NCEP ATP III (2001) criterion. MS was associated with all types of stroke (OR 2.05, 95% CI, 1.03 to 4.11, p = 0.042), and 65 strokes occurred during monitoring, of which 47 were ischemic. It was observed that MS was associated with increased risk of ischemic type of stroke (OR 2.39, 95% CI, 1.17 to 4.89, p = 0.016) adjusted for changes in the test effort, LDL-c, fibrinogen, intake of saturated fatty acids and white blood cells.
Langenberg et al., (2006)[44]. United States	Total (n = 2118) 977 men 1141 women	1- men 2- women	Total: 40 to 94 years group 1: 71.1 years NM group 2: 70 years NM	NCEP ATP III (2001)	Prospective cohort 4 years	The prevalence of MS was approximately 17% in men and 15% in women. The gender and age adjusted risk rate for CAD and MS was 1.65 (1.25-2.18), 95%, p <0.001, and this association was not altered significantly after adjustment for gender, age or DM 2 for each of the interactions. The adjustments for adiponectin, leptin, and ghrelin exerted little influence on the association between MS and CVD mortality; the maximum change in the rate of risk was for adiponectin, that influenced this association by 15.4%. The association of CAD and MS was reduced by 25% after adjustment for interleukin 6, and by 35% after adjustment for C-reactive protein. The CVD mortality increased linearly with higher concentrations of interleukin 6 and C-reactive protein. We found no evidence of the influence of MS according to different concentrations of hormones that are involved with fat or inflammatory markers. However, IL 6 and C-reactive protein showed a significant linear relationship with CVD mortality after analysis adjusted for age and gender (p <0.001 for both).

Bibliographical Reference / (Country)	Population / Gender	Study Groups	Age Range (years) / Mean and SD (years)	Criteria used for the diagnosis of MS	Type of Study / Duration	Main Results
Meigs et al., (2006)[56]. United States	Total (n = 2902) 1302 men 1600 women	By BMI and with or without MS: 1 - ≤25 kg/m2 2 - 25 to 29.9 kg/m2 3 - ≥30 kg/m2	Total: NM group 1: with MS: 59 years (NM) without MS: 52 years (NM) group 2: with MS: 57 years (NM) without MS: 53 years (NM) group 3: with MS: 56 years (NM) without MS: 52 years (NM)	NCEP ATP III (2001)	Community based longitudinal 11-year follow-up	The prevalence of MS in normal individuals was 7% and the relative risk for DM 2 was OR 3.97 (95% CI, 1,35-11,6), and for CVDs it was 3.01 (CI 95 % 1.68 -5.41). In obese subjects the prevalence of MS was 63%, and the relative risk for DM 2 increased significantly: 10.3 (95% CI, 5.44 -19.5); and for CVDs by 2.13 (95% CI, 1.43-3.18). The results were similar in the analysis of the BMI and the categories of insulin resistance. The set of risk factors for MS and insulin resistance resulted in a high risk for DM 2 and CVDs associated mainly with BMI increase.
Najarian et al., (2006)[45]. United States	Total (n = 2097) 1059 men 1038 women	1- men 2- women	Total: 50 to 81 years; 59.1 ± 6.1 years group 1: 59.1 ± 6.2 years group 2: 59.1 ± 6.0 years	NCEP ATP III (2001)	Prospective cohort 14 years	The prevalence of MS was 30.3% in men and 24.7% of women. After a 14-year follow-up, 75 men and 55 women suffered the first stroke. The relative risk of stroke in individuals with DM 2 and MS was high (3.28, 95% CI, 1.82 to 5.92), higher than that of any other MS risk factor evaluated individually. In this study, MS had a high prevalence and was considered an independent risk factor for stroke in individuals without diabetes. However, prevention and control of MS and its risk factors may help in reducing the incidence of stroke.

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Bibliographical Reference / (Country)	Population / Gender	Study Groups	Age Range (years) / Mean and SD (years)	Criteria used for the diagnosis of MS	Type of Study / Duration	Main Results
Pollex et al., (2006)[23]. Canada	Total (n = 166) 66 men 100 women	1- with MS (n = 73) 2- without MS (n = 93)	Total: NM group 1: 42.2 ± 1.6 years group 2: 34.8 ± 1.6 years	NCEP ATP III (2001)	Cohort NM	The prevalence of MS in the study population was 44%. The group with MS showed significantly increased concentrations of total cholesterol and BMI when compared to the group without MS (p <0.0001). In this study, the carotid intima-media layer thickness and the total volume of platelets were evaluated in volunteers with and without MS. Only after adjustment for age and gender, statistical differences in the carotid artery intima-media layer thickness were observed between the groups with and without MS, 818 ± 18µm and 746 ± 20µm, respectively (p = 0.039). The greater the number of risk factors that characterize MS the greater the increase in the carotid intima-media layer thickness.
Tavil et al., (2006)[36]. Turkey	Total (n = 345) 143 men 202 women	1- with MS (n = 205) 2- without MS (n = 140)	Total: NM group 1: 53 ± 7 years group 2: 52 ± 6 years	NCEP ATP III (2001)	Cross-sectional NM	Patients with MS showed a significant increase in the values of the mean platelet volume, an indicator of the pathophysiological process of CAD, when compared to the control group. MS was associated with mean platelet volume independently of WC, fasting hyperglycemia and number of MS components. In addition, the values of mean platelet volume were significantly different in individuals with MS and with DAC. When patients with MS were divided into 3 subgroups, according to the severity of CAD, a progressive increase in the mean platelet volume was observed from the first to the last group. However, when the groups with and without MS were evaluated, no significant difference was observed when the severity of CAD was considered.

Bibliographical Reference / (Country)	Population / Gender	Study Groups	Age Range (years) / Mean and SD (years)	Criteria used for the diagnosis of MS	Type of Study / Duration	Main Results
Dekker et al., (2005)[13]. Netherland	Total (n = 1364) 615 men 749 women	1 - women with MS according to NCEP ATP III (2001) 2 - women with MS according to other criteria than the NCEP 3 - men with MS according to criteria of NCEP ATP III (2001) 4 - men with MS according to other criteria than the NCEP ATP III (2001).	Total: 50 to 75 years; NM group 1: 62.8 ± 7.6 years; group 2: 60.3 ± 7.2 years; group 3: 62.2 ± 7.2 years; group 4: 60.4 ± 7.1 years.	ACE (2003) NCEP ATP III (2001) WHO (1999) EGIR (1999)	Population based cohort 10-year follow-up of patients with morbidity and mortality from DCVs (Hoorn study).	According to the NCEP ATP III (2001) criterion, MS had a prevalence of 19% in men, and 26% in women, in this study, and it was associated with increased risk of morbidity and mortality from CVDs (twice more). Regardless of the method used for the diagnosis of MS, this study showed increased risk for fatal and nonfatal CVDs. The presence of only 1 or 2 risk factors was also associated with CVDs, particularly in women. When the number of risk factors was included as a linear variable, the rate of fatal and nonfatal risk for CVDs rose from 1.29 and 1.11 to 1.50 for each risk factor present in both genders.
Dursunoglu et al., (2005)[37]. Turkey	83 women	1- women with MS (n = 53) 2- healthy women (n = 30)	Total: NM group 1: 53.1 ± 6.9 years group 2: 52.8 ± 6.3 years	NCEP ATP III (2001)	Cross-sectional NM	Women with MS had mild left ventricular diastolic dysfunction in comparison to healthy women. MS was associated with greater left ventricular dysfunction and diastolic dysfunction with an increase in the overall index of myocardial performance. The presence of global dysfunction in patients with MS can lead to the development of heart failure. These findings suggest an association of MS with CVDs.
Girman et al., (2005)[24]. Netherland	Total (n = 1391) 631 men 760 women	1- men 2- women	Total: NM group 1: 60.8 ± 7.1 years group 2: 60.9 ± 7.3 years	NCEP ATP III (2001)	Population based cohort 11-year follow-up of morbidity and mortality from CVDs	MS had a positive association with CVDs; however, the higher the number of MS risk factors in these individuals, the higher was the risk for CVDs. In men, the risk was greater in the presence of 3 or more MS components, whereas in women the presence of 2 or more MS components increased the risk for CVDs. After a binary regression analysis of the cross-sectional data, this study suggests that MS components can not be equally weighted, and it also suggests that among the components of MS, the concentrations of triglycerides and HDL-c are the MS components with the greatest individual weight for CVDs, by the NCEP ATP III criterion (2001).

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Bibliographical Reference / (Country)	Population / Gender	Study Groups	Age Range (years) / Mean and SD (years)	Criteria used for the diagnosis of MS	Type of Study / Duration	Main Results
Iglseder et al., (2005)[46]. Austria	Total (n = 1588) 1001 men 587 women	1- control (men / women) 2- with MS (men / women)	Total: NM men: 40 to 55 years women: 50 to 65 years group 1: men: 49.1 ± 5.4 years women: 56.4 ± 4.2 years group 2: men: 50.5 ± 5.2 years women: 57.1± 4.7 years	NCEP ATP III (2001)	Prospective cohort NM	The extent of atherosclerotic plaques in the artery and the carotid intima-media layer thickness showed significant elevation in volunteers with MS. In logistic regression, after adjustment for age, BMI, smoking habit and LDL-c, the odds ratio for greater carotid intima-media layer thickness remained significant in women (OR, 2.26, 95% CI, 1.31 to 3.89, p = 0.003), but not in men (OR, 1.16, 95% CI, 0.77 to 1.15). The development of atherosclerosis was more pronounced in women when compared to that observed in men. Among the risk factors that characterize MS, HDL-c was the factor with the greater impact on the mean carotid intimal layer thickness in men, whereas blood glucose had greater impact in women.
Montalcini et al., (2005)[50]. Italy	Total (n = 265 menopausal women)	1- women with MS (n = 55) 2- women without MS (n = 210)	Total: 45 to 75 years NM group 1: 58.6 ± 7.5 years group 2: 56.4 ± 7.6 years	NCEP ATP III (2001)	Observational	MS was strongly associated with atherosclerosis in the extracranial carotid artery, a marker of CVDs in the study population. In women with normal concentrations of LDL-c or with borderline values, the incidence of atherosclerosis was significantly lower when compared to women with elevated LDL-c. The high plasma concentration of LDL-C was independently associated with atherosclerosis in the extracranial carotid artery (p = 0.026) among women with MS.

Bibliographical Reference / (Country)	Population / Gender	Study Groups	Age Range (years) / Mean and SD (years)	Criteria used for the diagnosis of MS	Type of Study / Duration	Main Results
Rutter et al., (2005)[25]. England	Total (n = 2898)	1- men	Total: 26 to 82 years 54 years (NM)	NCEP ATP III (2001)	Population based cohort 7 years	MS and insulin resistance have been individually related to CVDs, and age and gender-adjusted risk rates were 2.0 (95% CI, 1.5 to 2.6, p = 0.0001) for MS; and 1.9 (95% CI, 1.2 to 2.9, p = 0.003) for insulin resistance, according to the HOMA index. In this study, MS was considered as an independent predictor for CVDs.
	1302 men	2- women	group 1 NM			
	1596 women		group 2 NM			
Wilson et al., (2005)[26]. United States	Total (n = 3323)	1- men with MS	Total: 22 to 81 years NM	NCEP ATP III (2001)	Cohort 8 years	The prevalence of MS was 26.8% in men and 16.6% in women. In men, the relative risk of MS adjusted for age and for CVDs was 2.88 (95% CI, 1.99 to 4.16); for CAD it was 2.54 (95% CI, 1.62 to 3, 98); and for DM 2 it was 6.92 (95% CI, 4.47 to 10.81). In women, risk rates were lower for CVDs (2.25, 95% CI, 1.31 to 3.88) and CAD (1.54, 95% CI, 0.68 to 3.53), and similar for DM 2 (6.90, 95% CI, 4.34 to 10.94). The estimated risk of MS associated with CVDs, CAD and DM 2 were 34%, 29% and 62% in men, and 16%, 8%, 47% in women, respectively. MS showed association with CVDs and DM 2 in both genders.
	1524 men	2- men without MS	group 1: 53 ± 9 years;			
	1774 women	3- women with MS	group 2: 49 ± 10 years;			
		4- women without MS	group 3: 55 ± 9 years			
			group 4: 50 ± 10 years			
Zeller et al., (2005)[52]. France	Total (n = 633)	1- with MS (n = 290)	Total: NM	NCEP ATP III (2001)	Prospective NM	The prevalence of MS was 46%, and it was more prevalent in women. The rate of in-hospital mortality was higher in patients with MS, and also the incidence of severe heart failure without hospital death. Among the risk factors that characterize MS, hypertriglyceridaemia was the most critical in severe heart failure.
	475 men	2- without MS (n = 343)	group 1: 57 to 70 years 70 years NM			
	158 women		group 2: 52 to 74 years 63 years NM			

Bibliographical Reference /(Country)	Population / Gender	Study Groups	Age Range (years) / Mean and SD (years)	Criteria used for the diagnosis of MS	Type of Study / Duration	Main Results
Chinali et al., (2004)[27], United States	Total (n = 1434)	1- men with MS (n = 197)	Total: 45 to 74 years NM	NCEP ATP III (2001)	Cohort	Patients with MS had a larger left ventricle and greater vessel wall thickness, left atrial diameter (all with p ≤ 0.01) and higher prevalence of left ventricular hypertrophy (p <0.001). In the multiple regression model, only increased BP and WC showed association with the larger diameter of the left ventricle, and only increased BP showed association with higher left ventricular mass and left ventricular hypertrophy (p <0.001 for both).
	598 men	2- men without MS (n = 401)	group 1: 59 ± 5.1 years;		NM	
	838 women	3- women with MS (n = 415)	group 2: 58 ± 4.4 years;			
		4- women without MS (n = 423)	group 3: 60.2 ± 7.9 years			
			group 4: 58.6 ± 8.0 years			

Bibliographical Reference / (Country)	Population / Gender	Study Groups	Age Range (years) / Mean and SD (years)	Criteria used for the diagnosis of MS	Type of Study / Duration	Main Results
Gorter et al., (2004)[38].	Total (n = 1117)	1 - with CAD (n = 527)	Total: 18 a 80 years 60 ± 10 years	NCEP ATP III (2001)	Cross-sectional	The prevalence of MS in the study was 46% compared with 58% in patients with PAD, 41% in those with CAD, 43% in patients with CVDs and 47% in those with AAA.
Netherland	883 men	2 - with CVDs (n = 258)	group 1: men: (n = 434; 57 ± 9 years) women: (n = 93; 61 ± 9 years)		NM	In general, women had a higher prevalence of MS, 56%, when compared to men, 43%.
	234 women	3 - with PAD (n = 232)	group 2: men: (n = 192; 61 ± 11 years) women: (n = 66; 60 ± 11 years)			The increased BP component of MS was more frequently observed in volunteers, especially in women (78%). There was a high prevalence of MS in patients with manifestations of atherosclerotic vascular disease. Patients with MS had more often a medical history of vascular disease, particularly patients with CVDs and PAD.
		4 - with AAA (n = 100)	group 3: men: (n = 163; 58 ± 10 years) women: (n = 69; 59 ± 11 years)			
			group 4: men: (n = 94; 69 ± 6 years) women: (n = 6; 66 ± 10 years)			

Bibliographical Reference / (Country)	Population / Gender	Study Groups	Age Range (years) / Mean and SD (years)	Criteria used for the diagnosis of MS	Type of Study / Duration	Main Results
Kip et al., (2004)[28], United States	Total (n = 780 women with coronary angiography to evaluate suspected myocardial ischemia)	According To BMI. 1 - eutrophic (BMI <24.9 kg/m2, n = 184) 2 - overweight (BMI ≥ 25 and ≤ 29.9 kg/m2, n = 269) 3 - obese (BMI ≥ 30 kg/m2, n = 327) According to the presence of MS a - with MS (n = 451) b-MS without (n = 329)	Total: 21 to 86 years NM group 1: 59 ± 13 years group 2: 58 ± 11 years group 3: 57 ± 11 years a - NM b - NM	NCEP ATP III (2001)	Cohort 3 years	The prevalence of CAD (stenosis ≥ 50%) and the 3-year risk for CVD were evaluated and compared with BMI and MS. MS and BMI were strongly associated, but only MS had a significant association with CAD. MS increased the risk of mortality by 2.01, 95% CI, 1.26 to 3.20 and increased the risk of nonfatal MI, stroke, and CHF by 1.88 (95% CI, 1.38 to 2.57). Concentrations of C-reactive protein were more strongly associated with MS than BMI, but were not independently associated with risk of mortality after 3 years. However, MS can predict future risk of CVD in women.

Bibliographical Reference / (Country)	Population / Gender	Study Groups	Age Range (years) / Mean and SD (years)	Criteria used for the diagnosis of MS	Type of Study / Duration	Main Results
Malik et al., (2004)[47].	Total (n = 6255)	1 - 2872 patients without MS, without DM 2 and without CVDs.	Total: 30 to 74 years 49.7 years NM	NCEP ATP III (2001)	Prospective cohort	The presence of DM 2 was predictive for all-cause mortality. Those individuals with one or two metabolic abnormalities of MS had an increased risk for CAD and CVD mortality.
United States	2852 men		group 1 : 45.6 years NM		Mean follow-up period of 13-years by NHANES III	Above all, MS was a strong predictor for CAD, CVD, and all-cause mortality when compared to its individual components.
	3403 women	2- 1698 patients with MS	group 2: 51.4 years NM			
		3- 1178 patients with MS and without DM 2	group 3: 50.0 years NM			
		4- 520 patients with DM 2	group 4: 55.4 years NM			
		5- 1679 patients with CVDs	group 5: 50.6 years NM			
		6 - 1398 patients with pre- existing CVDs	group 6: 50.8 years NM			
		7 - 281 patients with DM 2 and CVDs	group 7 : 61.7 years NM			

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Bibliographical Reference / (Country)	Population / Gender	Study Groups	Age Range (years) / Mean and SD (years)	Criteria used for the diagnosis of MS	Type of Study / Duration	Main Results
Marroquin et al., (2004)[48]. United States	Total (n = 755 women)	1 - with MS 2 - without MS 3 - with DM 2	Total: NM group 1: 60 years NM group 2: 57 years NM group 3: 59 years NM	NCEP ATP III (2001)	Prospective cohort 4 years	When women with MS were compared to women without MS, a lower survival rate was observed after 4 years, in the group with MS. A 4-year absence of events (nonfatal MI, stroke or CHF) was 87.8% in the group with DM and 93.5% in the group without MS (p = 0.003). Women with MS and with angiographically significant CAD had a higher risk of developing cardiovascular events when compared to women without MS (OR 4.93, 95% CI, 1.02 to 23.76, p = 0.05).
Ninomiya et al., (2004)[29]. United States	Total (n = 15922) men and women NM	1 - MS with and without cardiovascular event (n = 14,824) 2 - with MS with AMI/stroke (n = 1098) 3 - with MS and AMI (n = 752) 4 - with MS and stroke (n = 464)	Total: 20 a 89 years NM group 1: 46.7 years NM group 2: 68.5 years NM group 3: 68.2 years NM group 4: 43.5 years NM	NCEP ATP III (2001) "Full Syndrome": patients with at least 3 of these five conditions: insulin resistance, abdominal obesity (by WC) hypertriglyceridemia, low HDL-c and HBP.	Cohort 6-year follow-up by NHANES III	After multivariate analysis, MS showed a significant relationship with AMI (OR, 2.01, 95% CI, 1.53 to 2.64), stroke (OR, 2.16; 95% CI, 1.48 to 3.16) and MI/stroke (OR, 2.05, 95% CI, 1.64 to 2.57). Among the risk factors for MS, insulin resistance (OR, 1.30, 95% CI, 1.03 to 1.66), low HDL-c (OR, 1.35; 95% CI, 1.05 to 1.74), HBP (OR, 1.44, 95% CI, 1.00 to 2.08) and hypertriglyceridemia (OR, 1.66; 95% CI 1.20 to 2.30) showed independent and significant relationship with MI/stroke. The results indicate strong and consistent association of MS with the prevalence of AMI and stroke.

Bibliographical Reference / (Country)	Population / Gender	Study Groups	Age Range (years) / Mean and SD (years)	Criteria used for the diagnosis of MS	Type of Study / Duration	Main Results
Reilly et al., (2004)[39]. United States	Total (n = 840) 443 men 397 women	1 - Men 2 - Women Both groups were composed of non-diabetic subjects with family history of premature CVDs and risks associated with coronary artery calcification.	Total: 40 to 57 years NM group 1: 40 to 51 years NM group 2: 44 to 57 years	NCEP ATP III (2001) WHO (1999)	Cross-sectional NM	MS, BP increase, WC and the HOMA index showed an association with coronary artery calcification in age-adjusted analysis. MS was an important marker of subclinical coronary atherosclerosis in non-diabetic subjects with family history of premature CVDs.
Scuteri et al. (2004)[40]. Italy	Total (n = 471) 200 men 271 women	1 - with MS (n = 95) 2 - without MS (n = 376)	Total: NM 59 ± 16 years group 1: 62 ± 15 years group 2: 57 ± 17 years	NCEP ATP III (2001)	Cross-sectional NM	MS resulted in increased thickness by more than 16% and increased stiffness by more than 32% in the carotid intima media layer (p <0.0001 for both) when compared to individuals in the control group. The multiple regression model that included age, gender, smoking habit, LDL-c, and MS risk factors showed MS as an independent factor for increasing the thickness (p = 0.002) and stiffness (p = 0.012) of the carotid intima media layer. MS components may synergistically interact to have an impact on the vascular thickness and stiffness of the coronary artery.

MS - metabolic syndrome; NCEP ATP III - National Cholesterol Education Program Adult Treatment Panel III (2001); WHO - World Health Organization (1999); EGIR - European Group for the Study of Insulin Resistance (1999); ACE - American College of Endocrinology (2003); IDF - International Diabetes Federation (2006); AHA/NHLBI - American Heart Association/National Heart, Lung and Blood Institute (2005); NM - not mentioned; CVDs - cardiovascular diseases; CAD - coronary artery disease; PAD - peripheral arterial disease; AAA - abdominal aortic aneurysm; BP - blood pressure; SBP - systolic blood pressure; HBP - high blood pressure; AMI - acute myocardial infarction; CVA - stroke; WC - waist circumference; DM 2 - diabetes mellitus Type 2; CHF - congestive heart failure; LC - lifestyle change; Hcy - homocysteine; Hhcy - hyperhomocysteinemia; OR - odds ratio; CI - confidence interval; SD - standard deviation; n - number of individuals.

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Study or Subgroup	Positivo Events	Positivo Total	Negativo Events	Negativo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Athyros 2007	1279	2369	1041	7300	16.2%	3.79 [3.54, 4.05]
Brevetti 2006	27	79	15	75	0.5%	1.71 [0.99, 2.95]
Carminit 2008	98	137	95	149	2.9%	1.12 [0.96, 1.32]
Eberly 2006	1532	4588	1431	6362	38.2%	1.48 [1.40, 1.58]
Empana2007	84	674	383	4911	2.9%	1.60 [1.28, 2.00]
Hajer 2007	195	886	172	1174	4.7%	1.50 [1.25, 1.81]
Iribarren 2006	209	267	184	519	4.0%	2.21 [1.93, 2.52]
Kasai 2008	98	167	232	489	3.8%	1.24 [1.06, 1.45]
Kip 2004	209	259	81	329	2.3%	3.28 [2.69, 4.00]
Langenberg 2006	65	337	228	1781	2.3%	1.51 [1.17, 1.93]
Malik 2004	336	1698	132	4557	2.3%	6.83 [5.63, 8.29]
Marroquin 2004	142	430	85	325	3.1%	1.26 [1.01, 1.58]
Meigs 2006	123	804	135	2098	2.4%	2.38 [1.89, 2.99]
Montalcini 2005	44	55	84	210	1.1%	2.00 [1.62, 2.47]
Najarian 2006	156	577	76	1520	1.3%	5.41 [4.18, 6.99]
Noto 2008	27	157	44	528	0.6%	2.06 [1.32, 3.22]
Reilly 2004	60	208	19	632	0.3%	9.60 [5.87, 15.69]
Scuteri 2004	38	95	113	376	1.5%	1.33 [1.00, 1.78]
Skoumas 2007	45	295	46	411	1.2%	1.36 [0.93, 2.00]
Wierzbicki 2008	93	176	105	224	2.9%	1.13 [0.93, 1.37]
Wilson l 2005	103	613	91	2710	1.1%	5.00 [3.83, 6.54]
Zeller 2005	114	290	152	343	4.4%	0.89 [0.74, 1.07]
Total (95% CI)		**15161**		**37023**	**100.0%**	**2.13 [2.06, 2.20]**
Total events	5077		4944			

Heterogeneity: Chi² = 993.73, df = 21 (P < 0.00001); I² = 98%
Test for overall effect: Z = 45.45 (P < 0.00001)

Risk Ratio M-H, Fixed, 95% CI: scale 0.001 0.1 1 10 1000 — Favours experimental Favours control
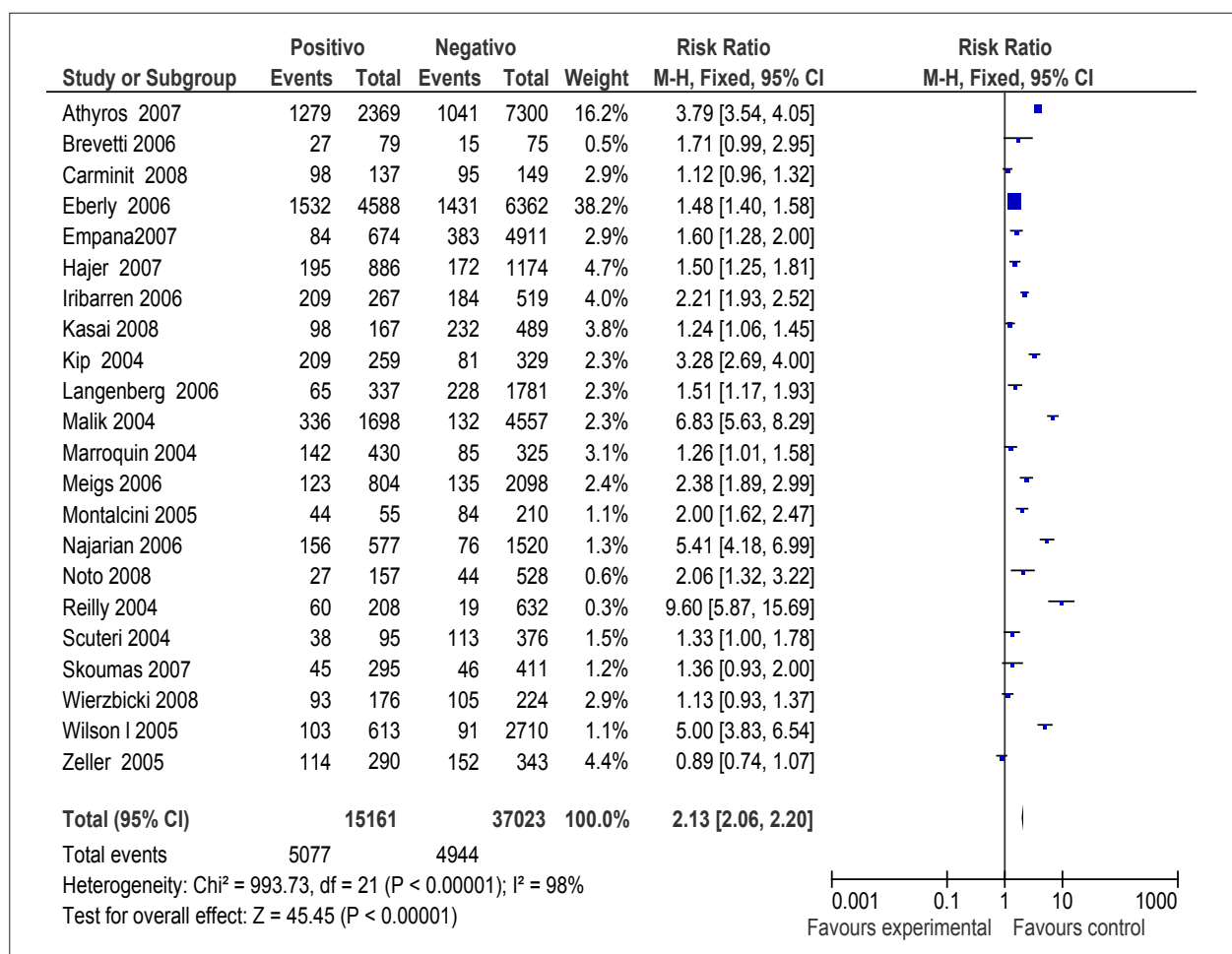
Fig. 1 - *Heterogeneity and risk for development of vascular occlusive or coronary disease or stroke: comparison between the groups with and without MS.*

the greater the risk for or the severity of the MS-related disease[15,23,24,31].

The studies selected in this systematic review have shown an association of MS with the development of or mortality from CVD[10,13,20,24,25,29,41,47,49,51], CAD[22,28,31,44,47,55], diabetes mellitus 2 (DM 2)[20,26,56], and stroke (CVA)[29,43,45]. Some studies also suggest that individuals with MS have higher mortality from CVDs[20,41] and higher prevalence of CVA[43], regardless of the presence of glucose intolerance or DM 2[20,41,45].

Among the selected articles, 4 assessed the mean carotid intima-media thickness[23, 40,42,46], showing an association of MS with the atherothrombotic process; increased blood pressure[42], decreased concentration of HDL-C in men, and fasting hyperglycemia in women[46] were the most important components of MS in this association. It was reported that the higher the number of risk factors that characterize MS the greater the increase in the mean carotid intima-media thickness[23].

Some studies report the association of MS with higher body mass index (BMI)[28,30,56]. It has been also highlighted that individuals with MS have higher BMI and higher risk of DM 2 and CVDs[56]. Other studies showed the association

of MS with increased cell adhesion molecular activity, hypoadiponectinemia[32], and increased concentrations of oxidized LDL[34,53] and C-reactive protein[35,55]. One study reports that there has been an increase of CVD mortality in patients with MS and increased concentration of C-reactive protein[44].

Studies that evaluated the concentration of circulating oxidized LDL showed that among the risk factors that characterize MS, those with a higher association with the oxidation of the lipoprotein are fasting hyperglycemia, hypertriglyceridemia, low concentration of HDL-C, and abdominal obesity[34,53]. The adjusted odds ratio for the dichotomous effect of risk factors that characterize MS, versus the fifth quintile of oxidized LDL were 2.1 (95% CI, 1.2 to 3.6) for abdominal obesity; 2.4 (95% CI, 1.5 to 3.8) for fasting hyperglycemia; and 2.1 (95% CI, 1.1 to 4.0) for hypertriglyceridemia[53].

Although hyperhomocysteinemia (Hhcy) is a known marker of occlusive vascular diseases, there are still few studies that assess its association with MS. Among the studies selected in this systematic review, only two assessed the association of Hhcy with MS and its risk factors[19,49]. A recent study showed that plasma homocysteine (Hcy) was higher in subjects with

MS when compared to those without MS. Its concentration also increased according to the number of risk factors that characterize MS. When individuals without MS were compared with those who had all five risk factors for MS, the plasma concentration of Hcy increased significantly (from 12.7 mmol/L to 15.9 mmol/L)[19]. These findings suggest that MS and Hhcy have synergistic effect in increasing the risk for occlusive vascular diseases.

Of the studies selected in this review, one showed no association of MS with CAD[54], and another showed no association of MS with atheromatous plaque formation[18]. However, most studies showed the association of MS and some of its components with higher risk of general morbidity and mortality and of CVD. Therefore, we must highlight the importance of taking measures for the prevention and control of MS and its associated risk factors, in order to reduce CVDs, the main cause of mortality worldwide.

The heterogeneity among the selected studies is shown in Figure 1, and probably is a result of the different markers used for the diagnosis of vascular disease or coronary occlusion. An increased probability (risk = 2.13) of individuals with MS to develop vascular or coronary disease has also been demonstrated. But the results remain contradictory and require further research to obtain more consistent results.

The adoption, preferably from childhood and by the entire population, of healthy lifestyles, such as a balanced diet and the regular practice of physical activity is a basic component of MS prevention. The benefits of the regular practice of physical exercise on the reduction of CVD morbidity have been shown in scientific literature as part of a lifestyle change (LC), along with a reduction in body fat deposition, especially in the abdominal region, which represents an important risk factor for the diagnosis of MS. The success of the intervention in the control and treatment of MS is closely related to the LC, and non-drug therapy is the treatment of choice, with a food plan for reducing body weight associated with physical activity[57], besides cessation of smoking and excessive alcohol consumption and reduction of stress. These behavioral changes may improve the quality of life and life expectancy of individuals with MS[11].

Although LC is essential for the prevention and treatment of MS, only one study revealed in its conclusion the importance of LC for the reduction of CVD and occlusive vascular disease morbidity and mortality in patients with MS[10]. Another study showed only the importance of the prevention of MS and its risk factors for the reduction in the incidence of stroke[29].

Therefore, in order to achieve the remission of MS and reduce the prevalence of CAD and occlusive vascular diseases, health professionals should encourage healthy eating habits, such as reducing the consumption of saturated and hydrogenated fats, increasing the consumption of fruits, vegetables, fiber, and whole grains, and lifestyle changes such as cessation of smoking, which is fundamental and a priority measure in preventing the individual components of MS. Moreover, the practice of aerobic physical exercise promotes a reduction in plasma triglycerides and an increase in HDL-c concentration[58], which are important risk factors that characterize MS.

A balanced diet combined with a regular practice of physical activity can promote body weight reduction and improve the clinical condition of patients with MS, with a reduction in the risks and the morbidity and mortality from CVD and vascular occlusive disease.

Conclusion

The aggregation of MS components and the pathophysiological mechanisms that trigger it are not yet fully understood. But despite controversial literature reports and heterogeneity among studies, the impact of MS on the occurrence of CAD and occlusive vascular diseases has been observed in this review.

Therefore, it is critical that randomized studies be conducted, using more reliable markers for the diagnosis of CAD and occlusive vascular diseases, and thus generating more consistent results.

Acknowledgments

References

1. 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: 2486-97.

2. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications: report of WHO a Consultation. Part 1: diagnosis and classification of diabetes mellitus. Genebra; 1999.

3. 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 (5): 442-3.

4. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005; 112 (17): 2735-52.

5. International Diabetes Federation (IDF). The IDF consensus worldwide definition of the metabolic syndrome. 2006 [Acessed on 2007 Oct 10]. Available from: http://www.idf.org/webdata/docs/Meta_syndrome_definition.pdf.

6. Eckel RH, Grundy SM, Zimmet PZ: The metabolic syndrome. Lancet. 2005; 365: 1415-28.

7. Grundy SM. Metabolic syndrome: what is it and how should I treat it? ACC Curr J Rev. 2003; 12 (3): 37-40.

8. Resnick HE, Jones K, Ruotolo G, Jain AK, Henderson J, Lu W, et al. Insulin resistance, the metabolic syndrome, and risk of incident cardiovascular disease in nondiabetic american indians. Diabetes Care. 2003; 26: 861-7.

9. Pereira MA, Jacobs DRJ, Van Horn L, Slattery ML, Kartashov AI, Ludwig DS. Dairy consumption, obesity, and the insulin resistance syndrome in young adults: the Cardia Study. JAMA. 2002; 287 (16): 2081-9.

10. Athyros VG, Ganotakis ES, Elisaf MS, Liberopoulos EN, Goudevenos IA, Karagiannis A. Prevalence of vascular disease in metabolic syndrome using three proposed definitions. Int J Cardiol. 2007; 117: 204-10.

11. Lerário DDG, Gimeno SG, Franco LJ, Iunes M, Ferreira SRG. Excesso de peso e gordura abdominal para a síndrome metabólica em nipo-brasileiros. Rev Saude Publica. 2002; 36 (1): 4-11.

12. Pousada JMDC, Britto MMS, Cruz T, Lima ML, Lessa I, Lemaire DC, et al. The metabolic syndrome in spanish migrants to Brazil: unexpected results. Diabetes Res Clin Pract. 2006; 72: 75-80.

13. Dekker JM, Girman C, Rhodes T, Nijpels G, Stehouwer CDA, Bouter LM, et al. Metabolic syndrome and 10-year cardiovascular disease risk in the Hoorn study. Circulation. 2005; 112: 666-73.

14. American College of Endocrinology. Executive summary of the position statement on the insulin resistance syndrome. Endocr Pract. 2003; 9 (3):237-9.

15. Hamburg NM, Larson MG, Vita JA, Vasan RS, Keyes MJ, Widlansky ME, et al. Metabolic syndrome, insulin resistance, and brachial artery vasodilator function in framingham offspring participants without clinical evidence of cardiovascular disease. Am J Cardiol. 2008; 101 :82-8.

16. Review Manager (RevMan) [Computer program]. Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.

17. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327: 557-60.

18. Wierzbicki AS, Nishtar S, Lumb PJ, Lambert-Hammill M, Crook MA, Marber MS, et al. Waist circumference, metabolic syndrome and coronary artery disease in a Pakistani cohort. Int J Cardiol. 2008; 128: 77-82.

19. Hajer GR, Graaf YVD, Olijhoek JK, Verhaar MC, Visseren FLJ. Levels of homocysteine are increased in metabolic syndrome patients but are not associated with an increased cardiovascular risk, in contrast to patients without the metabolic syndrome. Heart. 2007; 93: 216-20.

20. Lorenzo C, Williams K, Hunt KJ, Haffner SM. The National Cholesterol Education Program–Adult Treatment Panel III, International Diabetes Federation, and World Health Organization Definitions of the Metabolic Syndrome as Predictors of Incident Cardiovascular Disease and Diabetes. Diabetes Care. 2007; 30: 8-13.

21. Stein E, Kushnerc H, Giddingd S, Falknera B. Plasma lipid concentrations in nondiabetic African American adults: associations with insulin resistance and the metabolic syndrome. Metabolism. 2007; 56: 954-60.

22. Eberly LE, Prineas R, Cohen JD, Vazquez G, Zhi X, Neaton JD, et al. Metabolic syndrome. Diabetes Care. 2006; 29: 123-30.

23. Pollex RL, Al-Shali KZ, House AA, Spence JD, Fenster A, Mamakeesick M, et al. Relationship of the metabolic syndrome to carotid ultrasound traits. Cardiovasc Ultrasound. 2006; 4: 28.

24. Girman CJ, Dekker JM, Rhodes T, Nijpels G, Stehouwer CDA, Bouter LM, et al. An exploratory analysis of criteria for the metabolic syndrome and its prediction of long-term cardiovascular outcomes: the Hoorn Study. Am J Epidemiol. 2005; 162: 438-47.

25. Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB, Wilson PW. Insulin resistance, the metabolic syndrome, and incident cardiovascular events in the Framingham Offspring Study. Diabetes. 2005; 54: 3252-7.

26. Wilson MPWF, D'Agostino RB, Parise H, Sullivan L, James B. Metabolic syndrome as a precursor of cardiovascular disease and type 2 Diabetes Mellitus. Circulation. 2005; 112: 3066-72.

27. Chinali M, Devereux RB, Howard BV, Roman MJ, Bella JN, Liu JE, et al. Comparison of cardiac structure and function in american indians with and without the metabolic syndrome: the Strong Heart Study. Am J Cardiol. 2004; 93: 40-4.

28. Kip KE, Marroquin OC, Kelley DE, Johnson BD, Kelsey SF, Shaw LJ, et al. Clinical importance of obesity versus the metabolic syndrome in cardiovascular risk in women: a report from the Women's Ischemia Syndrome Evaluation (WISE) Study. Circulation. 2004; 109: 706-13.

29. Ninomiya J, L'Italien G, Criqui MH, Whyte JL, Gamst A, Chen R. Association of the Metabolic syndrome with history of myocardial infarction and stroke in the Third National Health and Nutrition Examination Survey. Circulation. 2004; 109: 42-6.

30. Caminiti G, Volterrani M, Marazzi G, Massaro R, Vitale C, Gatta L, et al. Metabolic syndrome predicts lower functional recovery in female but not in male patients after an acute cardiac event. Int J Cardiol. 2008. (In press).

31. Kasai T, Miyauchi K, Kubota N, Tamura H, Kojima T, Yokoyama K, et al. The relationship between the metabolic syndrome defined by various criteria and the extent of coronary artery disease. Atherosclerosis. 2008; 197: 944-50.

32. Gomez Rosso L, Benitez MB, Fornari MC, Berardi V, Lynch S, Schreier L, et al. Alterations in cell adhesion molecules and other biomarkers of cardiovascular disease in patients with metabolic syndrome. Atherosclerosis. 2008; 199: 415-23.

33. Ryan MC, Farin HMF, Abbasi F, Reaven GM. Comparison of waist circumference versus body mass index in diagnosing metabolic syndrome and identifying apparently healthy subjects at increased risk of cardiovascular disease. Am J Cardiol. 2008; 102: 40-6.

34. Lapointe A, Couillard C, Piche ME, Weisnagel SJ, Bergeron J, Nadeau A, et al. Circulating oxidized LDL is associated with parameters of the metabolic syndrome in postmenopausal women. Atherosclerosis. 2007; 191 (2): 362-8.

35. Brevetti G, Schiano V, Sirico G, Giugliano G, Laurenzano E, Chiariello M. Metabolic syndrome in peripheral arterial disease: relationship with severity of peripheral circulatory insufficiency, inflammatory status, and cardiovascular comorbidity. J Vasc Surg. 2006; 44: 101-7.

36. Tavil Y, Sen N, Yazici HU, Hizal F, Abaci A, Cengel A. Mean platelet volume in patients with metabolic syndrome and its relationship with coronary artery disease Thromb Res. 2007; 120: 245-50.

37. Dursunoglu D, Evrengül H, Tanriverdi H, Kuru Ö, Gür F, Kaftan A, et al. Do female patients with metabolic syndrome have masked left ventricular dysfunction? Anadolu Kardiyol Derg. 2005; 5: 283-8.

38. Gorter PM, Olijhoek JK, Graaf YVD, Algra A, Rabelink TJ, Visseren FLJ. Prevalence of the metabolic syndrome in patients with coronary heart disease, cerebrovascular disease, peripheral arterial disease or abdominal

aortic aneurysm. Atherosclerosis. 2004; 173: 363-9.

39. Reilly M, Wolfe ML, Rhodes T, Girman C, Mehta N, Rader DJ. Measures of insulin resistance add incremental value to the clinical diagnosis of metabolic syndrome in association with coronary atherosclerosis. Circulation. 2004; 110: 803-9.

40. Scuteri A, Najjar SS, Muller DC, Andres R, Hougaku H, Metter EJ, et al. Metabolic syndrome amplifies the age-associated increases in vascular thickness and stiffness. J Am Coll Cardiol. 2004; 43: 1388-95.

41. Noto D, Barbagallo CM, Cefalú AB, Falletta A, Sapienza M, Cavera G, et al. The metabolic syndrome predicts cardiovascular events in subjects with normal fasting glucose: results of a 15 years follow-up in a mediterranean population. Atherosclerosis. 2008; 197: 147-53.

42. Empana JP, Zureik M, Gariepy J, Courbon D, Dartigues JF, Ritchie K, et al. The metabolic syndrome and the carotid artery structure in noninstitutionalized elderly subjects the three-city study. Stroke. 2007; 38: 893-9.

43. Kurl S, Laukkanen JA, Niskanen L, Laaksonen D, Sivenius J, Nyyssonen K, et al. Metabolic syndrome and the risk of stroke in middle-aged men. Stroke. 2006; 37: 806-11.

44. Langenberg C, Bergstrom J, Scheidt-Nave C, Pfeilschifter J, Barret-Connor E. Cardiovascular death and the metabolic syndrome role of adiposity-signaling hormones and inflammatory markers. Diabetes Care. 2006; 29: 1363-9.

45. Najarian RM, Sullivan LM, Kannel WB, Wilson PWF, D'Agostino RB, Wolf PA. Metabolic syndrome compared with type 2 Diabetes Mellitus as a risk factor for stroke: the Framingham Offspring Study. Arch Intern Med. 2006; 166: 106-11.

46. Iglseder B, Cip P, Malaimare L, Ladurner G, Paulweber B. The metabolic syndrome is a stronger risk factor for early carotid atherosclerosis in women than in men. Stroke. 2005; 36: 1212-7.

47. Malik S, Wong ND, Franklin SS, Kamath TV, L'Italien GJ, Pio JR, et al. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. Circulation. 2004; 110: 1245-50.

48. Marroquin OC, Kip KE, Kelley DE, Johnson BD, Shaw LJ, Merz CNB, et al. Metabolic syndrome modifies the cardiovascular risk associated with angiographic coronary artery disease in women: a report from the women's ischemia syndrome evaluation. Circulation. 2004; 109: 714-21.

49. Bellia C, Bivona G, Scazzone C, Ciaccio M. Association between homocysteinemia and metabolic syndrome in patients with cardiovascular disease. Ther Clin Risk Manag. 2007; 3 (6): 999-1001.

50. Montalcini T, Gorgone G, Federico D, Ceravolo R, Emanuele V, Sesti G, et al. Association of LDL cholesterol with carotid atherosclerosis in menopausal women affected by the metabolic syndrome. Nutr Metab Cardiovasc Dis. 2005; 15: 368-72.

51. Wang J, Ruotsalainen S, Moilanen L, Lepisto, P, Laakso M, Kuusisto J. The metabolic syndrome predicts cardiovascular mortality: a 13-year follow-up study in elderly non-diabetic Finns. Eur Heart J. 2007; 28: 857-64.

52. Zeller M, Steg PG, Ravisy J, Laurent Y, Janin-Manificat L, L'Huillier I, et al. Prevalence and impact of metabolic syndrome on hospital outcomes in acute myocardial infarction. Arch Intern Med. 2005; 165: 1192-8.

53. Holvoet P, Lee DH, Steffes M, Gross M, Jacobs DR Jr. Association between circulating oxidized low-density lipoprotein and incidence of the metabolic syndrome. JAMA. 2008; 299 (19): 2287-93.

54. Skoumas J, Papadimitriou L, Pitsavos C, Masoura C, Giotsas N, Chrysohoou C, et al. Metabolic syndrome prevalence and characteristics in Greek adults with familial combined hyperlipidemia. Metabolism. 2007; 56: 135-41.

55. Iribarren C, Go AS, Husson G, Sidney S, Fair JM, Quertermous T, et al. Metabolic syndrome and early-onset coronary artery disease. Is the whole greater than its parts?. J Am Coll Cardiol. 2006; 48: 1800-7.

56. Meigs JB, Wilson PWF, Fox CS, Vasan RS, Nathan DM, Sullivan LM, et al. Body Mass Index, Metabolic Syndrome, and Risk of Type 2 Diabetes or Cardiovascular Disease. J Clin Endocrinol Metab. 2006; 91: 2906-12.

57. Sociedade Brasileira de Cardiologia. I Diretriz brasileira de diagnóstico e tratamento da síndrome metabólica. Arq Bras Cardiol. 2005; 84 (1): 15-24.

58. Sociedade Brasileira de Cardiologia. IV Diretriz brasileira sobre dislipidemias e prevenção da aterosclerose. Arq Bras Cardiol. 2007; 88 (1): 2-19.