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Metabolic syndrome, hypertension, and nervous system injury: Epidemiological correlates

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ABSTRACT

Metabolic syndrome (MetS) is a common and complex disorder combining hypertension, obesity, dyslipidemia, and insulin resistance. MetS represents a risk factor for changes in cognitive functions in older age, and several studies have suggested that MetS may be linked to dementia. This article reviews the main evidences about the relationship between MetS and neurodegenerative disease. Starting from an epidemiological point of view, the article analyzes medico-social aspects related to MetS, considering the reduction of work capacity and the condition of disability that it involves. Some authors affirm that on the basis of current Italian legislation, it is possible to consider the syndrome as a disability. This is because all the diseases that make up MetS are high-risk clinical pathological conditions. For these reasons, a joint action is required to contain the incidence of MetS, the high social costs, and the loss of productivity related to the syndrome. In conclusion, healthcare initiatives could be adopted in order to increase the understanding of the pathogenic contributions of each element on MetS and how they can be modified. These actions will be useful to reduce healthcare costs and can lead to more effective prevention of metabolic disease, thus promoting good health.

Abbreviations: MetS: Metabolic syndrome; WHO: World Health Organization; CVD: cerebrovascular diseases; AD: Alzheimer's Disease; VaD: Vascular Dementia; IDF: International Diabetes Federation; T2DM: type 2 diabetes mellitus; CAD: coronary artery disease; MCI: mild cognitive impairment; NCDs: Non Communicable Diseases; BMI: Body Mass Index; ICIDH: International classification of impairments, disabilities and handicaps

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Introduction

Metabolic syndrome (MetS) is a common and complex disorder combining obesity, dyslipidemia, insulin resistance, and hypertension. It represents a dangerous risk factor for cardiovascular disease and diabetes. The concept of MetS, also known as insulin resistance syndrome, was introduced in 1988 (1). Since then, various definitions of MetS have been proposed from the World Health Organization (WHO) (2), the European Group for Study of Insulin Resistance (EGIR) (3), the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (4) and the International Diabetes Federation (IDF) (5). The pathogenesis of MetS remains little known and the difficulty of the study of this condition is compounded by the heterogeneity of the different phenotypes, determined by different combinations of risk factors.

Several investigations have suggested that MetS may be linked to the risk of developing cognitive decline and Vascular Dementia (VaD) (6). Recently, a systematic review and meta-analysis of 19,522 subjects aged 59–85 years from 13 longitudinal population-based studies was conducted to examine the association between MetS and longitudinal changes in cognitive functions (7).

MetS is also a medicolegal and especially a medico-social problem, if we consider the reduction of work capacity and the condition of disability that it involves. In industrialized countries, cardio-cerebrovascular diseases (CVDs) are the leading cause of morbidity and disability. MetS also has a socioeconomic impact if we consider that costs will rise as the elderly population increases.

According to Alzheimer's Disease International (ADI), the cost of dementia including informal care provided by family and others, social care provided by community care professionals, and the direct costs of medical care are daunting for the growing numbers of people involved (8). This situation will require an increase in long-term care for elderly people with MetS-related cerebrovascular disease.

In the European Union countries, particularly in Italy, this situation has triggered various initiatives and projects aimed at informing and educating the population toward healthier lifestyles (9). It has been shown that simply by acting on prevention it will be possible to contain the social costs of MetS and diseases related to it. It is important to note that attention is on research and prevention to improve the quality of life as well as reduce the social costs of the disease.

Metabolic syndrome definition

In 1999, WHO defined MetS as glucose intolerance, impaired glucose tolerance (IGT) or type-2 diabetes

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mellitus (T2DM), and/or insulin resistance, together with two or more of the following components: raised arterial pressure, raised plasma triglyceride, central obesity, microalbuminuria (2).

In due course of time, various authors contributed to identify MetS, with the aim of reaching a common and shared definition, modifying risk factors, and reference values. The European Group for Study of Insulin Resistance (EGIR) proposed a modification of the WHO definition, using the term *insulin resistance syndrome* rather than MetS introducing the waist circumference (WC) for evaluation of abdominal obesity and elevated plasma insulin (Tables 1) (3).

After this, the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) proposed to define MetS in a subject exhibiting three or more of the following criteria: abdominal obesity, hypertrigliceridemia, low HDL-C, high blood pressure (BP), high fasting glucose (10). The American Association of Clinical Endocrinologists (AACE) considered as major criteria IGT, elevated triglycerides, reduced HDL-C, elevated BP, and obesity (Table 1) (11).

A last definition of MetS was proposed by the International Diabetes Federation (IDF). Those involved in establishing the definition agreed that diabetes and insensitivity to insulin had been overemphasized in the earlier definitions, and that the 'essential' component is central obesity – measured by waist circumference (WC). Ethnicity-specific cut-off points have been selected based on available data linking waist circumference to other components of the MetS in different populations (12).

The IDF definition takes into account the mounting evidence that central adiposity is common to each of the components of MetS (Tables 1). An increased waist circumference, an accepted proxy measurement for abdominal adiposity, is now a necessary requirement for a diagnosis of the syndrome. Thus, the initial screening test for MetS, by simply measuring the waist with a tape measure, can be carried out easily and cheaply – anywhere in the world. Research has shown that between population groups, there are varying levels of central obesity at which the risk of other illnesses begins to rise. Therefore, ethnicity-specific waist circumference cut-off points have been incorporated in the IDF global definition. For example, for people of south and Southeast Asian origin, 90 cm and 80 cm are the cut-off points for men and women, respectively (5,13,14). In 2005, the American Heart Association (AHA), and the National Heart, Lung, and Blood Institute (NHLBI), different from IDF, maintained the ATP III criteria except for minor modifications (Table 1). This decision was based on the conclusion that ATP III criteria are simple to use in a clinical setting and have the advantage of avoiding emphasis on a single cause (15).

Finally, a simplified definition of MetS was given by a research group that has proposed that WC be replaced by Index of Central Obesity (ICO) in all definitions of MetS. The group suggested that replacing waist circumference with ICO

Table 1. Criteria for clinical diagnosis of metabolic syndrome.

Clinical Measure	WHO(1998)	EGIR (1999)	ATP III (2001)	AACE (2003)	IDF (2005)	AHA (2005)
Insulin resistance	IGT, IFG, T2DM, or lowered insulin sensitivity plus any 2 of the following	Plasma insulin >75th percentile plus any 2 of the following	None, but any 3 of the following 5 features	IGT or IFG plus any of the following based on clinical judgment	None	None
Body weight	Men: waist-to-hip ratio >0.90; women: waist-to-hip ratio >0.85 and/or BMI >30 kg/m^2	WC ≥94 cm in men or ≥80 cm in women	WC ≥102 cm in men or ≥88 cm in women	BMI ≥25 kg/m^2	Increased WC (population specific) plus any 2 of the following	Waist circumference ≥ 102 cm in men ≥ 88 cm in women
Lipid	TG ≥150 mg/dL and/or HDL-C <35 mg/dL in men or <39 mg/dL in women	TG ≥150 mg/dL and/or HDL-C <39 mg/dL in men or women	TG ≥150 mg/dL HDL-C <40 mg/dL in men or <50 mg/dL in women	TG ≥150 mg/dL and HDL-C <40 mg/dL in men or <50 mg/dL in women	TG ≥150 mg/dL or on TG Rx HDL-C <40 mg/dL in men or <50 mg/dL in women or on HDL-C Rx	TG ≥150 mg/dL (1.7 mmol/L) Or On drug treatment for elevated triglycerides <40 mg/dL (1.03 mmol/L) in men <50 mg/dL (1.3 mmol/L) in women
Blood pressure	≥140/90 mm Hg	≥140/90 mm Hg or on hypertension Rx	≥130/85 mm Hg	≥130/85 mm Hg	≥130 mm Hg systolic or ≥85 mm Hg diastolic or on hypertension Rx	≥130 mm Hg systolic blood pressure or ≥85 mm Hg diastolic blood pressure or on antihypertensive drug treatment in a patient with a history of hypertension
Glucose	IGT, IFG, or T2DM	IGT or IFG (but not diabetes)	>110 mg/dL (includes diabetes)	IGT or IFG (but not diabetes)	≥100 mg/dL (includes diabetes)	IFG≥100 mg/dL or On drug treatment for elevated glucose
Other	Microalbuminuria	None	None	Other features of insulin resistance	Other	None

T2DM, type 2 diabetes mellitus; WC, waist circumference; BMI, body mass index; TG, triglycerides; IGT, impaired glucose intolerance; IFG, impaired fasting glucose; HDL-C, High Density Lipoprotein-Cholesterol. Modified from [15].

in definitions of MetS might make it uniformly applicable across genders and races. It also has the advantage of identifying additional subjects who qualify to have MetS by the NCEP ATP III definition but are missed by IDF global consensus definition (16).

Effects of metabolic syndrome on the brain

MetS, as previously stated, is a multifactorial disorder represented by the co-occurrence of several vascular conditions related to central obesity that also includes impaired glucose metabolism, dyslipidemia, high BP and that depicts a risk status for both T2DM and coronary artery disease (CAD). Traditionally, vascular risk factors taken separately, such as hypertension, dyslipidemia, and diabetes, have been shown to play an important role in the development of Mild Cognitive Impairment (MCI), dementia, and Alzheimer's Disease (AD) (17).

Most of the components of MetS have also been shown to be independent risk factors for CAD and stroke. On the other hand, MetS was already shown to be an independent risk factor for CAD, and fatal and nonfatal stroke (18–21). MetS appeared to increase the risk for age-related cognitive decline (ARCD) (22–27), while for some authors, the findings for MCI and its progression to dementia were too limited to draw any conclusions (21,28,29). In fact, a study found an association between MetS and the number of its components and the risk of developing cognitive impairment in older women with osteoporosis from clinical centers (28).

In a large longitudinal Italian population-based sample with a 3.5-year follow-up, in a total of 2,097 participants from a sample of 5,632 65- to –84-year-old subjects from the Italian Longitudinal Study on Aging, among MCI patients, those with MetS had a higher risk of progression to dementia compared with those without MetS (22). Furthermore, several studies suggested that MetS may be linked to the risk of developing dementia and Vascular Dementia (VaD) (21,30–32). Several individual components of MetS have been linked to risk of developing dementia and cognitive impairment. Among the five MetS components, hyperglycemia, lower HDL levels, and elevated triglyceride levels were the components with increased risk for predementia syndromes and for VaD (17,21,32)

In research conducted between 2009 and 2010, the authors found that being afflicted by MetS is associated with a high risk of developing mild cognitive impairment (amnestic type). Among MetS components, central obesity showed a significant association with amnestic mild cognitive impairment (aMCI) (OR = 1.77; 95% CI 1.11–2.82). The association between MetS and aMCI remained significant on repeated analysis among subjects free of heart disease and stroke (33).

Another research published in 2011, by the authors of The Italian Longitudinal Study on Aging, also reiterated that among MCI patients the presence of MetS independently predicted an increased risk of progression to dementia over 3.5 years of follow-up (21).

In contrast, some studies indicate that MetS could be protective in some aged populations. In spite of what has been said up to now, research conducted among men aged 75 and over in Taiwan showed that age and central obesity were significant risk factors in cognitive decline, but late-life MetS, however defined, had a protective effect on cognitive function. The last conclusion of these papers was that further investigation is needed to clarify the possible mechanism of MetS and cognitive function in older adults (34).

Recently, a systematic review and meta-analysis, including 19,522 subjects aged 59–85 years from 13 longitudinal population-based studies, has been conducted to examine the association between MetS and longitudinal changes in cognitive functions. A small association was found in the younger old group (≤ 70), but not in the older group (>70 years). The conclusion was that age appears to modify the association between MetS and cognitive decline, and that these results emphasize the importance of age-stratified risk prediction models of dementia in subjects with chronic metabolic disorders (6,7).

Epidemiology

A total of 56 million deaths occurred worldwide during 2012. Of these, 38 million were due to noncommunicable diseases (NCDs), principally cardiovascular diseases, cancer, and chronic respiratory diseases (35). The number of NCD deaths has increased worldwide and in every region since 2000, when 31 million lives were lost to NCDs. While the annual number of deaths due to infectious diseases is expected to decline, the total annual number of NCDs deaths is expected to increase to 52 million by 2030 (36,37).

An estimated 17.5 million people died from CVD in 2012, representing 31% of all global deaths. Of these deaths, an estimated 7.4 million were due to coronary heart disease and 6.7 million were due to stroke. Over three-quarters of CVD deaths take place in low- and middle-income countries.

The causes of heart attacks and strokes are usually the presence of a combination of risk factors, such as tobacco use, unhealthy diet and obesity, physical inactivity and harmful use of alcohol, hypertension, diabetes, and hyperlipidemia (38).

In Italy, standardized death rates from pathologies correlated to MetS, such as T2DM, ischemic hearth diseases and cardiovascular disease, have been declining, while the mortality trend for AD and dementia is increasing (Tables 2). Overweight and obesity were estimated to account for 3.4 million deaths per year and 93.6 million Disability-Adjusted Life Years (DALYs) in 2010 (35). Obesity has been increasing in all countries. In 2014, 39% of adults aged 18 years and older (38% of men and 40% of women) were overweight. The worldwide prevalence of obesity nearly doubled between 1980 and 2014. In 2014, 11% of men and 15% of women worldwide were obese. Thus, more than half a billion adults worldwide are classed as obese (39).

In the European and Eastern Mediterranean Regions and Region of the Americas, over 50% of women are overweight, and in all three regions roughly half of overweight women are obese (25% in the European region, 24% in the Eastern Mediterranean Region, 30% in the Region of the Americas). In all WHO regions, women are more likely to be obese than men. In the African, Southeast Asia, and Eastern Mediterranean regions, women have roughly double the obesity prevalence of men (40).

Table 2. Deaths per 100,000 population in Italy (standardised rates).

	2000	2012
Circulatory system diseases	373.6	255.0
– Ischaemic Hearth Diseases	113.5	84.1
– Acute miocardial infarction	53.0	32.2
– Cerebrovascular diseases	105.1	67.2
Diabetes mellitus	27.1	24.3
Dementia	12.0	16.7
Alzheimer's Disease	9.6 (*)	11.8

(*) Italian data on Alzheimer start from 2003. Modified from The Organisation for Economic Co-operation and Development (OECD) [77].

In Italy, the Heart Project (Progetto Cuore) – Epidemiology and Prevention of Ischaemic Heart Diseases – coordinated by Istituto Superiore di Sanità (Italian Institute of Health), conducted two researches on the health status of the Italian population between 1998–2002 and 2008–2012 (9).

From these researches, some data have been emphasized:

- General population (35–74 years): the comparison between the two surveys (1998–2002 and 2008–2012) shows that LDL cholesterol levels rise in both men (from 128 to 133 mg/dl) and women (from 126 to 134 mg/dl). The prevalence of hypertrigliceridemia is unchanged in both genders (about 25%). MetS has reduced both in men (from 29.2% to 23.5%) and in women (from 29.6% to 18.5%). This trend was observed in all regions of Italy (north, center, south, and islands).
- Older people (75–79 years): total cholesterol is higher in women (217 mg/dl) than in men (193 mg/dl). The same trend was observed for HDL cholesterol (61 mg/dl women vs 51 mg/dl men) and LDL cholesterol (131 mg/dl women vs 118 mg/dl men). Hypercholesterolemia is higher in women than in men (54.8%, and 36.3%, respectively). High levels of LDL cholesterol were observed in 65% of women and in 51% of men. The prevalence of MetS in the period 2008–2012 was high and similar in both genders (35.9% in men, and 40.7% in women). It was observed that the prevalence of MetS is higher in the older population than in the general population.

The last data for Italy, published by WHO, refer to the period between 2012 and 2014. These data indicate an increase of body mass index (BMI) (from 25.9 to 26.0), of the overweight (from 57.2% to 58.8%), and also of obesity (from 19.6% to 21.0%) (41).

Diabetes is a well-recognized cause of premature death and disability, increasing the risk of cardiovascular disease, kidney failure, blindness, and lower-limb amputation (42). People with impaired glucose tolerance and impaired fasting glycemia are also at risk of future development of diabetes and cardiovascular disease (43)

Prediabetes, which is a combination of excess body fat and insulin resistance, is considered an underlying etiology of MetS. Prediabetes manifests as impaired fasting glucose and/or impaired glucose tolerance. Impaired fasting glucose is defined as a fasting blood glucose level of 100 to 125 mg/dL; impaired glucose tolerance requires a blood glucose level of 140 to 199 mg/dL 2 hours after a 75-g oral intake of glucose (44).

The prevalence of diabetes was estimated to be 9% in 2014, and was highest in the WHO Region of the Eastern Mediterranean Region (14% for both sexes) and lowest in the European and Western Pacific Regions (8% and 9% for both sexes, respectively). In Italy, data from WHO estimate the increase on the prevalence of diabetes in the period between 2012 and 2014 (from 6.3% to 6.6%) (41).

Social considerations

MetS has been found to be a risk factor for dementia, mild cognitive impairment, and its associated states. As previously introduced, a total of 56 million deaths occurred worldwide during 2012. Of these, 38 million were due to NCDs, principally cardiovascular diseases, cancer, and chronic respiratory diseases (36), although some data show a substantial decline in age-adjusted prevalence of fatal and nonfatal myocardial infarction in developed countries (45).

In Italy, disease-related cognitive dysfunctions show an increasing trend due to the increase of some deadly diseases. Italian people need to be protected against diseases of social interest whose incidence is directly related to social and economic factors (i.e., tumors, CVDs, AD, VaD, and T2DM). The protection can take the form of social insurance and also health insurance for national workers.

The latest recognition of MetS as an independent nosographic condition has not yet led to sufficient processing of theoretical practice of exclusive medicolegal interest.

Some authors (46) affirm that is possible to include the syndrome in the disability list according to the Italian current law (47) with a score in the range 11–20% disability.

The debilitating effects of MetS cannot be assessed simply by adding up its associated pathologies, as this does not give satisfactory answers to legal and medico-social issues. Conversely, it will be necessary to increase assessment scores to make sure that the final disability score is greater than the sum of the single pathologies that make it up.

The development of thought of Forensic Medicine has considered functional impairment as the basis for definition of damage to specific personal skills in relationship to life (social, family, work). In this way is possible to seize the difficulties that MetS can cause: sociocultural disabilities more than invalidity.

This is a dynamic abstract concept influenced by the particular historical-social period to which it refers. Moreover, Italian Legislative Decree no. 509/88 (48) institutionalized the disability evaluation table. It was only elaborated in

1992, and it is still in use today despite its apparent failure. That table was based on the International Classification of Diseases formulated by the WHO in 1980, namely, the International Classification of Impairments, Disabilities and Handicaps (ICIDH) (49), and overcame the simple list of pathologies. To consider the real impact of MetS, it became necessary to examine interactions between human activities and their social environment.

The WHO classification highlighted and redefined these old concepts. In the new classification, only the term "Impairment" has been preserved; Disability has been replaced by Activity (all that a person is able to do at various levels of complexity). To the inadequate notion of "Handicap," "Participation" was preferred, where the degree of this depends on the relationship between the disabled subject with compromised activity and environment. In May 2001, the audit trail of the WHO was concluded with the development of the International Classification of Functioning, Disability and Health (ICF) (50), subsequently supplemented and improved with annual updates.

Without doubt, disability is defined as a consequence or result of the relationship between the health condition of an individual and personal and environmental factors.

During working life it is often difficult to reduce stress levels, improve diet, and find time for physical activity. All these deficiencies favor the development of MetS; and this pathology increases the risk of serious diseases, which, first of all, affect health, but also social costs and productivity (51,52).

Recently, in Italy, private insurance has introduced products dedicated to the evaluation of MetS, with a diagnosis designed at controlling risk factors and preventing more serious clinical manifestations.

Insurance guarantees are justified by the real possibility of an early diagnosis, obtained by simple medical investigation and affordable screening. Furthermore, both the insured and the insurer have the advantage of controlling possible greater economic damage resulting from a late diagnosis, with the clinical risk of related diseases involving more demanding and costly care already established.

MetS is not only a medical-legal problem but also a medical-social dilemma. It is not possible to include MetS in a simple evaluation that is linked to only a reduced work capacity. It is necessary to review the concept of disability and talk of the social concerns associated with MetS. Action should be taken regarding the causes of the disease to decrease the level of disability defined as limitation of the activities of a subject with MetS.

In conclusion, the medicolegal aspects must be identified and the research and prevention of causes of MetS must increase. A joint action is required to contain the incidence of MetS, its high social costs, and correlated loss of productivity.

Costs of metabolic syndrome

It is not easy to evaluate the costs of MetS, while costs for each pathology (that contribute to identify MetS) are more easy to calculate, such as for medicolegal evaluations of this pathology.

To analyze social costs, it is necessary to consider three categories of costs: direct, indirect, and intangible (53,54). Direct costs derive from medical and non-medical care (e.g., prevention, diagnosis, and therapy). Indirect costs represent lack of wealth production due to the illness and the time relatives and caregivers devote to health care. Intangible costs are linked to pain, anxiety, physical, and psychological suffering of the patient and its relatives. These costs are difficult to evaluate, but are considerable in terms of their social and human aspects (55).

The direct cost burden of a person with diabetes varies considerably across countries. For example, in Italy in 2010, the costs for each patient were on average € 2,756,00 (of which €814 for drugs, €373 for check-ups and medical care, €1,569 for hospitalization). In the EU, France, Germany, and the UK have considerably higher costs per diabetes patient (€5,432; €5,899; €4,744, respectively) than in Spain (€1,708). Many diabetic patients experience multiple complications, compounding the complexity of treatment and thus costs (56).

In Italy, total expenditure on medicines in 2010 amounted to €2.34 billion (31.8% of total direct cost), of which €492 milion for antidiabetic drugs (6.2% of total direct cost) and the remainder for drugs treating comorbidities and complication of diabetes (56).

Regarding indirect costs, every year, diabetic people working in Italy (1.33 million) are absent from work for 33 days because of illness, with productivity costs of € 8 billion. The total indirect costs in Italy are evaluated as being €17 billion (56).

The same study highlighted that in the countries considered (Italy, France, UK, Germany, Spain), costs due to diabetes are about €200 billion per year (56).

Some authors developed a probabilistic prevalence Cost-of-Illness model in order to calculate an aggregate measure of the economic burden associated with diabetes, in terms of direct medical costs (drugs, hospitalizations, monitoring, and adverse events) and indirect costs (absenteeism and early retirement). The model estimated a predominance of 2.6 million patients undergoing drug therapy in Italy. The total economic burden of diabetic patients in Italy amounted to €20.3 billion per year (95% CI, from €18.61 to €22.29 billion), 54% of which are associated with indirect costs (95% CI, €10.10 to €11.62 billion) and 46% with direct costs only (95% CI, €8.11 to €11.06 billion) (57).

High blood pressure has long been recognized as a major health burden and particularly as a major risk factor for overall mortality affecting all segments of the population. During the first 25 years of the 21st century, the disease burden of hypertension is expected to increase by 60% globally, with an estimated 1.56 billion hypertensive individuals in the world. As morbidity and mortality shift from communicable diseases, high blood pressure will significantly increase in economically developing countries so as to represent nearly half of the disease burden due to increased hypertension-related outcomes (58).

In Italy, healthcare costs for hypertension amounted to €2783.2 million in 2011. Added to expenditure for lipid-lowering drugs, these costs amount to €4156.7 million (59).

In 2012, expenditure for cardiovascular drugs remains highest in Italy, with a figure of €4.350 million. Compared to other European countries, Italy has the highest public and private spending for cardiovascular drugs (24.7%), after Portugal (27.9%) and Greece (31.5%) (59).

Obesity is responsible for both high direct costs (due to treatment for associated illnesses such as diabetes, hypertension, and cardiovascular diseases) and indirect costs, for the decrease in workforce productivity due to illness and early deaths. In US adults, a study examined the impact of obesity on healthcare expenditures (payments for office and hospital-based care, home healthcare, dental services, vision aids, prescription medicines). It was found that, when compared to normal-weight adults, per capita healthcare expenditures were nearly 10% greater for the overweight, and about 23%, 45%, and 81% greater for persons with class I, II, III obesity, respectively (60). Studies from the USA suggest that the impact of obesity on annual medical spending is especially pronounced for prescription drugs, while European studies found that direct costs differ according to patient characteristics, for example, by health-status, socio-demographic, and economic aspects (61–63).

In Italy, the SiSSI project estimated that being overweight is responsible for 4% of costs (€4.5 billion in 2012). The same study reported that spending on healthcare is 3% higher in overweight people (BMI 25–29.9), 18% higher in obese people (BMI 30–34.9), 41% higher in severely obese people (BMI 35–39.9), and 50% higher in very severely obese people (BMI ≥ 40). In the author's opinion, a severe/very severe obese person costs 450–550 €/year more than a normal-weight person (64).

As previously shown, MetS is directly related to the development of CVD. Consequently, MetS could contribute to an increase in the frequency and costs of such diseases. In fact, based on estimates from the World Alzheimer Report 2010, the number of people with dementia has increased by 31.5% between 2010 (35.6 million) and 2015 (46.8 million). Between 2010 and 2015, the average worldwide cost per person (a weighted average across countries, calculated on a 'like for like' basis) increased from US$15,122 to US$17,483 US$ per year (an increase of 15.6% or 3.1% per year).

The global costs of dementia increased from US$ 604 billion in 2010 to US$ 818 billion in 2015, an augmentation of 35.4%. The proportion of worldwide costs incurred in upper-middle-income countries (UMICs) has increased from 5.4% to 10.5%. In 2015, the mean cost per person with dementia was US$ 43,680 in G7 countries, US$ 20,187 in G20 countries, and US$ 6,757 in countries that were members of neither G7 nor G20 (65). Total European 2010 cost of brain disorders was €798 billion, of which direct healthcare cost 37%, direct nonmedical cost 23%, and indirect cost 40%. The average cost per inhabitant was €5.550. The European average cost per person with a brain disorder ranged from €285 for headaches and €30,000 for neuromuscular disorders. In particular, the total annual cost of dementia (in billions of euros, 2010) was €105.2 (66).

Forecasts based on population projections in Europe seem to indicate an increase of about 43% of these costs by 2030 (67).

In Italy, each Alzheimer's patient costs about €60,000 per year. An amount that takes into account both direct costs for the purchase of services and benefits and indirect costs (care and supervision monetized hours). The first, amounting to €15,000, accounts for 25% of the total and are mainly supported by families (68).

Conclusion

Due to the importance of MetS and its relations with the CVD and AD, prevention is the most important strategy to fight the disease and its outcomes. Several authors agree on the importance of changes in lifestyle. In patients with prediabetes, the rate of progression to diabetes within 3 years can be decreased by approximately 58% with lifestyle modifications. These include weight loss through physical exercise (30 minutes or more of moderate physical activity on most, preferably all, days of the week) and dietary modifications as also recommended by IDF.

In fact, the primary strategy for MetS management, to reduce the risk of developing cardiovascular and cerebrovascular disease, is consuming an overall healthy diet for weight reduction and continuous weight maintenance (69–76). Healthy diets are recommended, particularly the Mediterranean diet (69).

For these reasons, it is important to focus on information and screening campaigns targeting most-at-risk populations (e.g., overweight or with a family history of diabetes), encouraging exercise in daily activity and including medical experts such as dieticians and psychologists, thus helping people achieve a good glycemic control and more generally an acceptable level of health

The best approach seems to be a combination of health strategies, aimed at individuals who are more at risk of obesity (children, middle-to-lower class income groups, and minority groups). In the studies taken into consideration, the cost of a package of health initiatives varies from $12 pp in Japan to $24 pp in Canada and the USA. In all these countries, where coverage and services are different, this cost unfortunately represents an extremely low percentage of total healthcare expenditure, including costs related to prevention.

According to OSCE, the highest costs are incurred by primary care, while tax measures are understandably the most cost-effective. In particular, Sassi (77) underlines the importance of directing various health initiatives to children, in other words to age-groups which are potentially prone to obesity. In this case, results can only be appreciated in the long term, but are more sustainable: community-based results, acting as a social-multiplier, exceed individually-based outcomes. The State, as a consequence, can and should intervene to avoid the increase of overweight and obesity rates (according to data from the PASSI study, in some regions of

the south, overweight and obesity rates in children under 15 years of age are equal to 50%) (78).

In the field of prevention, the European Union has supported its member states in their efforts. These initiatives can aid in the definition of shared objectives and indicators, sharing best practice, and ensuring regular observation and evaluation.

As has already been done for other pathologies, an International Study Group for MetS could be established. In view of cross-border healthcare, this would allow joint healthcare initiatives to be adopted, reducing healthcare costs as well as aiding in the prevention and promotion of good health.

Declaration of interest

The authors report no conflicts of interest.

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References

1. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37:1595–1607.
2. World Health Organization. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Report of a WHO consultation. Geneva: World Health Organization 1999, WHO/NCD/NCS/99.2 http://www.who.int/iris/handle/10665/66040. Accessed 15 Dec 2015
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;16:442–443.
4. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486–2497.
5. International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome. 1st International Congress on Prediabetes and the Metabolic Syndrome. Berlin, Germany, 2005.
6. Siervo M, Harrison SL, Jagger C, et al. Metabolic syndrome and longitudinal changes in cognitive function: a systematic review and meta-analysis. J Alzheimer's Dis 2014;41:151–161.
7. Frisardi V. Impact of metabolic syndrome on cognitive decline in older age: protective or harmful, where is the pitfall? J Alzheimers Dis 2014;41:163–167.
8. Colucci L, Bosco M, Fasanaro AM, et al. Alzheimer's disease costs: what we know and what we should take into account. J Alzheimer's Dis: JAD 2014;42:1311–1324.
9. Il progetto cuore: Epidemiologia e prevenzione delle malattie cerebro e cardiovascolari. http://www.cuore.iss.it/. Accessed Nov 30, 2015
10. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486–2497.
11. Einhorn D, Reaven GM, Cobin RH, et al. American College of Endocrinology position statement on the insulin resistance syndrome. Endocr Pract 2003;9:237–252.
12. Crepaldi G, Maggi S. The metabolic syndrome: a historical context. Diabetes Voice 2006;51:8–10
13. Zimmet P, Alberti G. The IDF definition: why we need a global consensus. Diabetes voice 2006;51:11–14.
14. Alberti KGMM., P. Zimmet, J. Shaw. Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabetic Med 2006;23:469–480.
15. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735–2752.
16. Parikh R, Mohan V, Joshi S. Should waist circumference be replaced by index of central obesity (ICO) in definition of metabolic syndrome? Diabetes Metab Res Rev 2012;28:3–5.
17. Frisardi V, Solfrizzi V, Seripa D, et al. Metabolic-cognitive syndrome: A cross-talk between metabolic syndrome and Alzheimer's disease. Age Res Rev 2010;9:399–417.
18. Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002;288:2709–2716.
19. Haffner SM, The metabolic syndrome: inflammation, diabetes mel- litus, and cardiovascular disease. Am J Cardiol. 2006;97:3A–11A.
20. Wang J, Ruotsalainen S, Moilanen L, et al. The metabolic syndrome predicts incident stroke: a 14-year follow-up study in elderly people in Finland. Stroke 2008;39:1078–1083.
21. Solfrizzi V, Scafato E, Capurso C, et al. Metabolic syndrome, mild cognitive impairment, and progression to dementia. The Italian Longitudinal Study on Aging. Neurobiol Aging 2011;32:1932–1941.
22. Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA 2004;292:2237–2242
23. Yaffe K, Haan M, Blackwell T, et al. Metabolic syndrome and cognitive decline in elderly Latinos: findings from the sacramento area Latino study of aging study. J Am Geriatr Soc 2007;55:758–762.
24. Dik MG, Jonker C, Comijs HC, et al. Contribution of metabolic syndrome components to cognition in older individuals. Diabetes Care 2007;30:2655–2660.
25. van den Berg E, Biessels GJ, de Craen AJ, et al. The metabolic syndrome is associated with decelerated cognitive decline in the oldest old. Neurology 2007;69:979–985.
26. Ho RC, Niti M, Yap KB, et al. Metabolic syndrome and cognitive decline in chinese older adults: results from the singapore longitudinal ageing studies. Am J Geriatr Psychiatry 2008;16:519–522.
27. Komulainen P, Lakka TA, Kivipelto M, et al. Metabolic syndrome and cognitive function: a population-based follow-up study in elderly women. Dement Geriatr Cogn Disord 2007;23:29–34.
28. Yaffe K, Weston AL, Blackwell T, Krueger KA. The metabolic syndrome and development of cognitive impairment among older women. Arch Neurol 2009;66:324–328.
29. Roberts RO, Geda YE, Knopman DS, et al. Metabolic syndrome, inflammation, and nonamnestic mild cognitive impairment in older persons: a population-based study. Alzheimer Dis Assoc Disord 2010;24:11–18.
30. Kalmijn S, Foley D, White L, et al. Metabolic cardiovascular syndrome and risk of dementia in Japanese–American elderly men. The Honolulu-Asia aging study. Arterioscler Thromb Vasc Biol 2000;20:2255–2260.

31. Roriz-Cruz M, Rosset I, Wada T, et al. Cognitive impairment and frontal-subcortical geriatric syndrome are associated with metabolic syndrome in a stroke-free population. Neurobiol Aging 2007;28:1723–1736.
32. Raffaitin C, Gin H, Empana JP, et al. Metabolic syndrome and risk for incident Alzheimer's disease or vascular dementia: the Three-City Study. Diabetes Care 2009;32:169–174.
33. Feng L, Chong MS, Lim WS, et al. Metabolic syndrome and amnestic mild cognitive impairment: Singapore Longitudinal Ageing Study-2 findings. J Alzheimers Dis 2013;34:649–657.
34. Liu CL, Lin MH, Peng LN, et al. Late-life metabolic syndrome prevents cognitive decline among older men aged 75 years and over: one-year prospective cohort study. J Nutr Health Aging 2013;17:523–526.
35. World Health Organization. Global Health Estimates: Deaths by Cause, Age, Sex and Country, 2000–2012. Geneva: WHO, 2014.
36. World Health Organization. Projections of mortality and causes of death, 2015 and 2030 http://www.who.int/healthinfo/global_burden_disease/projections/en/. Accessed Nov 15, 2015
37. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3:e442.
38. World Health Organization. Media Centre. Cardiovascular diseases (CVDs). Fact sheet N°317 Updated January. 2015. http://www.who.int/mediacentre/factsheets/fs317/en/. Accessed Nov 15, 2015
39. World Health Organization. Obesity and overweight. Fact sheet N °311, 2015 http://www.who.int/mediacentre/factsheets/fs311/en/ Accessed Nov 15, 2015
40. World Health Organization. Overweight and obesity, Adults aged 18+. http://www.who.int/gho/ncd/risk_factors/overweight_text/en/. Accessed Nov 15, 2015
41. World Health Ogranization. Global status report on noncommunicable diseases. Attaining the nine global noncommunicable diseases targets; a shared responsibility 2014. http://apps.who.int/iris/bitstream/10665/148114/1/9789241564854_eng.pdf. Accessed Nov 15, 2015
42. Levitan B, Song Y, Ford ES, Liu S. Is nondiabetic hyperglycaemia a risk factor for cardiovascular disease? A meta-analysis of prospective studies. Arch Intern Med 2004;164:2147–2155.
43. Global status report on noncommunicable diseases 2010. Geneva: World Health Organization; 2011 http://www.who.int/nmh/publications/ncd_report_full_en.pdf
44. Mayans L. Metabolic syndrome: insulin resistance and prediabetes. FP Essent 2015;435:11–16.
45. Smolina K, Wright FL, Rayner M, Goldacre MJ. Determinants of the decline in mortality from acute myocardial infarction in England between 2002 and 2010: linked national database study. BMJ 2012;344:d8059.
46. Iacone G, Buccelli C. L'invalidità civile. Aspetti sostanziali, processuali, medico legali. Padova CEDAM 2008: 562–565.
47. Ministerial Decree - Ministry of health - approvazione della nuova tabella indicativa delle percentuali d'invalidità per le minorazioni e malattie invalidanti. Published in the Official Gazette no. 47, Office. February 26, 1992, n. 47, S.O.
48. Italian Legislative Decree no. 509, 23 November 1988. Norme per la revisione delle categorie delle minorazioni e malattie invalidanti, nonché dei benefici previsti dalla legislazione vigente per le medesime categorie, under art. 2, comma 1, Law 26 July 1988, no. 291.
49. International Classification of Impairment, Disabilities and Handicaps. A manual of classification relating to the consequences of disease (ICIDH). Geneva: World Health Organitation 1980
50. Cieza A, Brockow T, Ewert T, et al. Linking health-status measurements to the international classification of functioning, disability and health. J Rehabil Med 2002;34:205–210.
51. Burton WN, Chen CY, Schultz AB, Edington DW. The prevalence of metabolic syndrome in an eployed population and the impact on health and productivity. J Occup Environ Med. 2008;50:1339–1348.
52. Schultz Ab, Edington Dw. The association between changes in metabolic syndrome and changes in cost in a workplace population. J Occup Environ Med 2009;51:771–778.
53. Cavallo MC, Fattore G. I costi sociali della Malattia di Alzheimer: metodologia e risultati di una indagine preliminare. Mecosan 1994;10:12–23.
54. Tarricone R. Cost-of-illness analysis. What room in health economics? Health Policy 2006;77:51–63.
55. Le Demenze e la Malattia di Alzheimer: considerazioni etiche Comitato nazionale bioetica, presidenza Consiglio dei Ministri 24.06.2014.
56. Kanavos P, van den Aardweg S, Schurer W. Diabetes expenditure, burden of disease and management in 5 EU countries. LSE Health, London School of Economics 2012.
57. Marcellusi A, Viti R, Mecozzi A, Mennini FS. The direct and indirect cost of diabetes in Italy: a prevalence probabilistic approach. Eur J Health Econ 2014;17:1–9.
58. Lackland DT1, Weber MA. Global burden of cardiovascular disease and stroke: hypertension at the core Can J Cardiol. 2015;31:569–571.
59. Gruppo di Lavoro Agenzia Italiana del Farmaco. L'uso dei farmaci in Italia. Rapporto Nazionale anno 2011. Il Pensiero Scientifico Editore, Roma, 2012. www.epicentro.iss.it/farmaci. Accessed Nov 30, 2015.
60. Arterburn DE, Maciejewski MI, Tsevat J. Impact of morbid obesity on medical expenditures in adults. Int J Obesity 2005;29:334–339
61. Roux L. Cost-effectiveness of anti-obesity interventions. In Cawley JH (ed.). The Oxford handbook of the Social Science of Obesity, 1st ed. New York: Oxford University Press, 2011, pp. 832–847
62. Hammond RA, Levine R. The economic costs of obesity in the United States. Diabetes Metab Syndrome Obesity 2010;3:287–295
63. von Lengerke T, Krauth C. Economic costs of adult obesity: a review of recent European studies with a focus on subgroup-specific costs. Maturitas 2011;69:220–229.
64. Nicolucci A, Sbraccia P, Guerra R, et al. Il burden of disease dell'obesità in Italia. Heath policy in non-communicable diseases 2015;1:5–22.
65. World Alzheimer Report. The worldwide costs of dementia. In: The Global Impactof Dementia. An Analysis of Prevalence, Incidence, Cost and Trends. London, Alzheimer's Disease International, 2015: 56–67.
66. Olesen J, Gustavsson A, Svensson M, Wittchen HU, Jönsson B; CDBE2010 study group; European Brain Council. The economic cost of brain disorders in Europe. Eur J Neurol 2012;19:155–162
67. La situazione Sanitaria del paese. Le Malattie. A cura della Direzione Generale del Sistema informativo e Statistico Sanitario. Ministero della Salute. 2011 http://www.salute.gov.it/rssp/paginaParagrafoRssp.jsp?sezione=situazione&capitolo=malattie&id=2656. Accessed, Nov 30, 2015.
68. CNB, National Committee of Bioethics. \. http://presidenza.governo.it/bioetica/pdf/demenze_malattia_Alzheimer.pdf. Accessed, Nov 30, 2015.
69. Bragg DA, Walling A. Metabolic syndrome: hyperlipidemia. FP Essent 2015;435:17–23.
70. Minich DM, Bland JS. Dietary management of the metabolic syndrome beyond macronutrients. Nutr Rev 2008;66:429–444.
71. Panagiotakos DB, Pitsavos C, Chrysohoou C, et al. Impact of lifestyle habits on the prevalence of the metabolic syndrome among Greek adults from the ATTICA study. Am Heart J 2004;147:106–112.
72. Esposito K, Ciotola M, Giugliano D. Mediterranean diet and the metabolic syndrome. Mol. Nutr Food Res 200751:1268–1274.

73. Williams DE, Prevost AT, Whichelow MJ, et al. A cross-sectional study of dietary patterns with glucose intolerance and other features of the metabolic syndrome. Br J Nutr 2000;83:257–266.
74. Paletas K, Athanasiadou E, Sarigianni M, et al. The protective role of the Mediterranean diet on the prevalence of metabolic syndrome in a population of Greek obese subjects. J Am Coll Nutr 2010;29:41–45.
75. Mellendijk L, Wiesmann M, Kiliaan AJ. Impact of Nutrition on Cerebral Circulation and Cognition in the Metabolic Syndrome. Nutrients 2015;7:9416–9439.
76. Brown L, Poudyal H, Panchal SK. Functional foods as potential therapeutic options for metabolic syndrome. Obes Rev 2015;16:914–941.
77. Sassi F. Obesity and the economics of prevention: fit not fat. OECD Publishing, 2010.
78. Epicentro. Il portale dell'epidemiologia per la Sanità Pubblica a cura del Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute. La sorveglianza Passi Sovrappeso e obesità, 2015. http://www.epicentro.iss.it/passi/dati/sovrappeso.asp. Accessed. Nov, 30 2015.