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Metabolic syndrome across Europe: different clusters of risk factors

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Abstract

Background: Metabolic syndrome (MetS) remains a controversial entity. Specific clusters of MetS components – rather than MetS per se – are associated with accelerated arterial ageing and with cardiovascular (CV) events. To investigate whether the distribution of clusters of MetS components differed cross-culturally, we studied 34,821 subjects from 12 cohorts from 10 European countries and one cohort from the USA in the MARE (Metabolic syndrome and Arteries REsearch) Consortium.

Methods: In accordance with the ATP III criteria, MetS was defined as an alteration three or more of the following five components: elevated glucose (G), fasting glucose $\geq$110 mg/dl; low HDL cholesterol, $<$ 40mg/dl for men or $<$50 mg/dl for women; high triglycerides (T), $\geq$150 mg/dl; elevated blood pressure (B), $\geq$130/$\geq$85 mmHg; abdominal obesity (W), waist circumference $>$102 cm for men or $>$88 cm for women.

Results: MetS had a 24.3% prevalence (8468 subjects: 23.9% in men vs. 24.6% in women, $p < 0.001$) with an age-associated increase in its prevalence in all the cohorts. The age-adjusted prevalence of the clusters of MetS components previously associated with greater arterial and CV burden differed across countries ($p < 0.0001$) and in men and women ($p < 0.0001$). In details, the cluster TBW was observed in 12% of the subjects with MetS, but was far more common in the cohorts from the UK (32.3%), Sardinia in Italy (19.6%), and Germany (18.5%) and less prevalent in the cohorts from Sweden (1.2%), Spain (2.6%), and the USA (2.5%). The cluster GBW accounted for 12.7% of subjects with MetS with higher occurrence in Southern Europe (Italy, Spain, and Portugal: 31.4, 18.4, and 17.1% respectively) and in Belgium (20.4%), than in Northern Europe (Germany, Sweden, and Lithuania: 7.6, 9.4, and 9.6% respectively).

Conclusions: The analysis of the distribution of MetS suggested that what follows under the common definition of MetS is not a unique entity rather a constellation of cluster of MetS components, likely selectively risky for CV disease, whose occurrence differs across countries.

Keywords

Blood pressure, epidemiology, Europe, glucose, HDL cholesterol, metabolic syndrome, triglycerides, waist circumference

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Introduction

Even though the metabolic syndrome (MetS) remains a controversial entity,[1,2] it has previously been shown to be associated with higher odds of CV events even in older subjects,[3–6] likely through increasing arterial stiffness and thickness (i.e. accelerating arterial ageing).[7,8] Yet, whether MetS is a single syndrome or a constellation of different syndromes carrying different CV risk remains an unanswered question and a scarcely investigated topic.[9] Of note, it was recently reported that specific clusters of altered MetS components – rather than MetS per se – were associated with accelerated arterial aging in the SardiNIA Study.[7] Similarly, only specific clusters of altered MetS components conferred a higher risk of CV events in the Framingham Study.[10]

The aim of the present study was to investigate whether the distribution of clusters of MetS components differed across countries and whether these differences were gender specific. To investigate this question, we studied 34,821 subjects from 12 cohorts representing 10 different European countries and the USA participating in the MARE (Metabolic syndrome and Arteries REsearch) Consortium.

Subjects and methods

The MARE Consortium

The original MARE Consortium was established as a collaboration among 11 European and one US centre studying population-based cohorts to identify whether any cross-cultural differences in clustering of MetS altered components and associations with arterial aging; to disentangle the specific role of genes and lifestyle factors (and their interactions) on the clinical presentation of MetS and on the CV risk attributable to MetS; and to develop new strategies to prevent CV events through identification of potential lifestyle changes. The MARE Consortium is open to additional participating cohorts, provided that data on the MetS components and on arterial properties are available for the recruited subjects.

Ethics statement

The cohorts participating to the present analysis are briefly described in Supplementary Material and Supplementary Table 1 (available online). The age distribution of the enrolled subjects are presented in Figure 1. Each cohort had its protocol approved by the local Ethic Committee. Each participant signed written informed consent form, previously approved by the site-specific Ethic Committee.

Definition of the metabolic syndrome

The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III)[11] defined the MetS as an alteration in three or more of the following five components: abdominal obesity (W), high triglycerides (T), low HDL cholesterol, elevated blood pressure (systolic or diastolic; B), and elevated fasting glucose (G). The following cut-off values are used to define each altered component: waist circumference >102 cm for men or >88 cm for women, triglycerides ≥150 mg/dl, HDL cholesterol <40 mg/dl for men or <50 mg/dl for women, blood pressure ≥130/≥85 mmHg, and fasting glucose ≥110 mg/dl. Because MetS is defined by the presence of three or more altered components, subjects with MetS may have different combinations of the individual components of MetS.

Statistical analysis

All analyses were performed using SAS version 9.1 for Windows (SAS, Cary, NC, USA). Data are presented as mean ± SD for continuous variables or as percentages for categorical variables. Differences in the prevalence for each of the measured variables among groups were compared by ANOVA. ANCOVA analysis was used to assess interactions between sex and cohort on the distribution of MetS components or clusters of components, independently of the possible effects of age on the same variables. A two-sided p-value <0.05 indicated statistical significance.

Results

Complete data were available for 34,821 subjects. MetS had in general a 24.3% prevalence (8468 subjects) that increased with advancing age (from 3.7 with age 20–29 years to over 30% with age ≥70 years; Figure 2a).

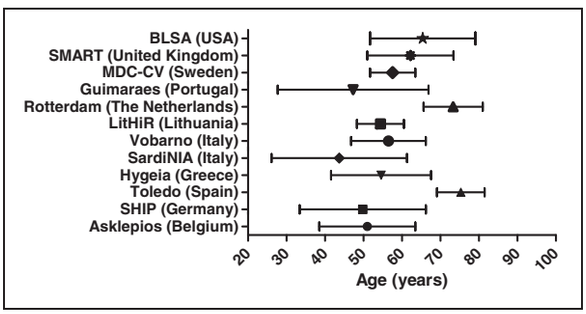

Figure 1. Age distribution of subjects enrolled in participating cohorts of the MARE Consortium.
Values are mean ± SD.

The significant difference in the MetS prevalence across countries illustrated in Figure 2b ($p < 0.0001$) likely reflects primarily different population characteristics (age distribution and general population vs. higher CV risk subjects), but it did not seem to parallel the prevalence of diabetes mellitus in the same populations. Overall, there was a small but significant gender difference in the prevalence of Mets (23.9% in men and 24.6% in women, $p < 0.001$; Figure 2c).

In subjects with MetS, the distribution of altered components differed between men and women and cross-country wise (Figure 3). Specifically, elevated glucose was highly prevalent in cohorts from Belgium, the

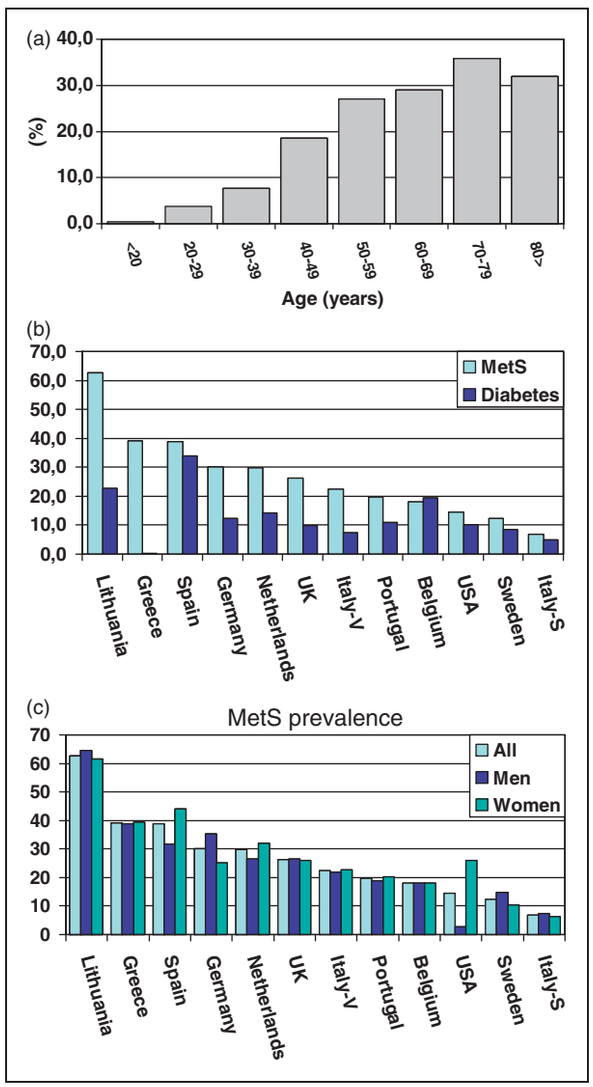

Figure 2. Overall prevalence of MetS in different age groups (a) and diabetes mellitus in participating cohorts (b) and gender-specific prevalence of MetS in participating cohorts (c) of the MARE Consortium.

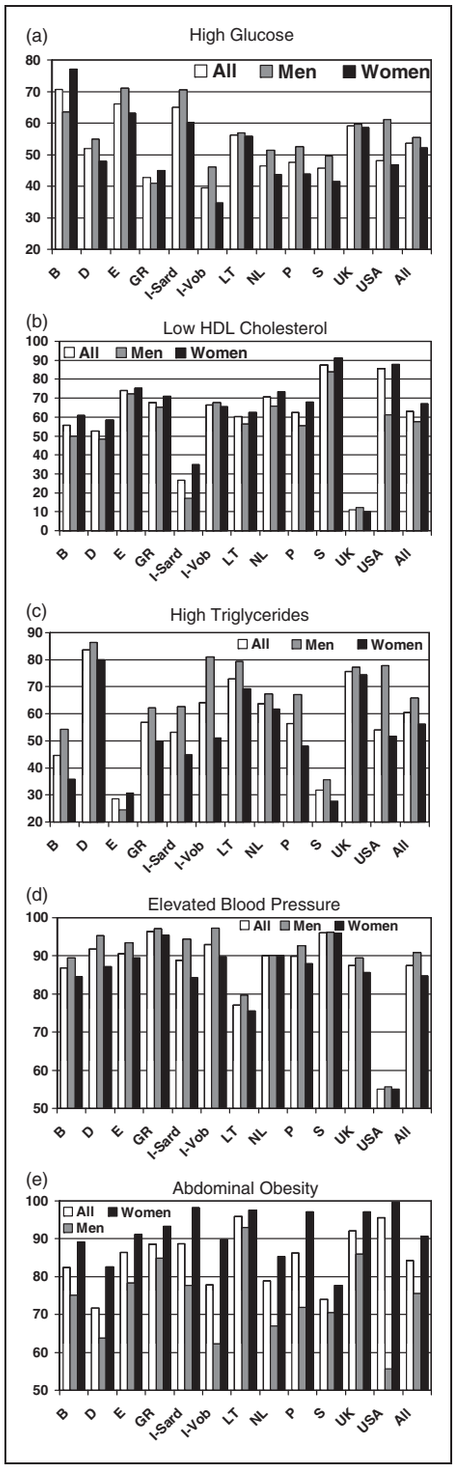

Figure 3. Distribution of MetS components in subjects with MetS in participating cohorts of the MARE Consortium: high glucose (a), low HDL cholesterol (b), high triglycerides (c), elevated blood pressure (d), and abdominal obesity (e).
B, Belgium; D, Germany; E, Spain; GR, Greece; I-Sard, Sardinia in Italy; I-Vob arno, Vobarno in Italy; LT, Lithuania; NL, Netherlands; P, Portugal; S, Sweden.

UK, Lithuania, Spain, and Sardinia in Italy, whereas the lowest prevalence was observed in the Greek cohort. Low HDL cholesterol showed the highest prevalence in the cohorts from Sweden, the USA, and the Netherlands and the lowest in Sardinia and the UK. Elevated triglycerides were highly prevalent in the cohorts from Germany, the UK, and Lithuania and less prevalent in Spain and Sweden. Elevated blood pressure had a prevalence >90% in the cohorts from Sweden, Germany, and Greece, and the lowest prevalence in the cohorts from the USA and Lithuania. The prevalence of abdominal obesity showed a wide significant gender difference (75.6% in men and 90.6% % in women, $p < 0.0001$). Of note, waist circumference exceeded the cut-off values in more than 90% of women from the USA, the UK, and Mediterranean countries, whereas it was less frequently altered in the Swedish cohort.

The age-adjusted prevalence of the clusters of MetS components previously associated with greater arterial and CV burden differed across European countries ($p < 0.0001$; Figure 4) and in men and women ($p < 0.0001$). The significant interaction term Gender*Cohort in the ANCOVA analyses also suggested that gender differences in the clusters of MetS components differed across countries.

In detail, the cluster TBW was observed in 12% of the subjects with MetS, but was far more common in the cohorts from the UK (32.3%), Sardinia in Italy (19.6%), and Germany (18.5%) but less prevalent in the cohorts from Sweden (1.2%), Spain (2.6%), and the USA (2.5%). The cluster GBW accounted for 12.7% of subjects with MetS with the highest occurrence in Southern Europe (Italy, Spain, and Portugal: 31.4, 18.4, and 17.1% respectively) and in Belgium (20.4%), and with the lowest occurrence in Northern Europe (Germany, Sweden, and Lithuania: 7.6, 9.4, and 9.6% respectively). The simultaneous alteration in all the five MetS components had a greater prevalence in Lithuania (13%) and a considerably lower prevalence in the Italian cohorts (2–3%). More details are provided in Supplementary Figures 1–9, where the overall and the gender-specific occurrence of each cluster of MetS with an overall prevalence ≥5% are illustrated.

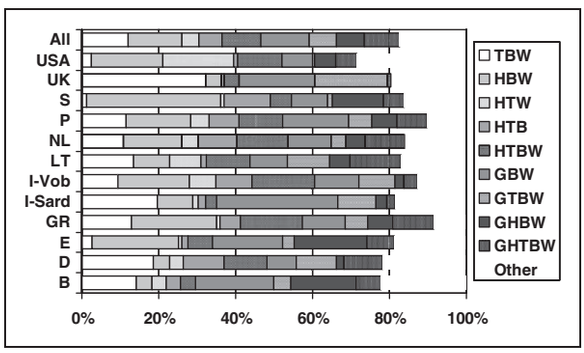

Figure 4. Age-adjusted prevalence of clusters of MetS components in subjects with MetS in participating cohorts of the MARE Consortium.
Cohorts: B, Belgium; D, Germany; E, Spain; GR, Greece; I-Sard, Sardinia in Italy; I-Vob arno, Vobarno in Italy; LT, Lithuania; NL, Netherlands; P, Portugal; S, Sweden.
Risk factors: B, elevated blood pressure; G, elevated glucose; H, low HDL cholesterol; T, high triglycerides; W, abdominal obesity.

Discussion

The main goal of the present study was not to investigate differences in MetS prevalence across studies, likely reflecting also differences in recruitment strategy across studies. Rather, we focused on subjects with MetS to identify whether, within subjects who had the same diagnosis (MetS defined in accordance with ATPIII criteria), clusters of MetS components significantly differed across studies and countries.

The occurrence of low HDL cholesterol or elevated triglycerides in subjects with MetS was far more common in North European countries and in the USA, whereas elevated blood pressure was observable in more than 90% of subjects with MetS in Southern Europe. Similarly, it is remarkable that abdominal obesity was present in virtually all women with MetS from Southern Europe, the UK, and the USA.

That the prevalence of specific clusters of MetS components may differ across countries can be expected based upon varying prevalence according to the various MetS definitions used – for instance, from the 'glucocentric' World Health Organization definition to the 'obesity-centric' International Diabetes Federation definition.[12–14] Similarly, there has been inconsistency concerning the CV burden of MetS when different definitions of MetS were adopted.[3,4,15–20] Yet, to date no study has investigated cross-country distribution of specific clusters of MetS components, which have been recognized previously as associated with greater arterial pathology or risk of CV events.[7,8,10]

The present study has some limitations. The included cohorts may be representative of the recruitment regions, but less representative of their countries. Further limitations arise from the fact that existing data were pooled; there was no harmonization of the studies prior to the data collection. Therefore, our findings cannot immediately be generalized.

An additional limitation may be represented by the adoption of the first ATP III MetS definition rather than of the harmonized 2009 definition.[12] This strategy will

result in a lower MetS and MetS components prevalence estimates. A similar effect may be the consequence of a population recruitment that occurred in different years across cohorts. Yet, the goal of the MARE Consortium is not primarily to provide the most accurate estimate of MetS prevalence in Western countries. Rather, we wanted to highlight cross-country differences in the distribution of separate phenotypes currently falling under the common definition of MetS.

The MARE Consortium cohorts have also major strengths. The large number of men and women of a broad age range from 12 different countries allow us to conclude that the current definition of MetS comprises constellation of syndromes rather than a single condition. An additional strength of the present findings is represented by the adoption of a single definition of MetS – namely the original ATP III definition – that favours comparison across studies.

The design of the present study does not allow speculation about whether different prevalence rate of MetS components and cluster of MetS components previously recognized to confer higher risk of arterial aging and CV events reflect cross-cultural differences in genetic 'risky' allele distribution, in lifestyle (including food consumption, nutritional intake, and physical exercise), or in public health policies. For instance, a larger waist circumference – a trait that has been reported to also predict new cases of MetS[21] – may be a consequence of lower socioeconomic status,[22] greater caloric intake,[6] or less physical exercise,that impacts skeletal muscle energy processing.[23–25]

We will further investigate whether the impact of specific clusters of MetS components are constantly associated with accelerated arterial aging (i.e. arterial stiffness and intima–media thickness)[26] across countries as well as in men and women and we will try to identify possible lifestyle and/or genetic factors differing among countries and potentially underlying cross-cultural differences in the distribution of clusters of MetS components.

In conclusion, what follows under the common definition of MetS is not a unique entity rather a constellation of cluster of MetS components, likely selectively risky for CV disease, whose occurrence differs across countries.

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Conflict of interest

None declared.

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