

Original Research

Risk Factors Clustering Within the Metabolic Syndrome: A Pattern or by Chance?

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Introduction: An accumulation of various cardiovascular risk factors has been noted to occur within the clinical diagnosis of metabolic syndrome. However, it remains unclear whether specific risk factors aggregate following a predefined pattern or whether this happens by chance.

Methods: This cross-sectional study involved 1715 adults, 37% males and 63% females, aged 34-80 years, who were consecutively recruited from cardiology and endocrinology outpatient clinics, and from internal medicine specialists in the primary healthcare physician office setting in Serbia, on a one-third basis. According to the AHA/NHLBI criteria, the actual prevalence of a combination of 3 or more of the following risk factors was determined: abnormal waist circumference, hypertension, high triglycerides, low high-density lipoprotein cholesterol, and abnormal fasting glucose. In addition, the prevalence of a corresponding combination of 3 factors was predicted from the prevalence of each factor in a given population, assuming that their combination occurred as the result of chance.

Results: The most frequent risk factor was hypertension (87%), followed by waist circumference (60%), dyslipidemia (55%), and abnormal fasting glucose level (50%). Metabolic syndrome was identified in 1135 participants (66.2%). The actual prevalence of the combination of increased waist circumference, elevated blood sugar and hypertension was found to be 5 times more frequent than would be expected to occur by chance (10% actual vs. 2% predicted; $p < 0.0001$).

Conclusions: A predefined aggregation pattern of risk factors within the metabolic syndrome was found for abdominal obesity, abnormal fasting glucose and hypertension. These risk factors do cluster more frequently than coincidental phenomena in the subjects of the given population, implying common underlying pathophysiological mechanisms.

The metabolic syndrome (MetS) is a cluster of multiple cardiometabolic abnormalities: central obesity, insulin resistance, dyslipidemia and hypertension. Each abnormality involved in the MetS is also a traditional risk factor for cardiovascular diseases (CVD). This “clustering” of metabolic abnormalities that occurs in the same individual appears

to confer a substantial additional cardiovascular risk over and above the sum of the risk associated with each abnormality.¹⁻³

It is estimated that around 20-25%, i.e. a quarter, of the world’s adult population have MetS and that they are twice as likely to die from and three times as likely to have a heart attack or stroke compared

with people who do not have the syndrome.^{1,4} In addition, people with MetS have a fivefold greater risk of developing type 2 diabetes (T2D).⁵ The clustering of CVD risk factors that typify the MetS is now considered the driving force for the CVD and T2D global epidemics. Regrettably, reports from the region also speak of the same trend in the Balkans and of poor awareness among the general population.^{6,7}

Understanding clustering mechanisms could lead to the earlier identification of individuals with MetS who would benefit from lifestyle interventions and treatment in terms to prevent development of T2D and/or CVD. Some studies have shown that risk factors tend to cluster within the clinical diagnosis of MetS, but it still remains unclear whether specific risk factors aggregate following a predefined pattern, or whether this happens by mere chance.⁸⁻¹²

To investigate the potential tendency of specific risk factors to cluster within the MetS definition, we analyzed the prevalence of a combination of risk factors in patients visiting cardiology and endocrinology outpatient clinics, and internal medicine specialists in a primary healthcare physician office setting in Serbia.

Methods

Study design and recruitment modalities

This was a national multicenter cross-sectional study conducted during October 2008 in 3 university hospital centers in the north, middle and south of the Republic of Serbia. The number of patients assigned to each recruiting center was proportionate to the population of the given geographical area. Physicians were involved from different clinical practice settings: office- or hospital-based cardiologists, endocrinologists/diabetologists, and internists in a primary healthcare physician office setting, on a one-third basis. During consulting days in a predetermined week, each participating physician recruited 20 consecutive patients, regardless of their condition or the reason for the consultation. Patient assessment was carried out during a single visit to the physician, with analysis of related fasting blood samples being completed up to a median of 7 days (maximum 3 weeks) after the visit.

Inclusion and exclusion criteria

All patients aged 35-80 years, of both sexes, who gave signed, informed consent to all study procedures, were

eligible for enrollment. Exclusion criteria were: current hospitalization, any major surgery within the previous 30 days, myocardial infarction or stroke within the previous 30 days, pregnant or breast-feeding women, pre-existing cirrhosis with ascites, hyper- or hypothyroidism, current treatment with oral retinoids (acne, psoriasis), systemic corticosteroids, antiretroviral drugs, anti-obesity drugs (e.g. sibutramine, orlistat), CB1 blocker, actual or anticipated geographic or social factors that would prevent the subject from providing the fasting blood sample. Information on all criteria was collected via a questionnaire.

Data collected

Demographic parameters (age, gender, level of education, professional activity/occupation and physical activity) and cardiovascular risk factors (personal history of hypertension, diabetes and dyslipidemia, smoking status and family history of CVD/T2D). After the medical interview, body height, body weight, waist circumference (WC), and blood pressure were measured and recorded for all individuals. A fasting blood sample was drawn for measurements of total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, triglyceride and glucose levels.

Metabolic syndrome definition

We used the AHA/NHLBI definition, which includes 3 or more of the following criteria: increased waist circumference (≥ 102 cm for males and ≥ 88 cm for females), hypertension (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or treatment for hypertension), high plasma triglycerides (≥ 1.69 mmol/L, or treatment), low HDL cholesterol (< 1.03 mmol/L for males and < 1.29 mmol/L for females, or treatment) and abnormal fasting glucose metabolism (fasting blood sugar ≥ 5.6 mmol/L, or treatment).^{13,14}

Actual and predicted prevalence of risk factors

According to the AHA/NHLBI criteria, the actual prevalence of a combination of 3 or more risk factors was determined within the clinical diagnosis of MetS. In addition, the prevalence of a corresponding combination of 3 factors was predicted from the prevalence of each factor in a given population, assuming that their combination occurs as a result of chance.

The prediction of prevalence of a combination of

3 or more factors of MetS was calculated as follows.¹² For example, the predicted prevalence of a combination of three factors is given by:

$$P_{(1+2+3)} = P_1 \times P_2 \times P_3 \times (1-P_4) \times (1-P_5)$$

where P_1 to P_5 represent the prevalence of factors 1 to 5 involved in MetS as mentioned above, and $1-P_4$ or $1-P_5$ represents the probability that the subject does not have the specified risk factor. All of the possible combinations of 3 or 4 factors were obtained, and finally the probability of a combination of 5 risk factors was calculated as follows:

$$P_{(1+2+3+4+5)} = P_1 \times P_2 \times P_3 \times P_4 \times P_5$$

Then the probabilities of each combination of 3 to 5 factors were expressed as percentages and compared with the actual ones.

The rationale of the study is that if the factors of MetS do really cluster, the actual prevalence of combinations of 3 or more factors should exceed the predicted ones, when the latter are calculated on the assumption that each factor behaves independently and that the combination is simply the result of chance.

Statistical analysis

Continuous data are expressed as mean values with standard deviations, while the prevalence of each feature of MetS, as well as the actual and predict-

ed prevalence of all combinations of these items are expressed as absolute numbers and percentages. To investigate whether some factors accumulate more than others in MetS, we determined the prevalence of each combination of risk factors appearing together and compared it with the predicted prevalence from the total examinees. If the prevalence of some combination of risk factors was higher in MetS compared to the predicted prevalence, these risk factors could be said to be clustering in this syndrome. All comparisons were made using the chi-square test. A p-value <0.05 was considered to be significant.

Results

Clinical and biochemical characteristics

The study involved 1715 adults, 37% (633) males and 63% (1082) females, aged 34-80 years, who were recruited from cardiology and endocrinology outpatient clinics, and primary healthcare physician office-based internists, on a one-third basis (31% vs. 38% vs. 31%, respectively). The patients' clinical and biochemical data are presented in Table 1.

The most frequent risk factor was hypertension 87.3% (1497), followed by WC 59.5% (1021), high triglycerides 58.3% (1000), abnormal fasting glucose

Table 1. Clinical and biochemical data of patients in different settings of clinical practice.

Variable	Unit	Overall (n=1715)	Men (n=633)	Women (n=1082)
Age	years	58.49 ± 9.84	58.19 ± 10.24	58.67 ± 9.59
BMI	kg/m ²	28.60 ± 4.96	28.70 ± 4.25	28.54 ± 4.96
WC	cm	96.02 ± 12.94	102.32 ± 11.24	92.34 ± 12.44
	inch	37.83 ± 5.09	40.28 ± 4.43	36.35 ± 4.90
sBP	mmHg	137.79 ± 20.00	137.55 ± 18.69	137.92 ± 20.74
dBP	mmHg	84.29 ± 10.70	84.58 ± 10.59	84.12 ± 10.76
HR	bpm	74.71 ± 9.79	74.65 ± 9.92	74.75 ± 9.73
TC	mmol/L	5.88 ± 1.29	5.63 ± 1.29	6.02 ± 1.28
	mg/dL	105.95 ± 23.24	101.44 ± 23.24	108.47 ± 22.70
HDL	mmol/L	1.34 ± 0.36	1.19 ± 0.29	1.43 ± 0.37
	mg/dL	24.14 ± 6.49	21.44 ± 5.23	25.77 ± 6.67
LDL	mmol/L	3.79 ± 1.11	3.69 ± 1.08	3.84 ± 1.13
	mg/dL	68.29 ± 20.00	66.49 ± 19.46	69.19 ± 20.36
TG	mmol/L	1.98 ± 1.37	2.12 ± 1.70	1.90 ± 1.37
	mg/dL	35.68 ± 24.68	38.19 ± 3.63	34.23 ± 24.68
FBG	mmol/L	6.32 ± 2.31	6.50 ± 2.41	6.21 ± 2.24
	mg/dL	113.87 ± 41.62	117.12 ± 43.43	111.89 ± 40.36

BMI – body mass index; WC – waist circumference; sBP – systolic blood pressure; dBP – diastolic blood pressure; HR – heart rate; bpm – beats per minute; TC – total cholesterol; HDL-c – HDL cholesterol; LDL-c – LDL cholesterol; Tg – triglycerides; FBG – fasting blood glucose.

Table 2. Prevalence of each feature of metabolic syndrome in patients from different settings of clinical practice.

Variable	Overall	Overall with Tx	Men	Men with Tx	Women	Women with Tx
WC>102/88 cm (M/F)	1021 (59.5%)	-	319 (50.4%)	-	702 (64.9%)	-
sBP≥130 mmHg and/or dBP≥85 mmHg or Tx	1497 (87.3%)	1257 (83.7%)	563 (88.9%)	459 (81.5%)	934 (86.3%)	798 (85.4%)
TG≥1.69 mmol/L or Tx	1000 (58.3%)	496 (49.6%)	403 (63.7%)	197 (48.9%)	597 (55.2%)	299 (50.1%)
HDL<1.03/1.29 mmol/L (M/F) or Tx	889 (51.8%)	496 (55.8%)	299 (47.2%)	197 (65.9%)	590 (54.5%)	299 (50.1%)
FBG≥5.6 mmol/L or Tx	891 (52.0%)	393 (44.1%)	357 (56.4%)	157 (44.0%)	534 (49.4%)	236 (44.2%)

Tx – therapy. Other abbreviations as in Table 1.

level 52.0% (891), and low HDL 51.8% (889). The prevalence of each feature of MetS by sex and therapy is shown in Table 2. The percentage of patients under therapy for each risk factor was calculated for the number of patients with a given risk factor.

Sixty-five patients (3.8%) had no risk factors, 1 risk factor was present in 200 (11.7%) patients, 2 in 315 (18.4%) patients, a combination of 3 or 4 risk factors was found in 397 and 413 patients, respectively (23.1% and 24.1%), while all 5 risk factors were present in 325 (19.0%) patients. The distribution of patients according to sex in relation with the number of risk factors present is shown in Figure 1.

Prevalence of the metabolic syndrome

MetS with 3 to 5 factors was diagnosed in 1135 (66.2%) of the 1715 examinees. It was found in 65.9% of men and 66.4% of women. In men, it ranged from 50.0% to 72.8% for each age decade, with the peak in the 5th decade, while in women it ranged from 45.5% to 78.1% in each decade and peaked in the 7th decade (Table 3).

Actual vs. predicted prevalence of a combination of risk factors

Obesity and fasting hyperglycemia were found in 848 (74.7%) and 771 (67.9%) patients with MetS, while their original prevalence was 59.5% and 52.0%, respectively. Both risk factors were 1.3 times more frequent in MetS compared to the original prevalence in the total examinees. Low HDL cholesterol and high triglyceride levels were found in 833 (73.4%) and 922 (81.2%) patients with MetS, respectively, and they were 1.4 times frequent than in the total population. Hypertension was found in 1094 (96.4%) of MetS patients, 1.1 times higher than expected.

The actual prevalence of a combination of 3 factors varied from 0.5% to 10.0%: the highest was the combination of abnormal WC, blood pressure and

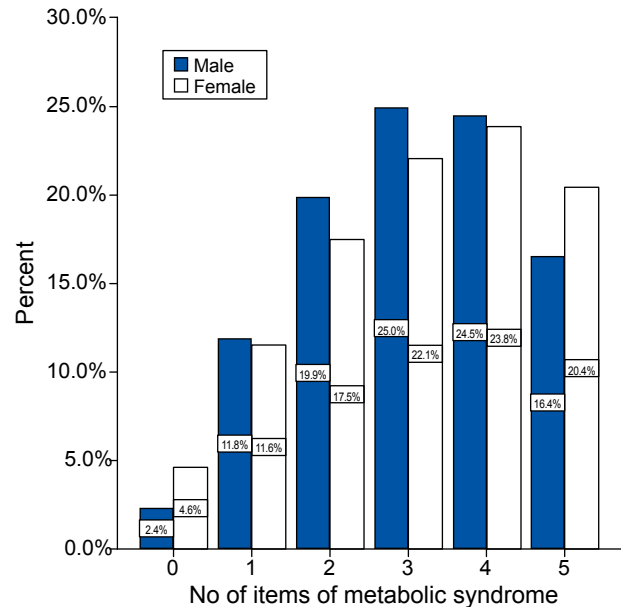


Figure 1. Distribution of patients according to sex in relation to the number of risk factors present.

Table 3. Prevalence of metabolic syndrome by age and gender in patients from different settings of clinical practice.

Variable	No. of examinees	No. with MetS	% with MetS
Male			
<50	130	82	63.1%
50-59	224	163	72.8%
60-69	175	121	69.1%
≥70	102	51	50.0%
Female			
<50	178	81	45.5%
50-59	394	248	62.9%
60-69	349	265	75.9%
≥70	155	121	78.1%

glucose, and the lowest was that of abnormal WC, glucose and triglycerides, as well as abnormal WC, glucose and HDL (Figure 2). The actual prevalence of a combination of 4 factors was between 0.8% and 13.7% and that of 5 factors was 28.6%.

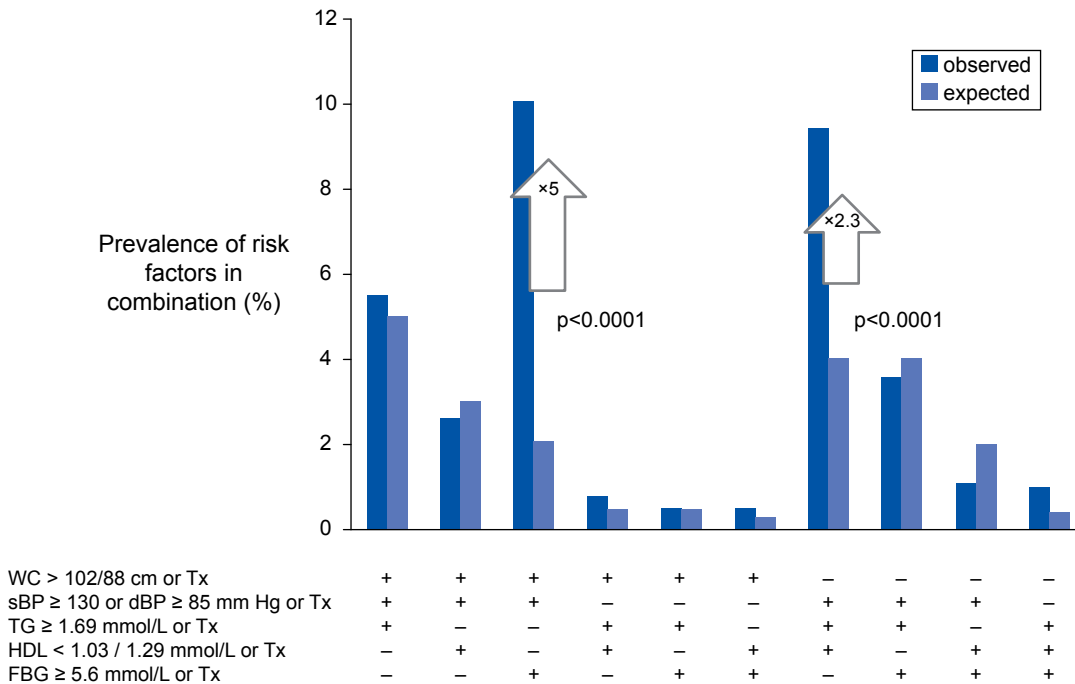


Figure 2. The actual and predicted prevalence of 3 risk factors combined in the overall population. WC – waist circumference; sBP – systolic blood pressure; dBP – diastolic blood pressure; TG – triglycerides; HDL – HDL-cholesterol; FBG – fasting blood glucose; Tx – therapy.

The predicted prevalence of combinations of 3 factors varied from 0.3% to 5% (Figure 2). The predicted prevalence of a combination of 4 factors was 1.1% to 13% and that of five factors was 29%. As shown in Figure 2, the actual prevalence of the combination of increased WC, elevated FBG and hypertension was found to be 5 times more frequent than that expected to occur by coincidence (10% actual vs. 2% predicted; $p < 0.0001$). For a combination of abnormal fasting blood glucose, triglyceride and HDL levels, the actual prevalence exceeded the predicted one by a factor of 2 (9.4% actual vs. 4% predicted; $p < 0.0001$). Other combinations of risk factors were not significantly different from the predicted ones ($p > 0.05$ for all).

The same conclusions were drawn from the analysis performed for the male and female population separately (Figures 3 and 4). This indicated that obesity, hyperglycemia and hypertension clustered in MetS more than hypertension, triglycerides and HDL, but both combinations clustered too frequently for it to be a coincidental phenomenon, implying the existence of a common predefined aggregation pattern.

Discussion

MetS is a constellation of risk factors of metabolic origin that are associated with an increased risk for

CVD and T2D. These risk factors include obesity, abnormal lipids, elevated blood pressure, and increased plasma glucose.¹⁵⁻¹⁷ While body mass index was previously used as a criterion for determining obesity, nowadays increased WC is considered the best obesity-related risk hallmark.^{18,19} Dyslipidemia included in the MetS definition encompasses elevated triglyceride levels and decreased HDL cholesterol. Elevated plasma glucose depicts either pre-diabetes or diabetes.

A considerable number of studies have demonstrated that, in patients with MetS, the relative risk for CVD ranges from 1.5 to 3.0, depending on the stage of progression.^{1,20-30} When diabetes is not yet present, the risk for progression to T2D averages about 5 times greater compared with those without the syndrome.³¹⁻³⁵ Once T2D develops, cardiovascular risk increases even more.^{36,37}

Gami et al recently conducted a systematic review and meta-analysis of 37 longitudinal studies, including 43 cohorts with a total of 172,573 individuals, and demonstrated a significantly increased risk of cardiovascular events and death in individuals with MetS.³⁷ Their random effects meta-analyses showed that MetS had a relative risk (RR) of cardiovascular events and death of 1.78 (95% confidence interval, CI: 1.58 to 2.00).

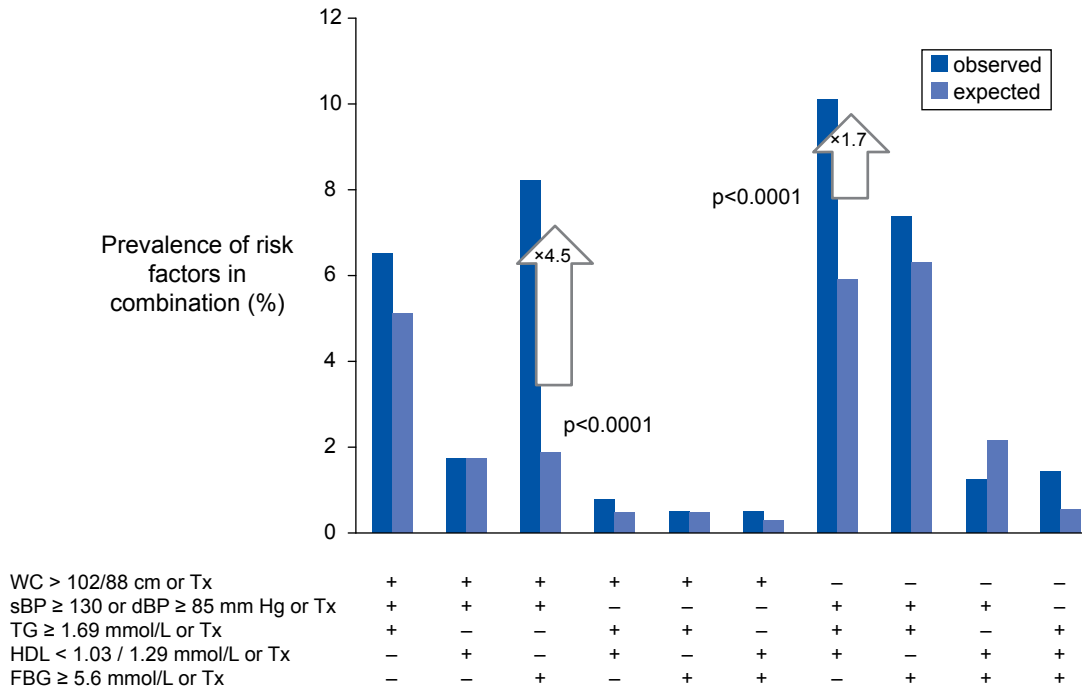


Figure 3. The actual and predicted prevalence of three risk factors combined in men. Abbreviations as in Figure 2.

It could be said that the participation of MetS as a driving force in the CVD and T2D global epidemics is insistent. However, there are only few studies dealing with detection of possible mechanisms as mediators of the observed association between MetS and cardiovascular risk. The question that arises is whether there is a common pathophysiological mechanism that brings together certain risk factors, too often for it to be a coincidence, and which can facilitate our understanding of MetS.

Aizava et al found that 2 or more cardiovascular risk factors occur more frequently than can be explained by coincidence.¹¹ Sprecher and Pearce also found a clustering of the “deadly quartet” of risk factors in patients who underwent primary isolated coronary artery bypass graft surgery, and a poor prognosis was found to be associated with the total of the risk factors.³⁸ These two studies recruited patients with documented coronary ischemia, whereas a later study by Aizava et al investigated subjects from the general population who were not under any medical treatment.¹² A peak in the prevalence of MetS was found around the 6th-7th decade in men and the 7th-8th decade in women, followed by a decline at higher ages; this was explained by the fact that subjects who had developed cardiovascular events were excluded from the subsequent annual examination. In our study, we

found a similar peak – earlier for men (5th-6th decade) than for women (7th-8th decade) – even though subjects who had developed cardiovascular events were not excluded from the subsequent examination.

The assumption is that, if each risk factor behaves independently without affecting others, any combination of risk factors can be predicted by the probability for that combination. The fact that the actual prevalence of some combinations of risk factors is higher than the expected one will mean that there is a tendency for these risk factors to cluster. In Aizawa’s study, the actual prevalence of any combination of 3 or more risk factors exceeded the predicted one. This finding supports the idea that the risk factors included in MetS really cluster, rather than occurring by coincidence.

A key mechanism that causes a clustering of risk factors within MetS has not yet been exposed, but visceral obesity and insulin resistance are often considered to play a central role.^{21,26,27,35,39-44} Aizawa’s group showed that the prevalence of obesity or insulin resistance was 2.6 or 2.9-fold greater in patients with MetS compared to the total examinees. Similarly, a higher prevalence was observed in hypertension and high triglyceride levels, but the increase was relatively modest: from 1.9 to 2.1-fold.¹² This finding suggests that obesity and insulin resistance cluster more often than other risk factors.

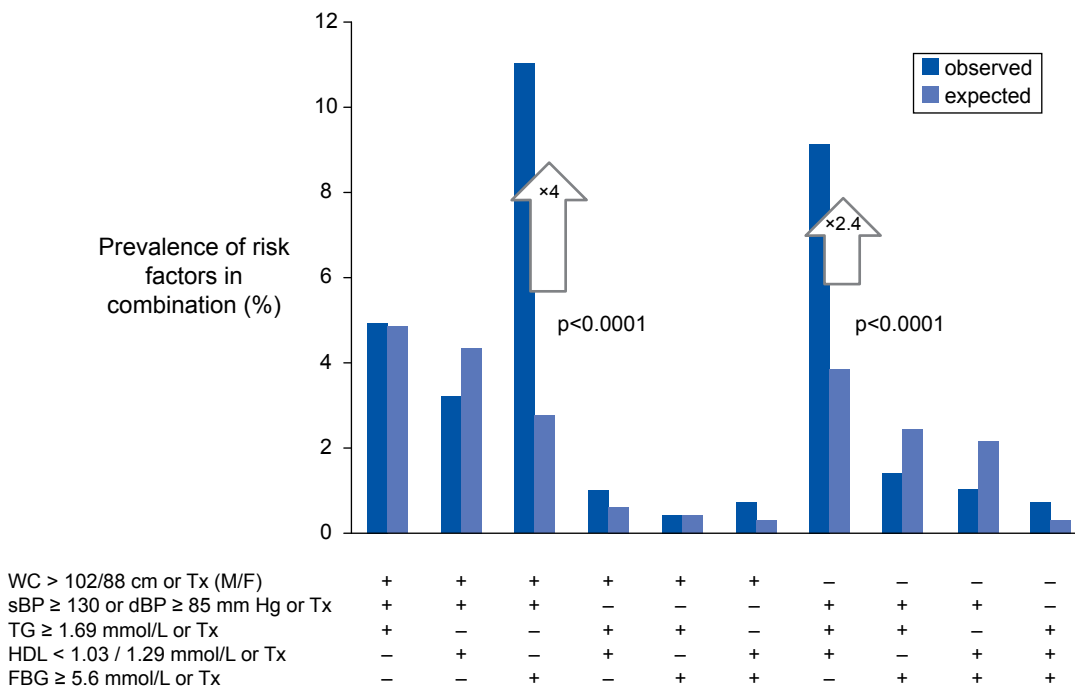


Figure 4. The actual and predicted prevalence of 3 risk factors combined in women. Abbreviations as in Figure 2.

In contrast to Aizawa (who used a body mass index cutoff of 25 kg/m² and over as an obesity marker), we used WC, as specified in the AHA/NHLBI and ATP III definitions. We found similar associations, but with a greater increase in risk: the actual prevalence of the combination of increased WC, elevated fasting blood glucose and hypertension was 5 times more than the value predicted by coincidence, while the combination of abnormal lipid levels together with hypertension exceeded the predicted one by 2 times.

The pathogenesis of MetS is a multifactorial one, but the major underlying risk factors seem to be obesity and hyperglycemia.¹⁴⁻¹⁷ Hyperglycemia can be secondary to obesity, but it can also have a genetic component *per se*. The relation of elevated blood pressure to MetS is complex. Multivariate techniques, such as factor analysis, show that hypertension tends to segregate independently of other variables in MetS. However, the clear correlation between hypertension and body weight, the higher incidence of hypertension in diabetic patients, the negative correlation between insulin sensitivity and hypertension, and the interactive role of hypertension and other factors in atherosclerotic risk, support the predominance of hypertension and central obesity in MetS risk factor clustering.⁴⁵⁻⁴⁷

This study was conducted in cardiology and endo-

crinology outpatient clinics, as well as in the primary healthcare physician offices of internal medicine specialists, since it was a feasible way of recruiting large numbers of individuals who were at high risk for having MetS with the intention to determine possible clustering of specific risk factors within its definition. Therefore, the prevalence of MetS was found to be high in the subjects of the given population. Consequently, these results cannot be extrapolated to the general population, but only to high-risk cohorts.

In conclusion, a predefined aggregation pattern was found for abdominal obesity, hyperglycemia and hypertension. This finding suggests that these risk factors do cluster more frequently than can be explained by chance phenomena, implying that they share common underlying pathophysiological mechanisms. A follow-up of this study is ongoing, aiming to prove that subjects with MetS are more prone to developing atherosclerotic cardiovascular diseases.

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