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Reproducibility and validity of a non-invasive method for the early detection of metabolic syndrome in a working population

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ABSTRACT

Objectives. A non-invasive method for the early detection of Metabolic Syndrome (NIN-MetS) using only Waist to Height Ratio (WHtR) and Blood Pressure (BP) has recently been published, with fixed cut-off values for gender and age. The aim of this study was to reproduce and validate this method in a large sample of Spanish workers.

Desing. We carried on a cross-sectional study to assessment the reproducibility and a diagnostic test accuracy to assessment the validity.

Setting. Occupational Health Sevices and working population.

Participants. The studies were conducted in 2012-2016 on a sample of 60,799 workers from the Balearic Islands (Spain).

Interventions. The NCEP-ATPIII criteria were used. NIM-MetS has been devised using classification trees (the CHAID, Chi-squared Automatic Interaction Detection method).

Main outcome measures. Anthropometric and biochemical variables to diagnostic MetS. To measure the accuracy of the diagnostic test the sensitivity, specificity, validity index and Youden Index were analysed.

Results. As regards the validity of the method, the sensitivity was 59.7%, specificity 94.9% and validity index 91.2%. The cut-off value for WHtR obtained was 0.544 for the total sample, and by age group, ranged from 0.514 (lower age group) and 0.563 (higher). As for the reproducibility of the method, the variables more closely associated with MetS WHtR (AUC=0.85 CI 95% 0.84-0.86) and Systolic Blood Pressure (AUC=0.79 CI 95% 0.78-0.8). The final cut-off values for the non-invasive method were WHtR≥0.558 and BP≥128/80 mmHg, which includes four levels of risk of MetS (very low, low, moderate and high).

Conclusions. The analysed method has shown a validity high validity index (greater than 91%) for the early detection of MetS. It is a non-invasive method which is easy to apply and interpret in any health care setting. This method

provides a scale of MetS risk which allows for more accurate detection and more effective intervention.

Strengths and limitations of this study

- The NIN-MetS has proved to be a valid method for the early detection of MetS in a healthy worker population.
- It is a simple, economical and quick non-invasive test which is easy to apply and interpret in any health care setting (primary health care, hospitals, occupational health) as well as in other settings (education, sport, etc.).
- The NIM-MetS obtains a very high specificity (94.9%) and diagnostic validity (91.2%) and provides a gradient or risk scale which allows a more accurate and earlier detection of CVD in subjects with risk of MetS.
- WHtR is the best predictor of MetS and its cut-off point can be used for both genders and for different age groups.
- NIM-MetS has shown lower sensitivity than the original method is likely due to differences in study populations.

INTRODUCTION

The obesity epidemic which currently affects the world population has resulted in a general increase in the prevalence of metabolic syndrome (MetS) [1-3]. Overweight and obesity are factors related to the onset of type 2 diabetes, hypertension, dyslipidemia and cardiovascular diseases (CVD). In particular, central obesity, which is defined as an excessive accumulation of abdominal fat, is an important predictor of cardiovascular risk and MetS [4, 5]. Metabolic syndrome is defined as a pluripathological state characterized by the joint presence of several cardiovascular risk factors such as abdominal obesity, high blood pressure and altered glucose and lipid metabolism (low HDL-cholesterol and high triglycerides) [6].

Although there are several analytical/instrumental techniques for measuring the amount and distribution of body fat, there is no consensus about which the ideal method to calculate central adiposity is, nor how to decide which cut-off points provide greater accuracy, efficiency, sensitivity and specificity in all cases [7, 8].

A simple and inexpensive alternative to these instruments as a way of quantifying abdominal fat is to make anthropometric measurements of central obesity [9]. Waist circumference (WC), body mass index (BMI), waist to height ratio (WHtR), waist to hip ratio (WHR), hip to height ratio (HHR), body adiposity index (BAI), visceral adiposity index (VAI), body shape index (ABSI) and percentage of body fat (%BF) are some examples that can be found in numerous epidemiological studies, in which they try to relate indirectly intra-abdominal (visceral) fat with parameters such as morbidity and mortality, and also with prevalence of hypertension, diabetes, MetS, etc. [10-13].

Since the mid-1990s, the WHtR has been the most widely used anthropometric indicator and the one which has obtained the best predictive results for cardiovascular risk [14]. In a previous publication, a non-invasive method for early detection of MetS (NIM-MetS) using only two anthropometric variables (WHtR and blood pressure (BP)) has been proposed and validated [15]. This method suggests

WHtR≥0.55 as the predictive threshold for the early detection of MetS for both men and women and, also, for any age stratum.

The aim of this study is to reproduce and validate the NIM-Mets method in a large representative sample of Spanish workers, to determine its predictive ability and to find out the stability of the cut-off value of WHtR≥0.55 by gender and age.

MATERIAL AND METHODS

Design and sample

A double epidemiological study was carried out:

1. A cross-sectional study conducted on a working population from the Balearic Islands (Spain) during the period 2011-2015. The mid-term active population of workers was 621,600. Subjects participating in the study were randomly selected during their work health periodic assessments. Every day, each worker was assigned a number and half of the examined workers were randomly selected using a random number table. A total of 69,581 workers were invited to participate in the study. However, 8,782 (12.6%) refused to participate and, thus, the final number of participants was 60,799 (57.3% males and 42.7% females), aged 20 to 70 years old (10.2% of the active population) and belonging to different economic sectors (public administration, health services, etc.). The accuracy obtained with this sample was 0.23%, with a reference population of 621,600 individuals, a security rate of 95% and an expected prevalence of MetS of 10%.
2. A study of diagnostic tests was conducted in 2016 and carried out on the same sample of the cross-sectional study in order to validate the NIM-MetS method for screening for MetS in a healthy population. To determine the sample size, the following indicators were used: 95% expected specificity, 10% prevalence of MetS, 95% confidence and 0.2% accuracy. The sample size obtained was 50,687 workers.

Participants were informed of the purpose of the study before they provided written informed consent to participate. The study protocol complied with the Declaration of Helsinki for conducting medical research involving human subjects, and was approved by the Institutional Review Board of the Mallorca Health Management Ethical Review Committee of GESMA.

Data collection and definition of variables

To carry out the anthropometric measurements, recommendations contained in the manual "International Standards for Anthropometric Assessment (ISAK)" were followed [16]. All the measurements were made by specifically trained staff in order to minimize the variation coefficients. Each measurement was performed three times, taking the average as the final value.

The independent variables were classified into the following categories:

a) Personal and health habits: gender, age and tobacco consumption.

b) Anthropometric measurements:

- Waist circumference (WC) in cm.
- Body mass index (BMI), calculated as body weight (kg) divided by height (m) squared, in Kg/m^2.
- Percentage of body fat (%BF), calculated according to the Deurenberg equation: %BF = 1.2x(BMI) + 0.23x(Age in years) – 10.8x(Gender) – 5.4. Gender: females (0), males (1)
- Waist-to-height ratio (WHtR), calculated as waist circumference divided by height, both in cm.
- Body shape index (ABSI), calculated as $WC/[(BMI)^{2/3}(height)^{1/2}]$.

c) Blood measurements:

- Systolic blood pressure (SBP) in mm Hg.
- Diastolic blood pressure (DBP) in mm Hg.
- Total Cholesterol (mg/dL), LDL-Cholesterol (mg/dL), HDL-Cholesterol (mg/dL), glucose (mg/dL) and triglycerides (mg/dL).

Body weight was measured to the nearest 0.1 kg with an electronic scale (Seca 700 scale, Seca GmbH, Hamburg). Height was measured to the nearest 0.5 cm with a stadiometer (Seca 220 (CM) Telescopic Height Rod for Column Scales, Seca GmbH, Hamburg). Waist circumference was measured half-way between the lower costal border and the iliac crest. The measurement was taken at the end of a

normal expiration with the subject standing up, with their feet together and their arms hanging down by their sides.

Venous blood samples were taken from the antecubital vein in suitable vacutainers without anticoagulant in order to obtain serum. The blood samples were taken after a 12 h overnight fast. Participants sat and rested for at least 15 minutes before the blood samples were taken. Serum was obtained after centrifugation (15 min, 1,000xg, 4ºC) of the blood samples. The serum was stored at -20ºC and analyses were performed within 3 days. Concentrations of glucose, cholesterol and triglycerides were measured in serum following the standard procedures used in clinical biochemistry laboratories with an autoanalyser (SYNCHRON CXH9 PRO, Beckman Coulter, Brea, CA, USA).

Blood pressure was determined after the subjects had rested in the supine position for 10 minutes, using an automatic and calibrated sphygmomanometer (OMRON M3, OMRON Healthcare Europe, Spain). As in the case of the anthropometrical measurements, blood pressure was measured three times, leaving a one-minute gap between each measurement, and the average value was then calculated.

Presence of MetS was ascertained by using the criterion suggested by the NCEP-ATPIII definition (when 3 of 5 of the following characteristics are present, a diagnosis of metabolic syndrome can be made):

- Abdominal obesity (WC≥102 cm in males and WC ≥88 cm in females).
- Triglycerides ≥150 mg/dL.
- HDL-cholesterol <40 mg/dL in males and <50 mg/dL in females.
- Blood pressure ≥130/85 mm Hg.
- Fasting glucose ≥100 mg/dL.

Non-invasive method for the early detection of Mets (NIM-MetS)

NIM-Mets is a new tool for screening for MetS based on the following anthropometric variables and cut-off values: WHtR≥0.55 and BP≥128/85 mm Hg.

This method classifies the population into two groups with different levels of risk:

- Workers with high risk of MetS (probability>61.7%): this group would contain those subjects with both positive variables, i.e. WHtR≥0.55 and BP≥128/85 mm Hg.
- Workers with low risk of MetS (probability of 0.5-16.9%): this group would contain those subjects who have any of the other possible combinations between the two variables considered.

Statistical Analysis

The quantitative variables were presented with a 95% mean and confidence interval and the qualitative ones with absolute frequency and percentage. To test the goodness of fit, the Kolmogorov-Smirnov test was applied to a normal distribution of the data with the Lilliefors correction.

The prevalence of MetS and distribution of the study variables in subjects with and without MetS were determined.

For the bivariate analysis, Student's t-test was used for calculating means for variables normally distributed (using the Levene test for variance equality) and non-parametric tests such as the U Mann-Whitney test (independent samples) were used for variables showing non-normal distribution. For categorical variables, the Chi-squared test and Fisher's exact test were used whenever necessary for each contingency table. We also calculated correlation and regression measurements when necessary for the continuous variables. In addition, ANOVA tests were carried out with the post-hoc Bonferroni contrast method.

Receiver Operator Characteristic (ROC) curves were performed and the Area Under the Curve (AUC) was calculated to find which explanatory variables best predict the onset of MetS. We obtained the cut-off value for each explanatory variable through the Youden index (JI) as JI = Sensitivity + Specificity – 1.

To measure the accuracy of the diagnostic test, sensitivity (S), specificity (SP), positive and negative predictive values (PPV and NPV), likelihood ratios (LH+ and LH-), validity index (VI) and JI were analysed.

The modification of NIM-MetS was obtained from a clinical decision tree (classification) using the CHAID (Chi-squared Automatic Interaction Detection) technique as a growth method. The statistical significance level for splitting nodes and merging categories was $p<0.05$, and significance values were corrected by the Bonferroni method, with a maximum number of iterations of 2,000.

The following programs have been used for statistical and epidemiological data treatment: IBM SPSS Statistics 22.0 software (SPSS / IBM, Chicago, IL, USA) and Epidat version 4.2. (Department of Sanidade, Xunta de Galicia, Galicia, Spain). The level of statistical significance was fixed in all the contrasts for an alpha error below 5%, and the confidence intervals were calculated with a 95% level of confidence.

RESULTS

Characteristics of the study sample

Of the 60,799 workers, 34,827 were male (57.3%). The overall mean age was 40 (39.9-40.1) (Table 1). Men had higher values than women for all the anthropometric and analytical indicators ($p<0.001$) except for %BF and HDL-Cholesterol. The prevalence of smokers was 34.8% (36.6% in men and 32.5% in women), and 17.6% of participants were obese (20% in men and 14.4% women). With regard to drug treatments, 6.6% were undergoing antihypertensive treatment, 3.2% lipid lowering treatments and 1.73% antidiabetic treatments. Finally, the overall prevalence of MetS was 9.0%, with 11.8% in men and 5.4% in women ($p<0.001$).

NIM-MetS validation

Table 2 shows the results of diagnostic tests after applying the NIM-Mets method compared with NCEP-ATP III as a control test. Overall, the indicators of the NIM-MetS method validity were as follows: S = 54.7% (53.4-56), SP = 94.9% (94.7-95), and VI = 91.2% (91-91.5). The sensitivity was higher in men (59.4%) than in women (40.9%).

As regards the NIM-MetS safety indicators, results in the total sample were: PPV = 51.3% (50-52.6) and NPV = 95.5 (95.3-95.7). By gender, PPV was higher in men (51.4%) than in women (50.8%), while NPV was higher in women (96.7%) than in men (94.5%).

Finally, the overall JI was 0.5 (0.48 to 0.51), higher in men (0.52) than in women (0.39).

Comparison and behaviour of the cut-off value for WHtR (≥0.55) according to gender and age

A second question to be dealt with in this research was to compare the cut-off value for WHtR proposed by NIM-MetS with that obtained in the study sample, and

thus determine its variability according to the gender variable and in different age groups (Table 3). In the whole sample (n = 60.799), a cut-off value of 0.544 was obtained for WHtR. In the group of men (n = 34,827), the resulting threshold was 0.558, while for women (n = 25,972) it was 0.525.

It can be seen how the cut-off point increases with age. For men, it ranged from 0.553 (20-30 years old) to 0.563 (≥51 years), whereas for women it was between 0.514 (20-30 years) and 0.55 (≥51 years). The differences between the cut-off values for men and women become narrower as the age increased.

Reproducibility of the NIM-MetS and the new method proposed

The aim was to determine the degree of reproducibility of the NIM-MetS and to propose the required amendments and adjustments depending on the results. To do this, the original procedure for the construction of the NIM-MetS was followed: to select the anthropometric variables which best predict MetS and, working from these, to set up a clinical decision tree using the CHAID method.

Figure 1 shows the results for the anthropometric variables' ROC curves. WHtR achieved the highest AUC 0.85 (0.84 to 0.86), with a cut-off value of 0.544, reaching top values of S = 68.5%, SP = 87% and JI = 0.56. The second variable with the highest AUC was WC, with 0.83 (0.82 to 0.84), a cut-off value of 89.1 cm and S = 72.5, SP = 77.6% and JI = 0.5. BMI with an AUC = 0.8 BMI and SBP with AUC = 0.79 also stood out.

After that, different clinical decision trees were made with a range of cut-off values for WHtR and BP (Table 4). Thus, the range of cut-offs for WHtR was defined by 8 thresholds between 0.535 and 0.57, and included, among others, the cut-off value proposed by NIM-MetS (WHtR≥0.55) and the cut-off value for the total sample (WHtR≥0.544). In addition, three models were established for BP: BP≥128/80 mmHg (cut-off values obtained for SBP and DBP as ROC curves, shown in Figure 2); BP≥128/85 mmHg (BP cut-off values proposed by NIM-MetS); and finally, only SBP≥ 128 mm Hg (second covariate with the highest adjusted OR in

the multiple logistic regression). In this way, 24 clinical decision trees were set up using CHAID methodology. Each tree comprised of a parent node (Node 0), two primary subsidiary nodes (Nodes 1 and 2) and four secondary subsidiary nodes (Nodes 3, 4, 5 and 6). Each of the last four nodes denoted the probability of having MetS. Thus, Node 3 corresponds to the probability that a worker has MetS when both anthropometric variables are negative (below cut-off values). Node 4 indicates the probability that a worker has MetS when BP is above the cut-off value and WHtR below. Node 5 represents the probability that a worker has MetS when BP is lower than the cut-off value and WHtR is above. Finally, Node 6 shows the probability that a worker suffers from MetS when both variables are positive (above the cut-off values). The model BP≥128/80 mmHg was chosen because it had the highest Youden index value (greatest sensitivity and specificity combined) at each of the WHtR cut-off points (Table 4).

The next step was to select the final cut-off value for WHtR. To do this, the method's probability of detection (Node 6 value) and the Youden index for the BP model chosen (BP BP≥128 / 80 mmHg) were plotted for each WHtR cut-off value (Figure 2).

It was noted that the probability of detection of MetS in each tree (Node 6 value) and the WHtR threshold, as well as the Youden index and the WHtR threshold, follow linear functions, in which the equations of its lines are as follows:

- Probability MetS (Node 6) = 5.534*WHtR -2.58
- Youden index = -1.758*WHtR + 1.486

Thus, the final threshold value for WHtR was determined by the cut-off point of both lines: WHtR = 0.558 (Figure 2).

The resulting new method for the early detection of MetS (new NIM-MetS) includes these conditions: WHtR≥0.558 and BP≥128/80 mmHg. Figure 3 shows the decision tree created from these variables and cut-off points. The sensitivity of the proposed method was 56.4%, specificity was 94.5%, validity index was 91.1% and the Youden index 0.51.

Finally, from the probabilities obtained in Nodes 3, 4, 5 and 6, a risk gradient for MetS was developed, according to the WHtR and BP covariates and the proposed cut-off values. Thus, those subjects with lower WHtR and BP values than the cut-off point have a very low probability of suffering from MetS (pMetS = 0.4%). Low risk (pMetS=8.3%) would be found only in those individuals with BP values over 128/80 mmHg but low WHtR. A moderate level of risk (pMetS = 16.3%) would include normotensive subjects who had a WHtR≥0.558. Finally, subjects with WHtR≥0.558 and BP≥128/80 mmHg, would have a 50.5% risk of having MetS.

DISCUSSION

The validity and reproducibility of a non-invasive method for the early detection of MetS (NIM-MetS) has been determined. The validation was carried out from a study of diagnostic tests conducted in Spanish Caucasian adult workers and using, as a reference test, the NCEP-ATP III criteria for the diagnosis of MetS. The early detection of MetS is the key to improving the quality of life of our population, since it prevents the appearance of associated complications such as CVD, type 2 Diabetes Mellitus and, even, cancer [17-20].

NIM-MetS has shown a high validity index both in men (88.6%) and in women (94.7%). Overall, for every 100 workers, the method classified properly 91 cases. Similarly, NIM-MetS has proved to be highly specific, reaching an overall specificity of 94.9% (92.5% in men and 97.8% in women). Both VI and the SP recorded values above those achieved by this method in another Spanish population [15], where it obtained an IV = 89.5% and 91.5% Specificity. For sensitivity, the overall figure was 56.4% (59.4% for men and 40.9% for women), while in the original population, the overall sensitivity was 77.9%.

Although the indicators of validity and accuracy of a screening test (sensitivity and specificity) are intrinsic properties of the test itself and do not depend on the prevalence of the disease considered, this does not prevent these indicators from being affected by characteristics of the population they are applied to [21]. In fact, the most common observation is that a test for early detection or diagnosis alters its sensitivity and specificity depending on these characteristic features of the population. Therefore, the main differences between the two populations (the Balearic and the one considered in the previous study [15]) were analysed, highlighting those features of the Balearic population which contributed to a decreased sensitivity: a younger population (40 vs. 45.1 years), more females (42.7% vs. 32.1%), more smokers (34.8% vs. 28.6%) and lower values for WC (82.95 vs. 87.8 cm), WHtR (0.49 vs. 0.52) and BMI (26.1 vs. 26.5 kg/m^2).

As regards the safety indicators of the test, the positive and negative predictive values, they are definitely affected by the prevalence of the population, lowering the PPV when the prevalence of MetS is lower. In this way, although we found a lower prevalence of MetS in the Balearic Islands than in Cordoba (9% vs. 13.9%), the NIM-Mets produced a lower PPV in the Balearic Islands (51.3% vs. 61.7%), while the negative predictive value remained very similar (95.5% vs. 95.9%).

Screening tests are often used in clinical practice. However, there are very few methods for the early detection of MetS other than the currently known diagnostic criteria, and there are even fewer non-invasive screening tests. A study in the Republic of Korea examined the validity of a test for the early detection of MetS based on the muscle-to-fat ratio [22]. The study was conducted on 6,256 particpants, with a sensitivity of 68.6% in men and 76% in women, and a specificity of 63.8% in men and 53.8% in women. Miller et al. [23] proposed a screening method for MetS in 745 young adults (18-29 years old) in the United States, based on making decision trees with the CHAID methodology and using all the criteria for MetS. The method had a validity rate of 89.4% and a sensitivity rate of 61.7%. Finally, De Kroon et al. [24] conducted a screening test for MetS in 642 young people (aged 17-28) in the Netherlands using anthropometric variables (BMI, WC and BP). The sensitivity of the method was 68.75% and the validity index was 95.6%.

Another hypothesis put forward in this research was to test whether the cut-off value proposed by NIM-MetS for WHtR (≥0.55) would be reproduced in a large sample (60,799 workers from the Balearic Islands), and if it was also valid for both men and women and also for different age groups. WHtR had a cut-off value of 0.544 for the total sample, with 0.558 men and 0.525 for women. As regards age groups, the WHtR threshold increased with age, with 0.553-0.563 for men and 0.514-0.55 for women. These differences were reduced in the total sample (0.53-0.558).

It is noteworthy that several authors have proposed a universal 0.5 cut-off point for WHtR, both to detect MetS and to predict cardiometabolic risk and overall cardiovascular mortality [25-28]. However, in Spain, a cross-sectional study in the general population (n = 6,279, mean age = 43 years) showed that WHtR was the best anthropometric predictor of MetS (NCEP-ATP III), and the authors proposed a cut-off value of 0.55, with which they obtained a sensitivity of 91% and a specificity of 64% [28]. This cut-off value is very similar to the one proposed from the results obtained in the present study.

In Chile, two important child population studies were conducted by Arnaiz et al., showing results which match the value of the cut-off point proposed in the present study. Thus, in the first study, conducted on 209 schoolchildren (mean age of 11.5), the authors obtained a cut-off value of 0.55 WHtR for MetS [29], while in the second study, performed in 2,980 children aged 6-14 (mean age of 9.9), the authors concluded that the WHtR did not change with age and gender and, therefore, a universal cut-off value could be agreed for both children and adults [30].

The prospective study by Koch et al. [31] carried out in Chile on about 6,714 men and 6,340 women, evaluating the relationship between various anthropometric indices of adiposity, cardiovascular risk factors and mortality for a cut-off value of 0.55 obtained a sensitivity of 75.8 % and a specificity of 73.3% for men, and a sensitivity of 77.6% and specificity of 56.3% for women.

In addition, several investigations conducted in non-European and non-Hispanic populations also concur on this threshold of WHtR for MetS. Thus, Obeidat et al. [32] in a study on a Jordanian population (n = 630, aged 20-70 years) reported a cut-off value of 0.56 in men and 0.52 in women; in India, Rajput et al. [33], achieved a threshold of 0.52 for men and women (n = 3,042) in all locations (rural or urban areas); and in China, He et al. [34], in a descriptive study of 1,068 adult subjects, reported a cut-off value for WHtR of 0.5 for men and women alike.

As for the reproducibility of the NIM-MetS method in this new, larger sample of 60,799 workers from the Balearic Islands, the method has produced again the same variables obtained in Cordoba. In the multiple logistic regression, WHtR and BP achieved the highest adjusted OR values. Thus, WHtR was the anthropometric index that best discriminated MetS presence, with an adjusted OR value of 4.4 (3.9-4.9), while SBP obtained an adjusted OR value of 3.8 (3.5-4.1).

Several investigations have confirmed the high predictive ability of WHtR for MetS and CVD. In the systematic review conducted by Ashwell et al. [35], in which 10 out of the 31 studies analysed the association between anthropometric measurements of central obesity and MetS, WHtR had the highest AUC value 0.76 (men) and 0.75 (women). This contrasted with WC, which obtained an AUC value of 0.75 (equal for men and women) and BMI, with an AUC value of 0.72 (men and women). Similarly, a meta-analysis conducted by Savva et al. [36], in which 8 out of the 24 studies included compared WHtR (cut-off point 0.5) with BMI (cut-off point of 23 for the Asian population and 25 for the rest) for cardiometabolic risk in an Asian and non-Asian population, and concluded that WHtR showed a stronger association with MetS than with BMI.

Through the present study, the NIM-MetS method has been corrected, and definitive cut-off values have been proposed for WHtR (0.558) and BP (128-80 mmHg), from which a sensitivity rate of 56.4%, a specificity rate of 94.5%, a validity index of 91.1% and a Youden index of 0.51 are obtained. On the other hand, finally, the long-term ability of MetS to predict CVD has shown to be limited by the dichotomous (binary) and qualitative nature of the classic diagnostic criteria for MetS. An innovative aspect that NIM-MetS brings is to provide a gradient or scale of risk of developing MetS which is divided into four risk levels: Very low risk (probability = 0.4%), low risk (probability = 8.3%), moderate risk (probability = 16.4%) and high risk (probability = 50.5%). In this way, health professionals can take certain steps depending on the level of risk of MetS and promote a more accurate and early detection of the possible complications associated with CVD and

MetS. Along the same lines, there have been several studies using methods based on scores to quantify the amount of risk accumulated by the presence of the components that define the metabolic syndrome (Metabolic Syndrome Severity Score) [37, 38].

Conclusions

The NIN-MetS has proved to be a valid method for the early detection of MetS in a healthy worker population. It is a simple, economical and quick non-invasive test which is easy to apply and interpret in any health care setting (primary health care, hospitals, occupational health) as well as in other settings (education, sport, etc.). WHtR is the best predictor of MetS and its cut-off point can be used for both genders and for different age groups. The clinical decision tree that produces the NIM-MetS uses WHtR (0.558) and BP (128/80 mm Hg), and obtains high specificity and diagnostic validity. The NIM-MetS provides a gradient or risk scale which allows a more accurate and earlier detection of CVD in subjects with risk of MetS.

Contributor ship statement.

Manuel Romero-Saldana contributed to the conception, design, acquisition and analysis/interpretation of data, drafted the manuscript, critically revised the manuscript and gave his final approval to the text, while also agreeing to be accountable for the integrity and accuracy of all aspects of the work.

Pedro Tauler contributed to the data collection, analysis, critically revised the manuscript, gave his final approval, and agrees to be accountable for the integrity and accuracy of all aspects of the work.

Manuel Vaquero-Abellán contributed to the analysis and interpretation, critically revised the manuscript, gave his final approval, and agrees to be accountable for the integrity and accuracy of all aspects of the work.

Angel A. Lopez-Gonzalez contributed to the data collection, analysis, critically revised the manuscript, gave his final approval, and agrees to be accountable for the integrity and accuracy of all aspects of the work.

Francisco J. Fuentes-Jimenez contributed to the analysis, critically revised the manuscript, gave his final approval, and agrees to be accountable for the integrity and accuracy of all aspects of the work.

Antoni Aguilo contributed to the conception, critically revised the manuscript, gave his final approval, and agrees to be accountable for the integrity and accuracy of all aspects of the work.

Carlos Alvarez-Fernandez contributed to the conception, critically revised the manuscript, gave his final approval, and agrees to be accountable for the integrity and accuracy of all aspects of the work.

Guillermo Molina-Recio contributed to the analysis and interpretation, critically revised the manuscript, gave her final approval and agrees to be accountable for the integrity and accuracy of all aspects of the work.

Miquel Bennasar-Veny contributed to the design and the acquisition of data, critically revised the manuscript, gave his final approval, and agrees to be accountable for the integrity and accuracy of all aspects of the work.

Competing interests.

None declared.

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Data sharing statement

We are willing to share the study data with other research groups

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Table 1. Characteristics of the sample according to gender.

Variable	Total n=60,799	Men n= 34,827	Women n= 25,972	p
Age	40 (39.9 – 40.1)	40.4 (40.3 – 40.5)	39.5 (39.3 – 39.6)	<0.001
Smoke (yes) n (%)	21,177 (34.8%)	12,746 (36.6%)	8,431 (32.5%)	<0.001
BMI (Kg/m^2)	26.1 (26 – 26.1)	26.9 (26.8 – 26.9)	25 (25 – 25.1)	<0.001
WC (cm)	82.95 (82.9 – 83)	88.6 (88.5 – 88.7)	75.4 (75.3 – 75.5)	<0.001
WHtR	0.49 (0.49 – 0.49)	0.51 (0.50 – 0.51)	0.47 (0.46 – 0.47)	<0.001
ABSI	0.0735 (0.073 - 0.0735)	0.0735 (0.0735 - 0.0735)	0.07 (0.07 -0.07)	<0.001
BF (%)	28.9 (28.9 – 29)	25.3 (25.3 – 25.4)	33.7 (33.6 – 37.8)	<0.001
SBP (mm Hg)	120.8 (120.6 -120.9)	125.4 (125.2 – 125.6)	114.6 (114.4 – 114.8)	<0.001
DBP (mm Hg)	73.6 (73.5 – 73.7)	76 (75.9 -76.1)	70.4 (70.3 – 70.5)	<0.001
Glucose (mg/dL)	88.3 (88.1- 88.5)	90.6 (90.4 – 90.8)	85.2 (85 – 85.4)	<0.001
Cholesterol (mg/dl)	195.2 (194.9 - 195.5)	196.9 (196.5 -197.3)	193 (192.6 – 193.4)	<0.001
HDL-Cholesterol (mg/dL)	52.4 (52.3 - 52.5)	50.5 (50.4 – 50.6)	55 (54.9 – 55.1)	<0.001
LDL-Cholesterol (mg/dL)	121.2 (120.9 - 121.5)	121.8 (121.4 – 126.2)	120.5 (120 – 120.9)	<0.001
Triglycerides (mg/dL)	109.3 (108.7 – 109.9)	125.3 (124.4 – 126.2)	88.8 (88.2 – 89.4)	<0.001
MetS (yes) n (%)	5,487 (9.0%)	4,097 (11.8%)	1,390 (5.4%)	<0.001

BMI: Body Mass Index; WC: Waist circumference; WHtR: Waist to Height Ratio; ABSI: A body Shape Index; BF (%): Body Fat percentage calculated according to the Deurenberg equation; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MetS: Metabolic syndrome. P<0.05 indicates significant differences between genders

Table 2. Diagnostic test accuracy of NIM-MetS against NCEP-ATPIII

STANDARD REFERENCE NCEP APTIIII

		TOTAL			MEN			WOMEN		
		Yes	**No**	**Total**	**Yes**	**No**	**Total**	**Yes**	**No**	**Total**
NIM – MetS (n)	**Yes**	3,001	2,850	5,851	2,433	2,300	4,733	568	550	1,118
	No	2,486	52,462	54,948	1,664	28,430	30,094	822	24,032	24,854
	Total	5,487	55,312	60,799	4,097	30,730	34,827	1,390	24,582	25,972
Efficacy indicators, CI 95%										
Sensitivity		54.7 (53.4 – 56)			59.4 (57.9 – 60.9)			40.9 (38.2 – 43.5)		
Specificity		94.9 (94.7 – 95)			92.5 (92.2 – 92.8)			97.8 (97.6 – 98)		
PPV		51.3 (50 – 52.6)			51.4 (50 – 52.8)			50.8 (47.8 – 53.8)		
NPV		95.5 (95 – 95.7)			94.5 (94.2 – 94.7)			96.7 (96.5 – 96.9)		
VI		91.2 (91 – 91.5)			88.6 (88.3 – 89)			94.7 (94.4 – 95)		
LH +		10.6 (10.2 – 11.1)			7.9 (7.6 – 8.3)			18.3 (16.5 – 20.3)		
LH -		0.48 (0.46 – 0.49)			0.44 (0.42 – 0.46)			0.6 (0.58 – 0.63)		
JI		0.50 (0.48 – 0.51)			0.52 (0.5 – 0.53)			0.39 (0.36 – 0.41)		

PPV: Positive Predictive Value; NPV: Negative Predictive Value; VI: Validity Index; LH +: Likelihood ratio positive; LH -: Likelihood ratio negative; JI: Youden Index.

Table 3. Area under the curve (AUC) and cut-off values for WHtR according to gender and age groups

Age group (years)	n	Prevalence of MetS (%)[a]	AUC CI 95%	Cut-off value	Sensitivity (%)	Specificity (%)	JI
			MEN				
20-30	6,825	3.05	0.92 (0.9 – 0.95)	0.553	80.3	93.4	0.74
31-40	11,623	7.5	0.88 (0.86 – 0.89)	0.55	77.4	88.1	0.65
41-50	10,080	14.9	0.82 (0.81 – 0. 83)	0.561	66.4	87.7	0.541
≥51	6,659	23.1	0.75 (0.74 – 0.77)	0.563	58.9	83.01	0.42
Total	34,827	11.8	0.84 (0.83 – 0.85)	0.558	66.7	88.8	0.555
			WOMEN				
20-30	5,715	1.1	0.90 (0.85 – 0.95)	0.514	82	84	0.736
31-40	8,529	2.7	0.91 (0.89 – 0.93)	0.525	80.3	90.8	0.71
41-50	7,641	6.6	0.91 (0.89 – 0.93)	0,525	80.3	90.8	0.71
≥51	4,087	14.4	0.75 (0.73 – 0.77)	0,55	48.4	90.5	0.39
Total	25,972	5.4	0.85 (0.84 -0.86)	0.525	65.1	88.7	0.54
			TOTAL				
20-30	12,540	2.1	0.92 (0.9 – 0.94)	0.531	84.4	90.1	0.745
31-40	19,792	5,5	0.9 (0.89 – 0.91	0.541	78.2	88.5	0.67
41-50	17,721	11,3	0.83 (0.82 – 0.84)	0.544	69.6	84.3	0.539
≥51	10,746	19.8	0.76 (0.75 – 0.77)	0.558	57	85.3	0.423
Total	60,799	9	0.85 (0.84 – 0.86)	0.544	68.5	87	0.556

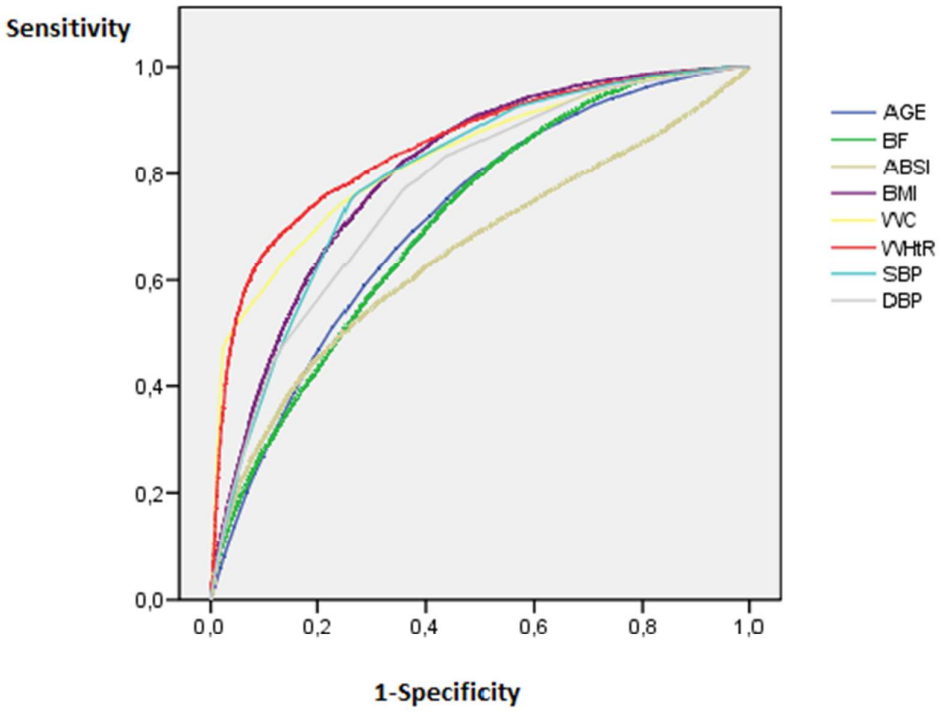
a: MetS according to NCEP ATPIII criterion; AUC: area under the curve; JI: Youden Index

Table 4. Probabilities of MetS (%) for nodes 3, 4, 5 and 6 in decision trees according to cut-off values of WtHR

WHtR range	BP model	Probabilities of MetS for nodes in the decision tree				Efficacy indicators for diagnostic test accuracy			
Cut-off points	BP	Node 3	Node 4	Node 5	Node 6	Sensitivity (%)	Specificity (%)	VI (%)	JI
0.535	BP[1]	0.3	7.4	10.3	38.4	63.9	89.7	87.5	0.536
	BP[2]	0.5	10.4	12.2	43.3	59.3	92.3	89.3	0.516
	SBP	0.6	10.5	13.7	43.3	57	92.6	89.4	0.496
0.54	BP[1]	0.3	7.6	11.5	40.7	62.7	90.9	88.4	0.536
	BP[2]	0.5	10.5	13.5	45.7	57.8	93.2	90	0.51
	SBP	0.6	10.7	15.2	45.7	55.6	93.5	90	0.491
0.544 [a]	BP[1]	0.4	7.7	12.5	42.8	61.6	91.8	89.1	0.534
	BP[2]	0.5	10.9	14.6	48	56.7	93.9	90.5	0.506
	SBP	0.6	10.8	16.4	48	54.5	94.1	90.6	0.486
0.550 [b]	BP[1]	0.4	7.9	14.2	46.1	59.6	93.1	90.1	0.527
	BP[2]	0.5	10.9	16.6	51.3	54.7	94.8	91.2	0.461
	SBP	0.7	11	18.5	51.4	52.6	95.1	91.2	0.477
0.555	BP[1]	0.4	8.2	15.7	49.1	57.8	94.1	90.8	0.519
	BP[2]	0.6	11.1	18.3	54.4	53	95.6	91.7	0.486
	SBP	0.7	11.3	20.3	54.5	51	95.8	91.7	0.468
0.560	BP[1]	0.5	8.5	17	51.8	55.7	94.9	91.3	0.506
	BP[2]	0.6	11.5	19.9	57.1	51	96.2	92.1	0.472
	SBP	0.8	11.6	21.9	57.2	49.1	96.4	92.1	0.455
0.565	BP[1]	0.5	8.8	18.6	54.9	53.4	95.6	91.8	0.49
	BP[2]	0.6	11.9	21.8	60.3	48.8	96.8	92.5	0.456
	SBP	0.8	12	23.9	60.4	47	96.9	92.4	0.439
0.570	BP[1]	0.5	9.1	19.9	57.4	51.4	96.2	92.2	0.476
	BP[2]	0.7	12.3	23.3	62.8	46.9	97.2	92.7	0.441
	SBP	0.9	12.4	25.5	63	45.2	97.4	92.7	0.426

BP: Blood Pressure; BP[1]: Blood pressure ≥128/80 mmHg; BP[2]: Blood pressure ≥128/85 mmHg; SBP: Systolic blood pressure≥128 mmHg; VI: Validity index; JI: Youden Index; a: Cut-off point for WHtR obtained in the total simple (n=60,799); b: Cut-off point proposed by NIM-MetS

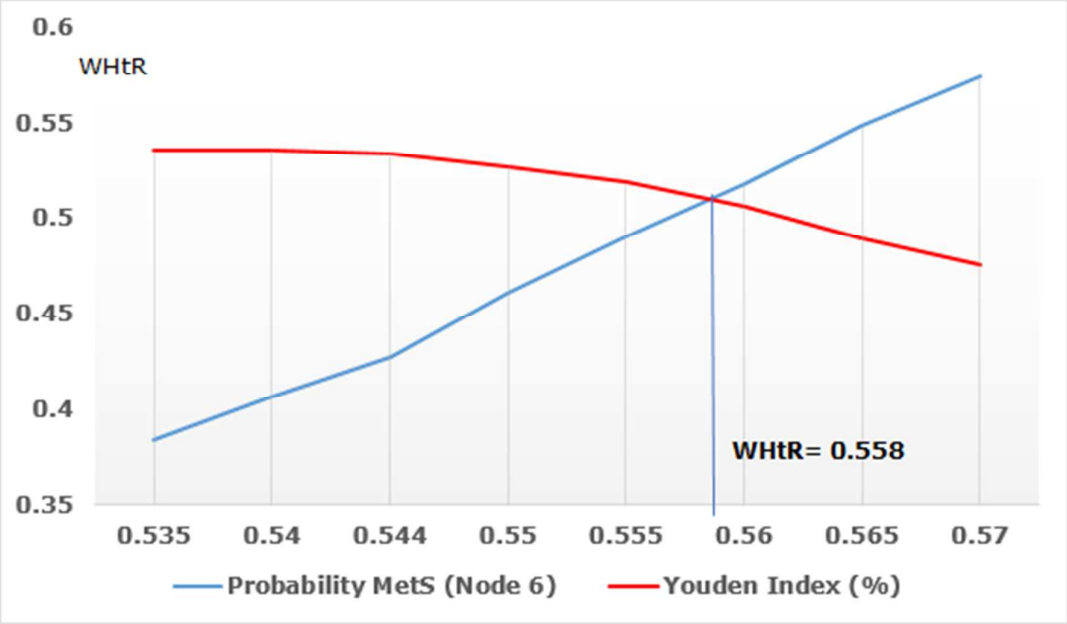
Figure 1. Anthropometric variables. ROC curves, area under the cuve, cut-off points and efficacy indicators



	AUC (CI 95%)	CP	Sensitivity (%)	Specificity (%)	JI
Age	0.71 (0.71- 0.72)	42.5	69.2	62.5	0.317
WHtR	0.85 (0.84 – 0.86)	0.54	68.5	87	0.56
WC	0.83 (0.82 – 0.84)	89.1	72.5	77.6	0.5
BMI	0.8 (0.8 – 0.81)	27.1	78.4	68.34	0.47
ABSI	0.65 (0.64 – 0.66)	0.0772	50.4	75.2	0.26
BF%	0.71 (0.7 – 0.72)	29.4	70.9	58.1	0.3
SBP	0.79 (0.79 – 0.8)	127.5	75.8	73.5	0.49
DBP	0.77 (0.76 – 0.78)	78.5	77.3	63.9	0.41

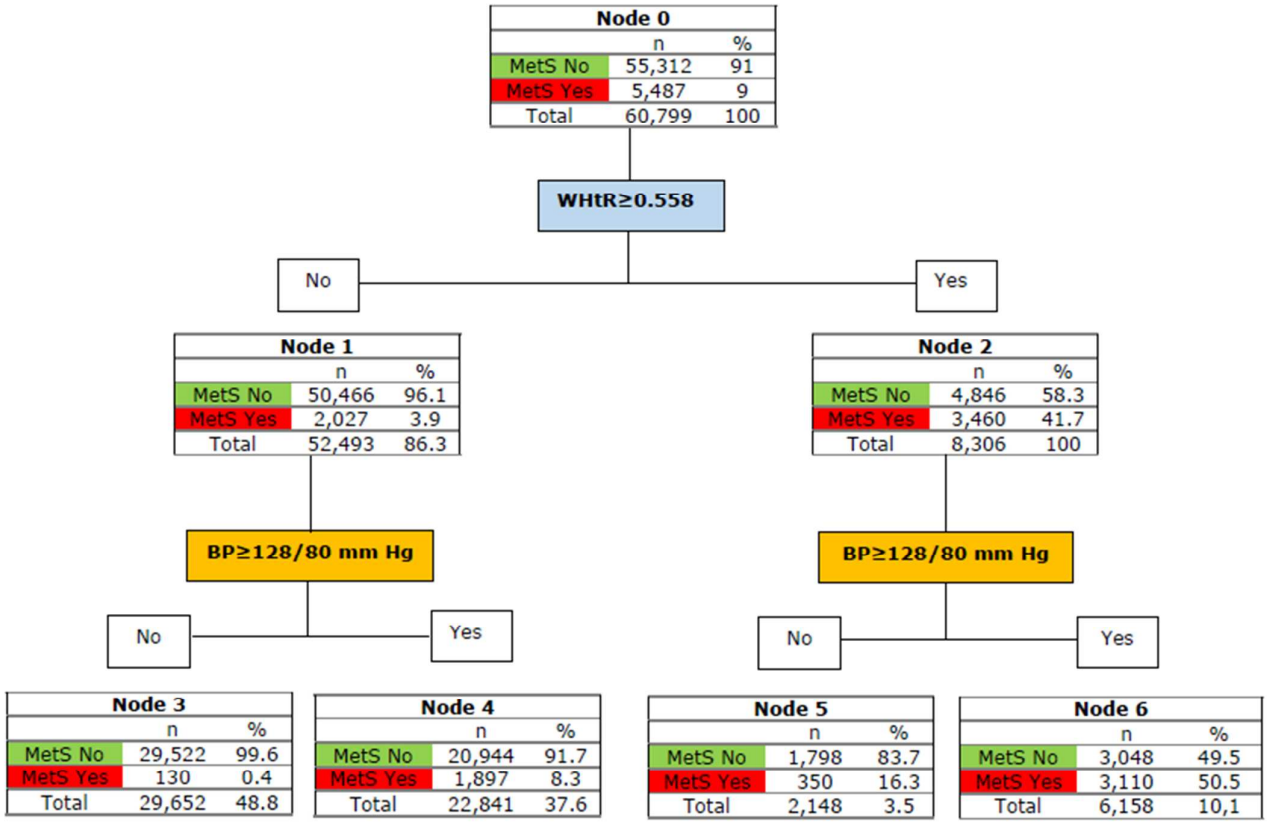
AUC: Area under curve CP: Cut-off point; JI: Youden Index; BMI: Body mass index; WC: Waist circumference; WHtR: Waist to height ratio; ABSI: A Body Shape Index; BF (%): Body Fat calculated according to the Deurenberg equation; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.

Figure 2. WHtR cut-off point resolution



WHtR: Waist to height ratio

Figure 3. Definitive decision tree, new NIM-Mets proposed



STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Checked in page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6-7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	9
		(*e*) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	11
		(c) Consider use of a flow diagram	Not necesary
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11-12
		(b) Indicate number of participants with missing data for each variable of interest	none
Outcome data	15*	Report numbers of outcome events or summary measures	11-12-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted	12-13-14

		estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	13-14
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not indicated
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-14
Discussion			
Key results	18	Summarise key results with reference to study objectives	16-17-18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17-18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section & Topic	No	Item	Checked in page
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	2
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	4
	4	Study objectives and hypotheses	4-5
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	6
Participants	**6**	Eligibility criteria	6
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	6
	8	Where and when potentially eligible participants were identified (setting, location and dates)	6
	9	Whether participants formed a consecutive, random or convenience series	6
Test methods	**10a**	Index test, in sufficient detail to allow replication	7
	10b	Reference standard, in sufficient detail to allow replication	7
	11	Rationale for choosing the reference standard (if alternatives exist)	
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	8
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	8
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	8-9
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	8-9
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	9-10
	15	How indeterminate index test or reference standard results were handled	9-10
	16	How missing data on the index test and reference standard were handled	9-10
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	
	18	Intended sample size and how it was determined	6
RESULTS			
Participants	**19**	Flow of participants, using a diagram	Not indicated
	20	Baseline demographic and clinical characteristics of participants	11
	21a	Distribution of severity of disease in those with the target condition	11-12
	21b	Distribution of alternative diagnoses in those without the target condition	11-12
	22	Time interval and any clinical interventions between index test and reference standard	Not necessary
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	12
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	12
	25	Any adverse events from performing the index test or the reference standard	None
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	17-18
	27	Implications for practice, including the intended use and clinical role of the index test	17-18-19
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	28	Registration number and name of registry	
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STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

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Validation of a non-invasive method for the early detection of metabolic syndrome: a diagnostic accuracy test in a working population

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Validation of a non-invasive method for the early detection of metabolic syndrome: a diagnostic accuracy test in a working population

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ABSTRACT

Objectives. A non-invasive method for the early detection of Metabolic Syndrome (NIM-MetS) using only Waist to Height Ratio (WHtR) and Blood Pressure (BP) has recently been published, with fixed cut-off values for gender and age. The aim of this study was to validate this method in a large sample of Spanish workers.

Design. A diagnostic test accuracy to assess the validity of the method was performed.

Setting. Occupational Health Services.

Participants. The studies were conducted in 2012-2016 on a sample of 60,799 workers from the Balearic Islands (Spain).

Interventions. The NCEP-ATP III criteria were used as the gold standard. NIM-MetS has been devised using classification trees (the CHAID, Chi-squared Automatic Interaction Detection method).

Main outcome measures. Anthropometric and biochemical variables to diagnose MetS. Sensitivity, specificity, validity index and Youden Index were determined to analyse the accuracy of the diagnostic test (NIM-MetS).

Results. Regarding the validation of the method, sensitivity was 54.7%, specificity 94.9% and validity index 91.2%. The cut-off value for WHtR was 0.54, ranging from 0.51 (lower age group) to 0.56 (higher) in the age groups. Variables more closely associated with MetS were WHtR (AUC=0.85; 95% CI: 0.84-0.86) and Systolic Blood Pressure (AUC=0.79; 95% CI: 0.78-0.80). The final cut-off values for the non-invasive method were WHtR≥0.56 and BP≥128/80 mmHg, which includes four levels of MetS risk (very low, low, moderate and high).

Conclusions. The analysed method has shown a high validity index (higher than 91%) for the early detection of MetS. It is a non-invasive method easy to apply and interpret in any health care setting. This method provides a scale of MetS risk which allows a more accurate detection and a more effective intervention.

Strengths and limitations of this study

- This is the first study assessing the validation of a non-invasive method for the early detection of metabolic syndrome (NIM-MetS).
- A diagnostic test study has been carried out in a large sample of healthy workers.
- MetS was ascertained by using the NCEP-ATP III definition, but there is a lack of consensus regarding MetS definition.
- A new procedure to measure MetS using variables with universal cut-off points (waist to height ratio and blood pressure) is suggested.
- The NIM-MetS method has shown high specificity, but low sensitivity.

INTRODUCTION

The obesity epidemic which currently affects the world population has resulted in a general increase in the prevalence of metabolic syndrome (MetS).[1-3] Overweight and obesity are factors related to the onset of type 2 diabetes, hypertension, dyslipidemia and cardiovascular diseases (CVD). In particular, central obesity, which is defined as an excessive accumulation of abdominal fat, is an important predictor of cardiovascular risk and MetS.[4,5] Metabolic syndrome is defined as a pluripathological state characterized by the joint presence of several cardiovascular risk factors such as abdominal obesity, high blood pressure and altered glucose and lipid metabolism (low HDL-cholesterol and high triglycerides).[6]

Although there are several analytical/instrumental techniques for measuring the amount and distribution of body fat, there is no consensus about which the ideal method to calculate central adiposity is, nor how to decide which cut-off points provide greater accuracy, efficiency, sensitivity and specificity in all cases.[7,8]

A simple and inexpensive alternative to these instruments as a way of quantifying abdominal fat is to make anthropometric measurements of central obesity[9]. Waist circumference (WC), body mass index (BMI), waist to height ratio (WHtR), waist to hip ratio (WHR), hip to height ratio (HHR), body adiposity index (BAI), visceral adiposity index (VAI), body shape index (ABSI) and percentage of body fat (%BF) are some examples that can be found in numerous epidemiological studies, in which they try to relate indirectly intra-abdominal (visceral) fat with parameters such as morbidity and mortality, and also with prevalence of hypertension, diabetes, MetS, etc.[10-13]

Since the mid-1990s, the WHtR has been the most widely used anthropometric indicator and the one which has obtained the best predictive results for cardiovascular risk.[14] In a previous publication, a non-invasive method for early detection of MetS (NIM-MetS) using only two anthropometric variables (WHtR and blood pressure (BP)) has been proposed and validated.[15] This method suggests

WHtR≥0.55 as the predictive threshold for the early detection of MetS for both men and women and, also, for any age stratum.

The aim of this study is to validate the NIM-Mets method in a large representative sample of Spanish workers, to determine its predictive ability and to find out the stability of the cut-off value of WHtR≥0.55 by gender and age.

MATERIAL AND METHODS

Design and sample

A diagnostic test using a cross-sectional study was carried out on a working population from the Balearic Islands (Spain) between 2012 and 2016. Subjects participating in the study were randomly selected during their work health periodic assessments. Every day, each worker was assigned a number and half of the examined workers were randomly selected using a random number table. A total of 69,581 workers were invited to participate in the study. However, 8,782 (12.6%) refused to participate and, thus, the final number of participants was 60,799 workers (10.2% of the active population) belonging to different economic sectors (public administration, health services, etc.), aged 20 to 70 years old, and with 57.3% of males and 42.7% of females.

Participants were informed of the purpose of the study before they provided written informed consent to participate. The study protocol complied with the Declaration of Helsinki for conducting medical research involving human subjects, and was approved by the Institutional Review Board of the Mallorca Health Management Ethical Review Committee of GESMA.

Data collection and definition of variables

To carry out the anthropometric measurements, recommendations contained in the manual "International Standards for Anthropometric Assessment (ISAK)" were followed.[16] All the measurements were made by specifically trained staff in order to

minimize the variation coefficients. Each measurement was performed three times, taking the average as the final value.

The independent variables were classified into the following categories:

a) Personal and health habits: gender, age and tobacco consumption.

b) Anthropometric measurements:

- Waist circumference (WC) in cm.
- Body mass index (BMI), calculated as body weight (kg) divided by height (m) squared, in kg/m^2.
- Percentage of body fat (%BF), calculated according to the Deurenberg equation: %BF = 1.2x(BMI) + 0.23x(Age in years) – 10.8x(Gender) – 5.4. Gender: females (0), males (1)
- Waist-to-height ratio (WHtR), calculated as waist circumference divided by height, both in cm.
- Body shape index (ABSI), calculated as $WC/[(BMI)^{2/3}(height)^{1/2}]$.

c) Blood measurements:

- Systolic blood pressure (SBP) in mmHg.
- Diastolic blood pressure (DBP) in mmHg.
- Total Cholesterol (mg/dL), LDL-Cholesterol (mg/dL), HDL-Cholesterol (mg/dL), glucose (mg/dL) and triglycerides (mg/dL).

Body weight was measured to the nearest 0.1 kg with an electronic scale (Seca 700 scale, Seca GmbH, Hamburg). Height was measured to the nearest 0.5 cm with a stadiometer (Seca 220 (CM) Telescopic Height Rod for Column Scales, Seca GmbH, Hamburg). Waist circumference was measured half-way between the lower costal border and the iliac crest. The measurement was taken at the end of a normal expiration with the subject standing up, with their feet together and their arms hanging down by their sides.

Venous blood samples were taken from the antecubital vein in suitable vacutainers without anticoagulant in order to obtain serum. The blood samples were taken after a 12 h overnight fast. Participants sat and rested for at least 15

minutes before the blood samples were taken. Serum was obtained after centrifugation (15 min, 1,000xg, 4ºC) of the blood samples. The serum was stored at -20ºC and analyses were performed within 3 days. Concentrations of glucose, cholesterol and triglycerides were measured in serum following the standard procedures used in clinical biochemistry laboratories with an autoanalyser (SYNCHRON CXH9 PRO, Beckman Coulter, Brea, CA, USA).

Blood pressure was determined after the subjects had rested in the supine position for 10 minutes, using an automatic and calibrated sphygmomanometer (OMRON M3, OMRON Healthcare Europe, Spain). As in the case of the anthropometrical measurements, blood pressure was measured three times, leaving a one-minute gap between each measurement, and the average value was then calculated.

Presence of MetS was ascertained by using the criterion suggested by the NCEP-ATP III definition (when 3 of 5 of the following characteristics are present, a diagnosis of metabolic syndrome can be made):

- Abdominal obesity (WC≥102 cm in males and WC ≥88 cm in females).
- Triglycerides ≥150 mg/dL.
- HDL-cholesterol <40 mg/dL in males and <50 mg/dL in females.
- Blood pressure ≥130/85 mmHg.
- Fasting glucose ≥100 mg/dL.

Non-invasive method for the early detection of Mets (NIM-MetS)

NIM-Mets is a new tool for screening for MetS based on the following anthropometric variables and cut-off values: WHtR≥0.55 and BP≥128/85 mmHg. This method classifies the population into two groups with different levels of risk:

- Workers with high risk of MetS (probability>61.7%): this group would contain those subjects with both positive variables, i.e. WHtR≥0.55 and BP≥128/85 mmHg.

- Workers with low risk of MetS (probability of 0.5-16.9%): this group would contain those subjects who have any of the other possible combinations between the two variables considered.

Statistical Analysis

Statistical analysis was carried out using the IBM SPSS Statistics 22.0 software (SPSS / IBM, Chicago, IL, USA) and the Epidat version 4.2. (Department of Sanidade, Xunta de Galicia, Galicia, Spain). Continuous data are presented as mean values, standard deviation, and confidence interval at 95%. Categorical data are shown as frequency counts and percentages. All the data were tested for their normal distribution (Kolmogorov–Smirnov test with the Lilliefors adjustment).

Student's t-test and U Mann-Whitney test were used in the bivariate analyses for normal and non-normal distributed variables respectively. ANOVA tests with the post-hoc Bonferroni contrast method were carried out when more than two groups were considered in the analysis. The Levene test was used to determine the variance equality. The χ^2 test was applied to assess differences between groups in categorical variables.

Receiver Operator Characteristic (ROC) curves were performed and the Area Under the Curve (AUC) was calculated to find which explanatory variables best predict the onset of MetS. We obtained the cut-off value for each explanatory variable through the Youden index (JI) as JI = Sensitivity + Specificity – 1.

To measure the accuracy of the diagnostic test, sensitivity (S), specificity (SP), positive and negative predictive values (PPV and NPV), likelihood ratios (LH+ and LH-), validity index (VI) and JI were analysed. Validity index was calculated as the quotient between the sum of true positives and true negatives, divided by the total number of subjects, therefore representing the percentage of subjects properly classified by the test.

The modification of NIM-MetS was obtained from a clinical decision tree (classification) using the CHAID (Chi-squared Automatic Interaction Detection)

technique as a growth method. The statistical significance level for splitting nodes and merging categories was $p<0.05$, and significance values were corrected by the Bonferroni method, with a maximum number of iterations of 2,000.

The level of statistical significance was fixed in all the contrasts for an alpha error below 5%, and the confidence intervals were calculated with a 95% level of confidence.

Patient and public involvement

Patients were not involved in setting the research question and in the study design. All patients were randomly selected during their work health periodic assessments to participate in the study and they were interviewed face-to-face by trained researchers for detailed explanation of the purpose of this research and informed consent at the beginning. No patients were involved in data analysis or in the manuscript writing. Results of the research will not be disseminated to the patients.

RESULTS

Characteristics of the study sample

Of the 60,799 workers, 34,827 were male (57.3%). The overall mean age was 40 years (39.9-40.1) (Table 1). Among anthropometrical and blood parameters shown in Table 1, women showed higher %BF and HDL-Cholesterol values ($p<0.001$), while men showed significant higher values for the rest of the parameters shown in this table. The prevalence of smokers was 34.8% (36.6% in men and 32.5% in women), and 17.6% of participants were obese (20% in men and 14.4% women). With regard to drug treatments, 6.6% of participants were undergoing antihypertensive treatment, 3.2% lipid lowering treatments and 1.7% antidiabetic treatments. Finally, the overall prevalence of MetS was 9.0%, with 11.8% in men and 5.4% in women ($p<0.001$).

NIM-MetS validation

Table 2 shows the results of diagnostic tests after applying the NIM-Mets method compared with NCEP-ATP III as a control test. Overall, the indicators of the NIM-MetS method validation were as follows: S = 54.7% (53.4-56.0), SP = 94.9% (94.7-95.0), and VI = 91.2% (91.0-91.5). The sensitivity was higher in men (59.4%) than in women (40.9%).

As regards the NIM-MetS safety indicators, results in the total sample were: PPV = 51.3% (50.0-52.6) and NPV = 95.5 (95.3-95.7). By gender, PPV was higher in men (51.4%) than in women (50.8%), while NPV was higher in women (96.7%) than in men (94.5%). Finally, the overall JI was 0.5 (0.48 to 0.51), higher in men (0.52) than in women (0.39).

A second question to be dealt with in this research was to compare the cut-off value for WHtR proposed by NIM-MetS with that obtained in the study sample, and thus determine its variability according to the gender variable and in different age groups (Table 3). In the whole sample (n = 60.799), a cut-off value of 0.54 was obtained for WHtR. In the group of men (n = 34,827), the resulting threshold was 0.56, while for women (n = 25,972) it was 0.53.

It can be seen how the cut-off point increases with age. For men, it ranged from 0.55 (20-30 years old) to 0.56 (≥51 years), whereas for women it was between 0.51 (20-30 years) and 0.55 (≥51 years). The differences between the cut-off values for men and women become narrower as the age increased.

Figure 1 shows the results for the anthropometric variables' ROC curves. WHtR achieved the highest AUC 0.85 (95% CI: 0.84 to 0.86), with a cut-off value of 0.54, reaching top values of S = 68.5%, SP = 87.0% and JI = 0.56. The second variable with the highest AUC was WC, with 0.83 (95% CI: 0.82 to 0.84), a cut-off value of 89.1 cm and S = 72.5, SP = 77.6% and JI = 0.5. BMI with an AUC = 0.8 BMI and SBP with AUC = 0.79 also stood out.

Figure 1. Anthropometric variables. ROC curves, area under the cuve, cut-off points and efficacy indicators.

After that, different clinical decision trees were made with a range of cut-off values for WHtR and BP (Table 4). Thus, the range of cut-offs for WHtR was defined by 8 thresholds between 0.54 and 0.57, and included, among others, the cut-off value proposed by NIM-MetS (WHtR≥0.55) and the cut-off value for the total sample (WHtR≥0.54). In addition, three models were established for BP: BP≥128/80 mmHg (cut-off values obtained for SBP and DBP as ROC curves, shown in Figure 2); BP≥128/85 mmHg (BP cut-off values proposed by NIM-MetS); and finally, only SBP≥ 128 mmHg (second covariate with the highest adjusted OR in the multiple logistic regression). In this way, 24 clinical decision trees were set up using CHAID methodology. Each tree comprised of a parent node (Node 0), two primary subsidiary nodes (Nodes 1 and 2) and four secondary subsidiary nodes (Nodes 3, 4, 5 and 6). Each of the last four nodes denoted the probability of having MetS. Thus, Node 3 corresponds to the probability that a worker has MetS when both anthropometric variables are negative (below cut-off values). Node 4 indicates the probability that a worker has MetS when BP is above the cut-off value and WHtR below. Node 5 represents the probability that a worker has MetS when BP is lower than the cut-off value and WHtR is above. Finally, Node 6 shows the probability that a worker suffers from MetS when both variables are positive (above the cut-off values). The model BP≥128/80 mmHg was chosen because it had the highest Youden index value (greatest sensitivity and specificity combined) at each of the WHtR cut-off points (Table 4).

Figure 2. WHtR cut-off point resolution.

The next step was to select the final cut-off value for WHtR. To do this, the method's probability of detection (Node 6 value) and the Youden index for the BP

model chosen (BP≥128 / 80 mmHg) were plotted for each WHtR cut-off value (Figure 2).

It was noted that the probability of detection of MetS in each tree (Node 6 value) and the WHtR threshold, as well as the Youden index and the WHtR threshold, follow linear functions, in which the equations of its lines are as follows:

- Probability MetS (Node 6) = 5.534*WHtR -2.58
- Youden index = -1.758*WHtR + 1.486

Thus, the final threshold value for WHtR was determined by the cut-off point of both lines: WHtR = 0.56 (Figure 2).

The resulting new method for the early detection of MetS (new NIM-MetS) includes these conditions: WHtR≥0.56 and BP≥128/80 mmHg. Figure 3 shows the decision tree created from these variables and cut-off points. The sensitivity of the proposed method was 56.4%, specificity was 94.5%, validity index was 91.1% and the Youden index 0.51.

Figure 3. Definitive decision tree, new NIM-Mets proposed.

Finally, from the probabilities obtained in Nodes 3, 4, 5 and 6, a risk gradient for MetS was developed, according to the WHtR and BP covariates and the proposed cut-off values. Thus, those subjects with lower WHtR and BP values than the cut-off point have a very low probability of suffering from MetS (pMetS = 0.4%). Low risk (pMetS=8.3%) would be found only in those individuals with BP values over 128/80 mmHg but low WHtR. A moderate level of risk (pMetS = 16.3%) would include normotensive subjects who had a WHtR≥0.558. Finally, subjects with WHtR≥0.56 and BP≥128/80 mmHg, would have a 50.5% risk of having MetS.

DISCUSSION

The validation of a non-invasive method for the early detection of MetS (NIM-MetS) has been determined. The validation was carried out from a study of diagnostic tests conducted in Spanish Caucasian adult workers and using, as a reference test, the NCEP-ATP III criteria for the diagnosis of MetS. The early detection of MetS is the key to improving the quality of life of our population, since it prevents the appearance of associated complications such as CVD, type 2 Diabetes Mellitus and, even, cancer.[17-20]

NIM-MetS has shown a high validity index both in men (88.6%) and in women (94.7%). Overall, for every 100 workers, the method classified properly 91 cases. Similarly, NIM-MetS has proved to be highly specific, reaching an overall specificity of 94.9% (92.5% in men and 97.8% in women). Both VI and the SP recorded values above those achieved by this method in another Spanish population,[15] where it obtained an IV = 89.5% and 91.5% specificity. For sensitivity, the overall figure was 56.4% (59.4% for men and 40.9% for women), while in the original population, the overall sensitivity was 77.9%. Because it supposes a simple, easy to apply even in large populations and non-invasive method, it could be defined as a useful method in spite of the sensitivity found in the present study could be considered as moderate. The high specificity together with the high validity index shown for the screening of the cardiometabolic risk are characteristics that increase the acceptability of the method.

Although the indicators of validation and accuracy of a screening test (sensitivity and specificity) are intrinsic properties of the test itself and do not depend on the prevalence of the disease considered, this does not prevent these indicators from being affected by characteristics of the population they are applied to.[21] In fact, the most common observation is that a test for early detection or diagnosis alters its sensitivity and specificity depending on these characteristic features of the population. Therefore, the main differences between the two populations (the Balearic and the one considered in the previous study developed in Cordoba[15]) were analysed, highlighting those features of the Balearic population

which contributed to a decreased sensitivity: a younger population (40.0 vs. 45.1 years), more females (42.7% vs. 32.1%), more smokers (34.8% vs. 28.6%) and lower values for WC (82.9 vs. 87.8 cm), WHtR (0.49 vs. 0.52) and BMI (26.1 vs. 26.5 kg/m^2).

As regards the safety indicators of the test, the positive and negative predictive values, they are definitely affected by the prevalence of the population, lowering the PPV when the prevalence of MetS is lower. In this way, although we found a lower prevalence of MetS in the Balearic Islands than in Cordoba (9% vs. 13.9%), the NIM-Mets produced a lower PPV in the Balearic Islands (51.3% vs. 61.7%), while the negative predictive value remained very similar (95.5% vs. 95.9%).

Screening tests are often used in clinical practice. However, there are very few methods for the early detection of MetS other than the currently known diagnostic criteria, and there are even fewer non-invasive screening tests. A study in the Republic of Korea examined the validity of a test for the early detection of MetS based on the muscle-to-fat ratio.[22] The study was conducted on 6,256 participants, with a sensitivity of 68.6% in men and 76% in women, and a specificity of 63.8% in men and 53.8% in women. Miller et al.[23] proposed a screening method for MetS in 745 young adults (18-29 years old) in the United States, based on making decision trees with the CHAID methodology and using all the criteria for MetS. The method had a validity rate of 89.4% and a sensitivity rate of 61.7%. Finally, De Kroon et al.[24] conducted a screening test for MetS in 642 young people (aged 17-28) in the Netherlands using anthropometric variables (BMI, WC and BP). The sensitivity of the method was 68.75% and the validity index was 95.6%.

Another hypothesis put forward in this research was to test whether the cut-off value proposed by NIM-MetS for WHtR (≥0.55) would be reproduced in a large sample (60,799 workers from the Balearic Islands), and if it was also valid for both men and women and also for different age groups. WHtR had a cut-off value of 0.54 for the total sample, with 0.56 men and 0.53 for women. As regards age

groups, the WHtR threshold increased with age, with 0.55-0.56 for men and 0.51-0.55 for women. These differences were reduced in the total sample (0.53-0.56).

It is noteworthy that several authors have proposed a universal 0.50 cut-off point for WHtR, both to detect MetS and to predict cardiometabolic risk and overall cardiovascular mortality.[25-28] However, in Spain, a cross-sectional study in the general population (n = 6,279, mean age = 43 years) showed that WHtR was the best anthropometric predictor of MetS (NCEP-ATP III), and the authors proposed a cut-off value of 0.55, with which they obtained a sensitivity of 91% and a specificity of 64%.[28] This cut-off value is very similar to the one proposed from the results obtained in the present study.

In Chile, two important child population studies were conducted by Arnaiz et al., showing results which match the value of the cut-off point proposed in the present study. Thus, in the first study, conducted on 209 schoolchildren (mean age of 11.5), the authors obtained a cut-off value of 0.55 WHtR for MetS,[29] while in the second study, performed in 2,980 children aged 6-14 (mean age of 9.9), the authors concluded that the WHtR did not change with age and gender and, therefore, a universal cut-off value could be agreed for both children and adults.[30]

The prospective study by Koch et al.[31] carried out in Chile on about 6,714 men and 6,340 women, evaluating the relationship between various anthropometric indices of adiposity, cardiovascular risk factors and mortality for a cut-off value of 0.55 obtained a sensitivity of 75.8 % and a specificity of 73.3% for men, and a sensitivity of 77.6% and specificity of 56.3% for women.

In addition, several investigations conducted in non-European and non-Hispanic populations also concur on this threshold of WHtR for MetS. Thus, Obeidat et al.[32] in a study on a Jordanian population (n=630, aged 20-70 years) reported a cut-off value of 0.56 in men and 0.52 in women; in India, Rajput et al.,[33] achieved a threshold of 0.52 for men and women (n = 3,042) in all locations (rural or urban areas); and in China, He et al.,[34] in a descriptive study of 1,068 adult subjects, reported a cut-off value for WHtR of 0.5 for men and women alike.

When the NIM-MetS method was applied in this new larger sample of 60,799 workers from the Balearic Islands, the method has showed again the same variables obtained in the original study performed in Cordoba.[15] In the multiple logistic regression, WHtR and BP achieved the highest adjusted OR values. Thus, WHtR was the anthropometric index that best discriminated MetS presence, with an adjusted OR value of 4.4 (3.9-4.9), while SBP obtained an adjusted OR value of 3.8 (3.5-4.1). In addition, the cut-off values obtained for WHtR and for BP are very similar to those of the original method.

Several investigations have confirmed the high predictive ability of WHtR for MetS and CVD. In the systematic review conducted by Ashwell et al.,[35] in which 10 out of the 31 studies analysed the association between anthropometric measurements of central obesity and MetS, WHtR had the highest AUC value 0.76 (men) and 0.75 (women). This contrasted with WC, which obtained an AUC value of 0.75 (equal for men and women) and BMI, with an AUC value of 0.72 (men and women). Similarly, a meta-analysis conducted by Savva et al.,[36] in which 8 out of the 24 studies included compared WHtR (cut-off point 0.5) with BMI (cut-off point of 23 for the Asian population and 25 for the rest) for cardiometabolic risk in an Asian and non-Asian population, and concluded that WHtR showed a stronger association with MetS than with BMI.

Through the present study, the NIM-MetS method has been reproduced, and definitive cut-off values have been proposed for WHtR (0.56) and BP (128-80 mmHg), from which a sensitivity rate of 56.4%, a specificity rate of 94.5%, a validity index of 91.1% and a Youden index of 0.51 are obtained. On the other hand, finally, the long-term ability of MetS to predict CVD has shown to be limited by the dichotomous (binary) and qualitative nature of the classic diagnostic criteria for MetS. An innovative aspect that NIM-MetS brings is to provide a gradient or scale of risk of developing MetS which is divided into four risk levels: Very low risk (probability = 0.4%), low risk (probability = 8.3%), moderate risk (probability = 16.4%) and high risk (probability = 50.5%). In this way, health professionals can

take certain steps depending on the level of risk of MetS and promote a more accurate and early detection of the possible complications associated with CVD and MetS. Along the same lines, there have been several studies using methods based on scores to quantify the amount of risk accumulated by the presence of the components that define the metabolic syndrome (Metabolic Syndrome Severity Score).[37,38]

Limitations

This study presents some limitations that must be acknowledged. First, we must bear in mind that there are different definitions and criteria to determine the presence of MetS. In this study, presence of MetS was ascertained using the NCEP-ATP III definition as a gold standard, which supposes one of the definitions most used and widely accepted by the international community and the WHO. In addition, the study data refers to Caucasian population. Thus, results could not have great applicability to other populations.

Although in the present study NIM-MetS methodology has been tested in a very large sample of workers, the sensitivity found was lower than that obtained in the original study leading to the proposal of the method.[15] This could be related to differences in the study samples, with the workers from the Balearic Islands showing lower prevalence of SMet and obesity and being younger. Although the prevalence of MetS does not affect sensitivity and specificity, this lower prevalence influences PPV and NPV.

In spite of the percentage of participation is high (87.4%), we should take into account that it is not the total target population and, therefore, a bias could have been introduced in the results. Furthermore, participants highly concerned about their health, and thus probably healthier, along with those with a diagnosed disease, could represent the greater proportion of workers attending health examinations because these were not compulsory. This causes bias in the recruitment procedure as, in addition, it is not well-known whether the healthier

workers or the ones with a diagnosed disease are the ones with the greatest interest in the checks. Nor can we ignore the bias of the healthy worker, since those workers with serious illnesses would not be currently active. In addition, it is not well known if the healthiest workers or those with a diagnosed illness have the greatest interest in checks.

Conclusions

The NIM-MetS has proved to be a valid method for the early detection of MetS in a healthy worker population. It is a simple, economical and quick non-invasive test which is easy to apply and interpret in any health care setting (primary health care, hospitals, occupational health) as well as in other settings (education, sport, etc.). WHtR is the best predictor of MetS and its cut-off point can be used for both genders and for different age groups. The clinical decision tree that produces the NIM-MetS uses WHtR (0.56) and BP (128/80 mmHg), and obtains high specificity and diagnostic validity. The NIM-MetS provides a gradient or risk scale which allows a more accurate and earlier detection of CVD in subjects with risk of MetS.

Contributor ship statement

Manuel Romero-Saldana contributed to the conception, design, acquisition and analysis/interpretation of data, drafted the manuscript, critically revised the manuscript and gave his final approval to the text, while also agreeing to be accountable for the integrity and accuracy of all aspects of the work.

Pedro Tauler contributed to the data collection, analysis, critically revised the manuscript, gave his final approval, and agrees to be accountable for the integrity and accuracy of all aspects of the work.

Manuel Vaquero-Abellán contributed to the analysis and interpretation, critically revised the manuscript, gave his final approval, and agrees to be accountable for the integrity and accuracy of all aspects of the work.

Angel A. Lopez-Gonzalez contributed to the data collection, analysis, critically revised the manuscript, gave his final approval, and agrees to be accountable for the integrity and accuracy of all aspects of the work.

Francisco J. Fuentes-Jimenez contributed to the analysis, critically revised the manuscript, gave his final approval, and agrees to be accountable for the integrity and accuracy of all aspects of the work.

Antoni Aguilo contributed to the conception, critically revised the manuscript, gave his final approval, and agrees to be accountable for the integrity and accuracy of all aspects of the work.

Carlos Alvarez-Fernandez contributed to the conception, critically revised the manuscript, gave his final approval, and agrees to be accountable for the integrity and accuracy of all aspects of the work.

Guillermo Molina-Recio contributed to the analysis and interpretation, critically revised the manuscript, gave her final approval and agrees to be accountable for the integrity and accuracy of all aspects of the work.

Miquel Bennasar-Veny contributed to the design, acquisition and analysis/interpretation of data, critically revised the manuscript, gave his final approval, and agrees to be accountable for the integrity and accuracy of all aspects of the work.

Competing interests

None declared.

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Data sharing statement

All data is fully available under request to the corresponding author.

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Table 1. Characteristics of the sample according to gender

Variable	Total n=60,799	Men n= 34,827	Women n= 25,972	p
	Mean (95% CI) or n (%)	Mean (95% CI) or n (%)	Mean (95% CI) or n (%)	
Age (years)	40 (39.9 – 40.1)	40.4 (40.3 – 40.5)	39.5 (39.3 – 39.6)	<0.001
Smoker (yes)	21,177 (34.8%)	12,746 (36.6%)	8,431 (32.5%)	<0.001
BMI (kg/m^2)	26.1 (26 – 26.1)	26.9 (26.8 – 26.9)	25.0 (25 – 25.1)	<0.001
WC (cm)	82.9 (82.9 – 83)	88.6 (88.5 – 88.7)	75.4 (75.3 – 75.5)	<0.001
WHtR	0.49 (0.49 – 0.49)	0.51 (0.50 – 0.51)	0.47 (0.46 – 0.47)	<0.001
ABSI	0.0735 (0.07 -0.07)	0.0735 (0.07 -0.07)	0.07 (0.07 -0.07)	<0.001
BF (%)	28.9 (28.9 – 29)	25.3 (25.3 – 25.4)	33.7 (33.6 – 37.8)	<0.001
SBP (mmHg)	120.8 (120.6 -120.9)	125.4 (125.2 – 125.6)	114.6 (114.4 – 114.8)	<0.001
DBP (mmHg)	73.6 (73.5 – 73.7)	76.0 (75.9 -76.1)	70.4 (70.3 – 70.5)	<0.001
Glucose (mg/dL)	88.3 (88.1- 88.5)	90.6 (90.4 – 90.8)	85.2 (85 – 85.4)	<0.001
Cholesterol (mg/dL)	195.2 (194.9 - 195.5)	196.9 (196.5 -197.3)	193.0 (192.6 – 193.4)	<0.001
HDL-Cholesterol (mg/dL)	52.4 (52.3 - 52.5)	50.5 (50.4 – 50.6)	55.0 (54.9 – 55.1)	<0.001
LDL-Cholesterol (mg/dL)	121.2 (120.9 - 121.5)	121.8 (121.4 – 126.2)	120.5 (120 – 120.9)	<0.001
Triglycerides (mg/dL)	109.3 (108.7 – 109.9)	125.3 (124.4 – 126.2)	88.8 (88.2 – 89.4)	<0.001
MetS (yes)	5,587 (9.0%)	4,097 (11.8%)	1,390 (5.4%)	<0.001

BMI: Body Mass Index; WC: Waist circumference; WHtR: Waist to Height Ratio; ABSI: A body Shape Index; BF (%): Body Fat percentage calculated according to the Deurenberg equation; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MetS: Metabolic syndrome. P<0.05 indicates significant differences between genders

Table 2. Diagnostic test accuracy of NIM-MetS against NCEP-ATP III

STANDARD REFERENCE NCEP APTIIII

		TOTAL			MEN			WOMEN		
		Yes	**No**	**Total**	**Yes**	**No**	**Total**	**Yes**	**No**	**Total**
NIM – MetS	**Yes**	3,001	2,850	5,851	2,433	2,300	4,733	568	550	1,118
(n)	**No**	2,486	52,462	54,948	1,664	28,430	30,094	822	24,032	24,854
	Total	5,487	55,312	60,799	4,097	30,730	34,827	1,390	24,582	25,972
Efficacy indicators, 95% CI										
Sensitivity		54.7 (53.4 – 56)			59.4 (57.9 – 60.9)			40.9 (38.2 – 43.5)		
Specificity		94.9 (94.7 – 95)			92.5 (92.2 – 92.8)			97.8 (97.6 – 98)		
PPV		51.3 (50 – 52.6)			51.4 (50 – 52.8)			50.8 (47.8 – 53.8)		
NPV		95.5 (95 – 95.7)			94.5 (94.2 – 94.7)			96.7 (96.5 – 96.9)		
VI		91.2 (91 – 91.5)			88.6 (88.3 – 89)			94.7 (94.4 – 95)		
LH +		10.6 (10.2 – 11.1)			7.9 (7.6 – 8.3)			18.3 (16.5 – 20.3)		
LH -		0.48 (0.46 – 0.49)			0.44 (0.42 – 0.46)			0.6 (0.58 – 0.63)		
JI		0.50 (0.48 – 0.51)			0.52 (0.5 – 0.53)			0.39 (0.36 – 0.41)		

PPV: Positive Predictive Value; NPV: Negative Predictive Value; VI: Validity Index; LH +: Likelihood ratio positive; LH -: Likelihood ratio negative; JI: Youden Index.

Table 3. Area under the curve (AUC) and cut-off values for WHtR according to gender and age groups

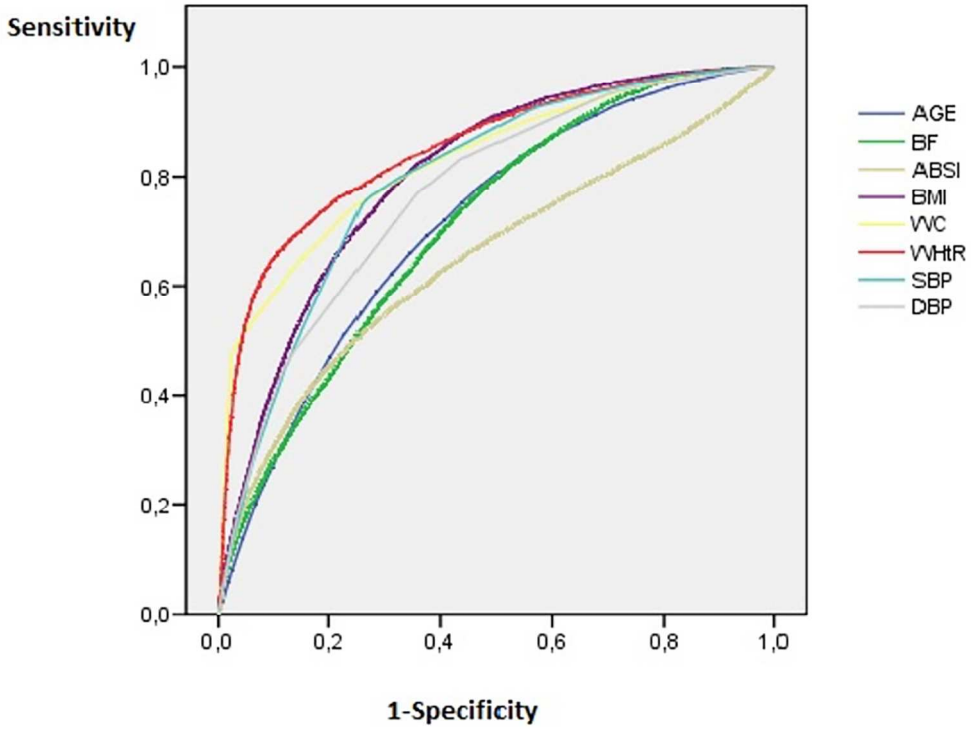
Age group (years)	n	Prevalence of MetS (%)[a]	AUC 95% CI	Cut-off value	Sensitivity (%)	Specificity (%)	JI
			MEN				
20-30	6,825	3.1	0.92 (0.9 – 0.95)	0.55	80.3	93.4	0.74
31-40	11,623	7.5	0.88 (0.86 – 0.89)	0.55	77.4	88.1	0.65
41-50	10,080	14.9	0.82 (0.81 – 0. 83)	0.56	66.4	87.7	0.54
≥51	6,659	23.1	0.75 (0.74 – 0.77)	0.56	58.9	83.0	0.42
Total	34,827	11.8	0.84 (0.83 – 0.85)	0.56	66.7	88.8	0.56
			WOMEN				
20-30	5,715	1.1	0.90 (0.85 – 0.95)	0.51	82.0	84.0	0.74
31-40	8,529	2.7	0.91 (0.89 – 0.93)	0.53	80.3	90.8	0.71
41-50	7,641	6.6	0.91 (0.89 – 0.93)	0.53	80.3	90.8	0.71
≥51	4,087	14.4	0.75 (0.73 – 0.77)	0.55	48.4	90.5	0.39
Total	25,972	5.4	0.85 (0.84 -0.86)	0.53	65.1	88.7	0.54
			TOTAL				
20-30	12,540	2.1	0.92 (0.9 – 0.94)	0.53	84.4	90.1	0.75
31-40	19,792	5.5	0.90 (0.89 – 0.91	0.54	78.2	88.5	0.67
41-50	17,721	11.3	0.83 (0.82 – 0.84)	0.54	69.6	84.3	0.54
≥51	10,746	19.8	0.76 (0.75 – 0.77)	0.56	57.0	85.3	0.42
Total	60,799	9.0	0.85 (0.84 – 0.86)	0.54	68.5	87.0	0.56

a: MetS according to NCEP ATP III criterion; AUC: area under the curve; JI: Youden Index

Table 4. Probabilities of MetS (%) for nodes 3, 4, 5 and 6 in decision trees according to cut-off values of WtHR

WHtR range	BP model	Probabilities of MetS for nodes in the decision tree				Efficacy indicators for diagnostic test accuracy			
Cut-off points	BP	Node 3	Node 4	Node 5	Node 6	Sensitivity (%)	Specificity (%)	VI (%)	JI
0.535	BP[1]	0.3	7.4	10.3	38.4	63.9	89.7	87.5	0.54
	BP[2]	0.5	10.4	12.2	43.3	59.3	92.3	89.3	0.52
	SBP	0.6	10.5	13.7	43.3	57.0	92.6	89.4	0.5
0.54	BP[1]	0.3	7.6	11.5	40.7	62.7	90.9	88.4	0.54
	BP[2]	0.5	10.5	13.5	45.7	57.8	93.2	90.0	0.51
	SBP	0.6	10.7	15.2	45.7	55.6	93.5	90.0	0.49
0.544 [a]	BP[1]	0.4	7.7	12.5	42.8	61.6	91.8	89.1	0.53
	BP[2]	0.5	10.9	14.6	48.0	56.7	93.9	90.5	0.51
	SBP	0.6	10.8	16.4	48.0	54.5	94.1	90.6	0.49
0.550 [b]	BP[1]	0.4	7.9	14.2	46.1	59.6	93.1	90.1	0.53
	BP[2]	0.5	10.9	16.6	51.3	54.7	94.8	91.2	0.46
	SBP	0.7	11.0	18.5	51.4	52.6	95.1	91.2	0.48
0.555	BP[1]	0.4	8.2	15.7	49.1	57.8	94.1	90.8	0.52
	BP[2]	0.6	11.1	18.3	54.4	53.0	95.6	91.7	0.49
	SBP	0.7	11.3	20.3	54.5	51.0	95.8	91.7	0.47
0.560	BP[1]	0.5	8.5	17.0	51.8	55.7	94.9	91.3	0.51
	BP[2]	0.6	11.5	19.9	57.1	51.0	96.2	92.1	0.47
	SBP	0.8	11.6	21.9	57.2	49.1	96.4	92.1	0.46
0.565	BP[1]	0.5	8.8	18.6	54.9	53.4	95.6	91.8	0.49
	BP[2]	0.6	11.9	21.8	60.3	48.8	96.8	92.5	0.46
	SBP	0.8	12.0	23.9	60.4	47.0	96.9	92.4	0.44
0.570	BP[1]	0.5	9.1	19.9	57.4	51.4	96.2	92.2	0.48
	BP[2]	0.7	12.3	23.3	62.8	46.9	97.2	92.7	0.44
	SBP	0.9	12.4	25.5	63.0	45.2	97.4	92.7	0.43

BP: Blood Pressure; BP[1]: Blood pressure ≥128/80 mmHg; BP[2]: Blood pressure ≥128/85 mmHg; SBP: Systolic blood pressure≥128 mmHg; VI: Validity index; JI: Youden Index; a: Cut-off point for WHtR obtained in the total simple (n=60,799); b: Cut-off point proposed by NIM-MetS



	AUC (95% CI)	CP	Sensitivity (%)	Specificity (%)	JI
Age	0.71 (0.71- 0.72)	42.5	69.2	62.5	0.32
WHtR	0.85 (0.84 – 0.86)	0.54	68.5	87.0	0.56
WC	0.83 (0.82 – 0.84)	89.1	72.5	77.6	0.50
BMI	0.8 (0.8 – 0.81)	27.1	78.4	68.3	0.47
ABSI	0.65 (0.64 – 0.66)	0.07	50.4	75.2	0.26
BF%	0.71 (0.7 – 0.72)	29.4	70.9	58.1	0.3
SBP	0.79 (0.79 – 0.8)	127.5	75.8	73.5	0.49
DBP	0.77 (0.76 – 0.78)	78.5	77.3	63.9	0.41

AUC: Area under curve CP: Cut-off point; JI: Youden Index; BMI: Body mass index; WC: Waist circumference; WHtR: Waist to height ratio; ABSI: A Body Shape Index; BF (%): Body Fat calculated according to the Deurenberg equation; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.

Figure 1

403x470mm (72 x 72 DPI)

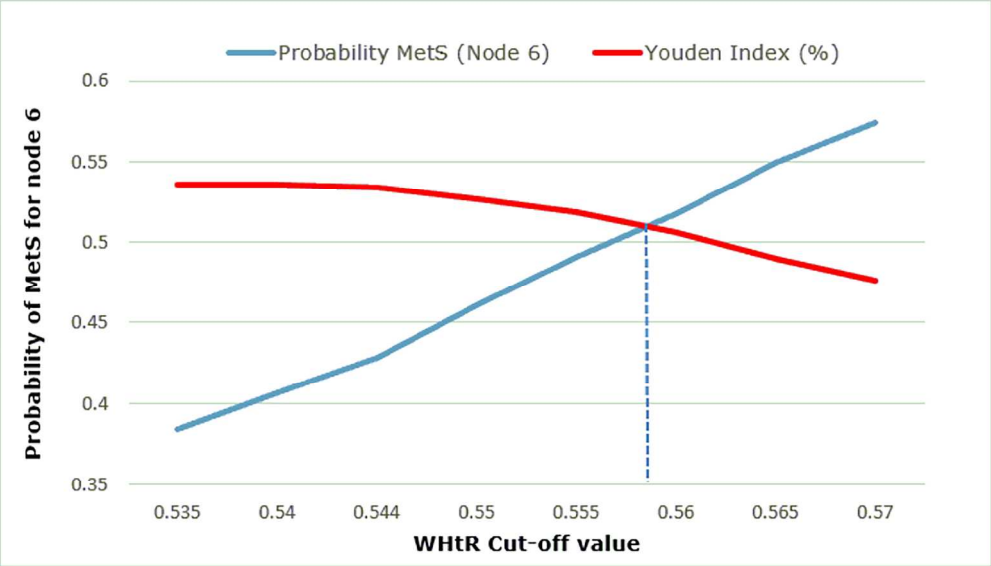


Figure 2

170x98mm (300 x 300 DPI)

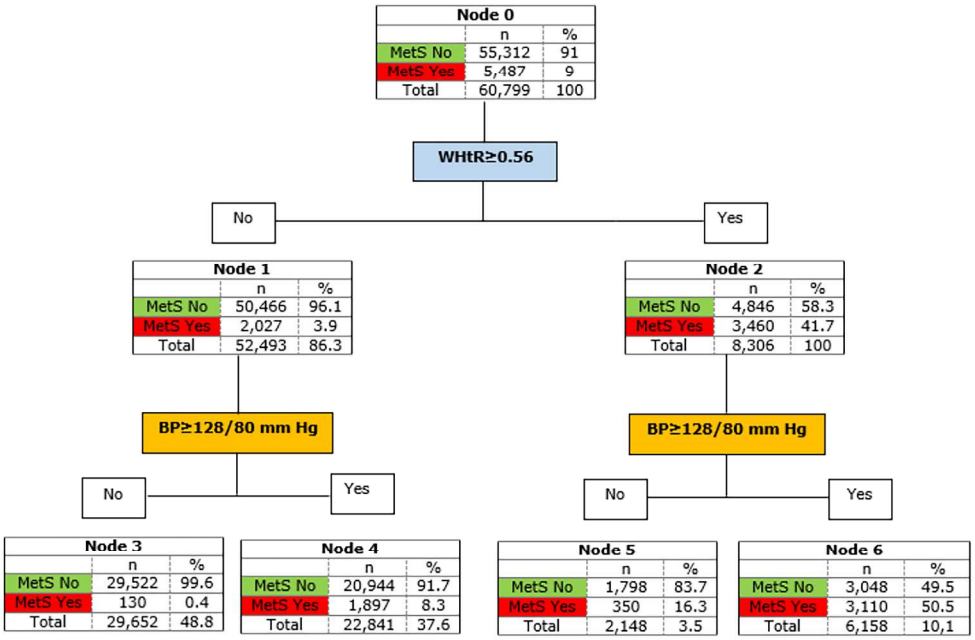


Figure 3

274x183mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Checked in page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6-7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	9
		(*e*) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	11
		(c) Consider use of a flow diagram	Not necesary
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11-12
		(b) Indicate number of participants with missing data for each variable of interest	none
Outcome data	15*	Report numbers of outcome events or summary measures	11-12-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted	12-13-14

		estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	13-14
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not indicated
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-14
Discussion			
Key results	18	Summarise key results with reference to study objectives	16-17-18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17-18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section & Topic	No	Item	Checked in page
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	2
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	4
	4	Study objectives and hypotheses	4-5
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	6
Participants	**6**	Eligibility criteria	6
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	6
	8	Where and when potentially eligible participants were identified (setting, location and dates)	6
	9	Whether participants formed a consecutive, random or convenience series	6
Test methods	**10a**	Index test, in sufficient detail to allow replication	7
	10b	Reference standard, in sufficient detail to allow replication	7
	11	Rationale for choosing the reference standard (if alternatives exist)	
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	8
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	8
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	8-9
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	8-9
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	9-10
	15	How indeterminate index test or reference standard results were handled	9-10
	16	How missing data on the index test and reference standard were handled	9-10
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	
	18	Intended sample size and how it was determined	6
RESULTS			
Participants	**19**	Flow of participants, using a diagram	Not indicated
	20	Baseline demographic and clinical characteristics of participants	11
	21a	Distribution of severity of disease in those with the target condition	11-12
	21b	Distribution of alternative diagnoses in those without the target condition	11-12
	22	Time interval and any clinical interventions between index test and reference standard	Not necessary
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	12
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	12
	25	Any adverse events from performing the index test or the reference standard	None
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	17-18
	27	Implications for practice, including the intended use and clinical role of the index test	17-18-19
OTHER INFORMATION			
	28	Registration number and name of registry	
	29	Where the full study protocol can be accessed	
	30	Sources of funding and other support; role of funders	20

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

BMJ Open

Validation of a non-invasive method for the early detection of metabolic syndrome: a diagnostic accuracy test in a working population

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Primary Subject Heading:	Occupational and environmental medicine
Secondary Subject Heading:	Cardiovascular medicine, Diagnostics, Epidemiology, Public health
Keywords:	metabolic syndrome, early detection, non invasive method, cardiovascular risk, working population

Validation of a non-invasive method for the early detection of metabolic syndrome: a diagnostic accuracy test in a working population

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ABSTRACT

Objectives. A non-invasive method for the early detection of Metabolic Syndrome (NIM-MetS) using only Waist to Height Ratio (WHtR) and Blood Pressure (BP) has recently been published, with fixed cut-off values for gender and age. The aim of this study was to validate this method in a large sample of Spanish workers.

Design. A diagnostic test accuracy to assess the validity of the method was performed.

Setting. Occupational Health Services.

Participants. The studies were conducted in 2012-2016 on a sample of 60,799 workers from the Balearic Islands (Spain).

Interventions. The NCEP-ATP III criteria were used as the gold standard. NIM-MetS has been devised using classification trees (the CHAID, Chi-squared Automatic Interaction Detection method).

Main outcome measures. Anthropometric and biochemical variables to diagnose MetS. Sensitivity, specificity, validity index and Youden Index were determined to analyse the accuracy of the diagnostic test (NIM-MetS).

Results. Regarding the validation of the method, sensitivity was 54.7%, specificity 94.9% and validity index 91.2%. The cut-off value for WHtR was 0.54, ranging from 0.51 (lower age group) to 0.56 (higher) in the age groups. Variables more closely associated with MetS were WHtR (AUC=0.85; 95% CI: 0.84-0.86) and Systolic Blood Pressure (AUC=0.79; 95% CI: 0.78-0.80). The final cut-off values for the non-invasive method were WHtR≥0.56 and BP≥128/80 mmHg, which includes four levels of MetS risk (very low, low, moderate and high).

Conclusions. The analysed method has shown a high validity index (higher than 91%) for the early detection of MetS. It is a non-invasive method easy to apply and interpret in any health care setting. This method provides a scale of MetS risk which allows a more accurate detection and a more effective intervention.

Strengths and limitations of this study

- This is the first study assessing the validation of a non-invasive method for the early detection of metabolic syndrome (NIM-MetS).
- A diagnostic test study has been carried out in a large sample of healthy workers.
- MetS was ascertained by using the NCEP-ATP III definition, but there is a lack of consensus regarding MetS definition.
- A new procedure to measure MetS using variables with universal cut-off points (waist to height ratio and blood pressure) is suggested.
- The NIM-MetS method has shown high specificity, but low sensitivity.

INTRODUCTION

The obesity epidemic which currently affects the world population has resulted in a general increase in the prevalence of metabolic syndrome (MetS).[1-3] Overweight and obesity are factors related to the onset of type 2 diabetes, hypertension, dyslipidemia and cardiovascular diseases (CVD). In particular, central obesity, which is defined as an excessive accumulation of abdominal fat, is an important predictor of cardiovascular risk and MetS.[4,5] Metabolic syndrome is defined as a pluripathological state characterized by the joint presence of several cardiovascular risk factors such as abdominal obesity, high blood pressure and altered glucose and lipid metabolism (low HDL-cholesterol and high triglycerides).[6]

Although there are several analytical/instrumental techniques for measuring the amount and distribution of body fat, there is no consensus about which the ideal method to calculate central adiposity is, nor how to decide which cut-off points provide greater accuracy, efficiency, sensitivity and specificity in all cases.[7,8]

A simple and inexpensive alternative to these instruments as a way of quantifying abdominal fat is to make anthropometric measurements of central obesity[9]. Waist circumference (WC), body mass index (BMI), waist to height ratio (WHtR), waist to hip ratio (WHR), hip to height ratio (HHR), body adiposity index (BAI), visceral adiposity index (VAI), body shape index (ABSI) and percentage of body fat (%BF) are some examples that can be found in numerous epidemiological studies, in which they try to relate indirectly intra-abdominal (visceral) fat with parameters such as morbidity and mortality, and also with prevalence of hypertension, diabetes, MetS, etc.[10-13]

Since the mid-1990s, the WHtR has been the most widely used anthropometric indicator and the one which has obtained the best predictive results for cardiovascular risk.[14] In a previous publication, a non-invasive method for early detection of MetS (NIM-MetS) using only two anthropometric variables (WHtR and blood pressure (BP)) has been proposed and validated.[15] This method suggests

WHtR≥0.55 as the predictive threshold for the early detection of MetS for both men and women and, also, for any age stratum.

The aim of this study is to validate the NIM-Mets method in a large representative sample of Spanish workers, to determine its predictive ability and to find out the stability of the cut-off value of WHtR≥0.55 by gender and age.

MATERIAL AND METHODS

Design and sample

A diagnostic test using a cross-sectional study was carried out on a working population from the Balearic Islands (Spain) between 2012 and 2016. Subjects participating in the study were randomly selected during their work health periodic assessments. Every day, each worker was assigned a number and half of the examined workers were randomly selected using a random number table. A total of 69,581 workers were invited to participate in the study. However, 8,782 (12.6%) refused to participate and, thus, the final number of participants was 60,799 workers (10.2% of the active population) belonging to different economic sectors (public administration, health services, etc.), aged 20 to 70 years old, and with 57.3% of males and 42.7% of females.

Participants were informed of the purpose of the study before they provided written informed consent to participate. The study protocol complied with the Declaration of Helsinki for conducting medical research involving human subjects, and was approved by the Institutional Review Board of the Mallorca Health Management Ethical Review Committee of GESMA.

Data collection and definition of variables

To carry out the anthropometric measurements, recommendations contained in the manual "International Standards for Anthropometric Assessment (ISAK)" were followed.[16] All the measurements were made by specifically trained staff in order to

minimize the variation coefficients. Each measurement was performed three times, taking the average as the final value.

The independent variables were classified into the following categories:

a) Personal and health habits: gender, age and tobacco consumption.

b) Anthropometric measurements:

- Waist circumference (WC) in cm.
- Body mass index (BMI), calculated as body weight (kg) divided by height (m) squared, in kg/m^2.
- Percentage of body fat (%BF), calculated according to the Deurenberg equation: %BF = 1.2x(BMI) + 0.23x(Age in years) – 10.8x(Gender) – 5.4. Gender: females (0), males (1)
- Waist-to-height ratio (WHtR), calculated as waist circumference divided by height, both in cm.
- Body shape index (ABSI), calculated as $WC/[(BMI)^{2/3}(height)^{1/2}]$.

c) Blood measurements:

- Systolic blood pressure (SBP) in mmHg.
- Diastolic blood pressure (DBP) in mmHg.
- Total Cholesterol (mg/dL), LDL-Cholesterol (mg/dL), HDL-Cholesterol (mg/dL), glucose (mg/dL) and triglycerides (mg/dL).

Body weight was measured to the nearest 0.1 kg with an electronic scale (Seca 700 scale, Seca GmbH, Hamburg). Height was measured to the nearest 0.5 cm with a stadiometer (Seca 220 (CM) Telescopic Height Rod for Column Scales, Seca GmbH, Hamburg). Waist circumference was measured half-way between the lower costal border and the iliac crest. The measurement was taken at the end of a normal expiration with the subject standing up, with their feet together and their arms hanging down by their sides.

Venous blood samples were taken from the antecubital vein in suitable vacutainers without anticoagulant in order to obtain serum. The blood samples were taken after a 12 h overnight fast. Participants sat and rested for at least 15

minutes before the blood samples were taken. Serum was obtained after centrifugation (15 min, 1,000xg, 4ºC) of the blood samples. The serum was stored at -20ºC and analyses were performed within 3 days. Concentrations of glucose, cholesterol and triglycerides were measured in serum following the standard procedures used in clinical biochemistry laboratories with an autoanalyser (SYNCHRON CXH9 PRO, Beckman Coulter, Brea, CA, USA).

Blood pressure was determined after the subjects had rested in the supine position for 10 minutes, using an automatic and calibrated sphygmomanometer (OMRON M3, OMRON Healthcare Europe, Spain). As in the case of the anthropometrical measurements, blood pressure was measured three times, leaving a one-minute gap between each measurement, and the average value was then calculated.

Presence of MetS was ascertained by using the criterion suggested by the NCEP-ATP III definition (when 3 of 5 of the following characteristics are present, a diagnosis of metabolic syndrome can be made):

- Abdominal obesity (WC≥102 cm in males and WC ≥88 cm in females).
- Triglycerides ≥150 mg/dL.
- HDL-cholesterol <40 mg/dL in males and <50 mg/dL in females.
- Blood pressure ≥130/85 mmHg.
- Fasting glucose ≥100 mg/dL.

Non-invasive method for the early detection of Mets (NIM-MetS)

NIM-Mets is a new tool for screening for MetS based on the following anthropometric variables and cut-off values: WHtR≥0.55 and BP≥128/85 mmHg. This method classifies the population into two groups with different levels of risk:

- Workers with high risk of MetS (probability>61.7%): this group would contain those subjects with both positive variables, i.e. WHtR≥0.55 and BP≥128/85 mmHg.

- Workers with low risk of MetS (probability of 0.5-16.9%): this group would contain those subjects who have any of the other possible combinations between the two variables considered.

Statistical Analysis

Statistical analysis was carried out using the IBM SPSS Statistics 22.0 software (SPSS / IBM, Chicago, IL, USA) and the Epidat version 4.2. (Department of Sanidade, Xunta de Galicia, Galicia, Spain). Continuous data are presented as mean values, standard deviation, and confidence interval at 95%. Categorical data are shown as frequency counts and percentages. All the data were tested for their normal distribution (Kolmogorov–Smirnov test with the Lilliefors adjustment).

Student's t-test and U Mann-Whitney test were used in the bivariate analyses for normal and non-normal distributed variables respectively. ANOVA tests with the post-hoc Bonferroni contrast method were carried out when more than two groups were considered in the analysis. The Levene test was used to determine the variance equality. The χ^2 test was applied to assess differences between groups in categorical variables.

Receiver Operator Characteristic (ROC) curves were performed and the Area Under the Curve (AUC) was calculated to find which explanatory variables best predict the onset of MetS. We obtained the cut-off value for each explanatory variable through the Youden index (JI) as JI = Sensitivity + Specificity – 1.

To measure the accuracy of the diagnostic test, sensitivity (S), specificity (SP), positive and negative predictive values (PPV and NPV), likelihood ratios (LH+ and LH-), validity index (VI) and JI were analysed. Validity index was calculated as the quotient between the sum of true positives and true negatives, divided by the total number of subjects, therefore representing the percentage of subjects properly classified by the test.

The modification of NIM-MetS was obtained from a clinical decision tree (classification) using the CHAID (Chi-squared Automatic Interaction Detection)

technique as a growth method. The statistical significance level for splitting nodes and merging categories was $p<0.05$, and significance values were corrected by the Bonferroni method, with a maximum number of iterations of 2,000.

The level of statistical significance was fixed in all the contrasts for an alpha error below 5%, and the confidence intervals were calculated with a 95% level of confidence.

Patient and public involvement

Patients were not involved in setting the research question and in the study design. All patients were randomly selected during their work health periodic assessments to participate in the study and they were interviewed face-to-face by trained researchers for detailed explanation of the purpose of this research and informed consent at the beginning. No patients were involved in data analysis or in the manuscript writing. Results of the research will not be disseminated to the patients.

RESULTS

Characteristics of the study sample

Of the 60,799 workers, 34,827 were male (57.3%). The overall mean age was 40 years (39.9-40.1) (Table 1). Among anthropometrical and blood parameters shown in Table 1, women showed higher %BF and HDL-Cholesterol values ($p<0.001$), while men showed significant higher values for the rest of the parameters shown in this table. The prevalence of smokers was 34.8% (36.6% in men and 32.5% in women), and 17.6% of participants were obese (20.0% in men and 14.4% women). With regard to drug treatments, 6.6% of participants were undergoing antihypertensive treatment, 3.2% lipid lowering treatments and 1.7% antidiabetic treatments. Finally, the overall prevalence of MetS was 9.0%, with 11.8% in men and 5.4% in women ($p<0.001$).

NIM-MetS validation

Table 2 shows the results of diagnostic tests after applying the NIM-Mets method compared with NCEP-ATP III as a control test. Overall, the indicators of the NIM-MetS method validation were as follows: S = 54.7% (53.4-56.0), SP = 94.9% (94.7-95.0), and VI = 91.2% (91.0-91.5). The sensitivity was higher in men (59.4%) than in women (40.9%).

As regards the NIM-MetS safety indicators, results in the total sample were: PPV = 51.3% (50.0-52.6) and NPV = 95.5 (95.3-95.7). By gender, PPV was higher in men (51.4%) than in women (50.8%), while NPV was higher in women (96.7%) than in men (94.5%). Finally, the overall JI was 0.50 (0.48 to 0.51), higher in men (0.52) than in women (0.39).

A second question to be dealt with in this research was to compare the cut-off value for WHtR proposed by NIM-MetS with that obtained in the study sample, and thus determine its variability according to the gender variable and in different age groups (Table 3). In the whole sample (n = 60,799), a cut-off value of 0.54 was obtained for WHtR. In the group of men (n = 34,827), the resulting threshold was 0.56, while for women (n = 25,972) it was 0.53.

It can be seen how the cut-off point increases with age. For men, it ranged from 0.55 (20-30 years old) to 0.56 (≥51 years), whereas for women it was between 0.51 (20-30 years) and 0.55 (≥51 years). The differences between the cut-off values for men and women become narrower as the age increased.

Figure 1 shows the results for the anthropometric variables' ROC curves. WHtR achieved the highest AUC 0.85 (95% CI: 0.84 to 0.86), with a cut-off value of 0.54, reaching top values of S = 68.5%, SP = 87.0% and JI = 0.56. The second variable with the highest AUC was WC, with 0.83 (95% CI: 0.82 to 0.84), a cut-off value of 89.1 cm and S = 72.5, SP = 77.6% and JI = 0.5. BMI with an AUC = 0.80 BMI and SBP with AUC = 0.79 also stood out.

Figure 1. Anthropometric variables. ROC curves, area under the curve, cut-off points and efficacy indicators.

After that, different clinical decision trees were made with a range of cut-off values for WHtR and BP (Table 4). Thus, the range of cut-offs for WHtR was defined by 8 thresholds between 0.54 and 0.57, and included, among others, the cut-off value proposed by NIM-MetS (WHtR≥0.55) and the cut-off value for the total sample (WHtR≥0.54). In addition, three models were established for BP: BP≥128/80 mmHg (cut-off values obtained for SBP and DBP as ROC curves, shown in Figure 2); BP≥128/85 mmHg (BP cut-off values proposed by NIM-MetS); and finally, only SBP≥ 128 mmHg (second covariate with the highest adjusted OR in the multiple logistic regression). In this way, 24 clinical decision trees were set up using CHAID methodology. Each tree comprised of a parent node (Node 0), two primary subsidiary nodes (Nodes 1 and 2) and four secondary subsidiary nodes (Nodes 3, 4, 5 and 6). Each of the last four nodes denoted the probability of having MetS. Thus, Node 3 corresponds to the probability that a worker has MetS when both anthropometric variables are negative (below cut-off values). Node 4 indicates the probability that a worker has MetS when BP is above the cut-off value and WHtR below. Node 5 represents the probability that a worker has MetS when BP is lower than the cut-off value and WHtR is above. Finally, Node 6 shows the probability that a worker suffers from MetS when both variables are positive (above the cut-off values). The model BP≥128/80 mmHg was chosen because it had the highest Youden index value (greatest sensitivity and specificity combined) at each of the WHtR cut-off points (Table 4).

Figure 2. WHtR cut-off point resolution.

The next step was to select the final cut-off value for WHtR. To do this, the method's probability of detection (Node 6 value) and the Youden index for the BP

model chosen (BP≥128 / 80 mmHg) were plotted for each WHtR cut-off value (Figure 2).

It was noted that the probability of detection of MetS in each tree (Node 6 value) and the WHtR threshold, as well as the Youden index and the WHtR threshold, follow linear functions, in which the equations of its lines are as follows:

- Probability MetS (Node 6) = 5.534*WHtR - 2.58
- Youden index = -1.758*WHtR + 1.486

Thus, the final threshold value for WHtR was determined by the cut-off point of both lines: WHtR = 0.56 (Figure 2).

The resulting new method for the early detection of MetS (new NIM-MetS) includes these conditions: WHtR≥0.56 and BP≥128/80 mmHg. Figure 3 shows the decision tree created from these variables and cut-off points. The sensitivity of the proposed method was 56.4%, specificity was 94.5%, validity index was 91.1% and the Youden index 0.51.

Figure 3. Definitive decision tree, new NIM-Mets proposed.

Finally, from the probabilities obtained in Nodes 3, 4, 5 and 6, a risk gradient for MetS was developed, according to the WHtR and BP covariates and the proposed cut-off values. Thus, those subjects with lower WHtR and BP values than the cut-off point have a very low probability of suffering from MetS (pMetS = 0.4%). Low risk (pMetS=8.3%) would be found only in those individuals with BP values over 128/80 mmHg but low WHtR. A moderate level of risk (pMetS = 16.3%) would include normotensive subjects who had a WHtR≥0.558. Finally, subjects with WHtR≥0.56 and BP≥128/80 mmHg, would have a 50.5% risk of having MetS.

DISCUSSION

The validation of a non-invasive method for the early detection of MetS (NIM-MetS) has been determined. The validation was carried out from a study of diagnostic tests conducted in Spanish Caucasian adult workers and using, as a reference test, the NCEP-ATP III criteria for the diagnosis of MetS. The early detection of MetS is the key to improving the quality of life of our population, since it prevents the appearance of associated complications such as CVD, type 2 Diabetes Mellitus and, even, cancer.[17-20]

NIM-MetS has shown a high validity index both in men (88.6%) and in women (94.7%). Overall, for every 100 workers, the method classified properly 91 cases. Similarly, NIM-MetS has proved to be highly specific, reaching an overall specificity of 94.9% (92.5% in men and 97.8% in women). Both VI and the SP recorded values above those achieved by this method in another Spanish population,[15] where it obtained an IV = 89.5% and 91.5% specificity. For sensitivity, the overall figure was 56.4% (59.4% for men and 40.9% for women), while in the original population, the overall sensitivity was 77.9%. Because it supposes a simple, easy to apply even in large populations and non-invasive method, it could be defined as a useful method in spite of the sensitivity found in the present study could be considered as moderate. The high specificity together with the high validity index shown for the screening of the cardiometabolic risk are characteristics that increase the acceptability of the method.

Although the indicators of validation and accuracy of a screening test (sensitivity and specificity) are intrinsic properties of the test itself and do not depend on the prevalence of the disease considered, this does not prevent these indicators from being affected by characteristics of the population they are applied to.[21] In fact, the most common observation is that a test for early detection or diagnosis alters its sensitivity and specificity depending on these characteristic features of the population. Therefore, the main differences between the two populations (the Balearic and the one considered in the previous study developed in Cordoba[15]) were analysed, highlighting those features of the Balearic population

which contributed to a decreased sensitivity: a younger population (40.0 vs. 45.1 years), more females (42.7% vs. 32.1%), more smokers (34.8% vs. 28.6%) and lower values for WC (82.9 vs. 87.8 cm), WHtR (0.49 vs. 0.52) and BMI (26.1 vs. 26.5 kg/m^2).

As regards the safety indicators of the test, the positive and negative predictive values, they are definitely affected by the prevalence of the population, lowering the PPV when the prevalence of MetS is lower. In this way, although we found a lower prevalence of MetS in the Balearic Islands than in Cordoba (9.0% vs. 13.9%), the NIM-Mets produced a lower PPV in the Balearic Islands (51.3% vs. 61.7%), while the negative predictive value remained very similar (95.5% vs. 95.9%).

Screening tests are often used in clinical practice. However, there are very few methods for the early detection of MetS other than the currently known diagnostic criteria, and there are even fewer non-invasive screening tests. A study in the Republic of Korea examined the validity of a test for the early detection of MetS based on the muscle-to-fat ratio.[22] The study was conducted on 6,256 participants, with a sensitivity of 68.6% in men and 76.0% in women, and a specificity of 63.8% in men and 53.8% in women. Miller et al.[23] proposed a screening method for MetS in 745 young adults (18-29 years old) in the United States, based on making decision trees with the CHAID methodology and using all the criteria for MetS. The method had a validity rate of 89.4% and a sensitivity rate of 61.7%. Finally, De Kroon et al.[24] conducted a screening test for MetS in 642 young people (aged 17-28) in the Netherlands using anthropometric variables (BMI, WC and BP). The sensitivity of the method was 68.7% and the validity index was 95.6%.

Another hypothesis put forward in this research was to test whether the cut-off value proposed by NIM-MetS for WHtR (≥0.55) would be reproduced in a large sample (60,799 workers from the Balearic Islands), and if it was also valid for both men and women and also for different age groups. WHtR had a cut-off value of 0.54 for the total sample, with 0.56 men and 0.53 for women. As regards age

groups, the WHtR threshold increased with age, with 0.55-0.56 for men and 0.51-0.55 for women. These differences were reduced in the total sample (0.53-0.56).

It is noteworthy that several authors have proposed a universal 0.50 cut-off point for WHtR, both to detect MetS and to predict cardiometabolic risk and overall cardiovascular mortality.[25-28] However, in Spain, a cross-sectional study in the general population (n = 6,279, mean age = 43 years) showed that WHtR was the best anthropometric predictor of MetS (NCEP-ATP III), and the authors proposed a cut-off value of 0.55, with which they obtained a sensitivity of 91.0% and a specificity of 64.0%.[28] This cut-off value is very similar to the one proposed from the results obtained in the present study.

In Chile, two important child population studies were conducted by Arnaiz et al., showing results which match the value of the cut-off point proposed in the present study. Thus, in the first study, conducted on 209 schoolchildren (mean age of 11.5), the authors obtained a cut-off value of 0.55 WHtR for MetS,[29] while in the second study, performed in 2,980 children aged 6-14 (mean age of 9.9), the authors concluded that the WHtR did not change with age and gender and, therefore, a universal cut-off value could be agreed for both children and adults.[30]

The prospective study by Koch et al.[31] carried out in Chile on about 6,714 men and 6,340 women, evaluating the relationship between various anthropometric indices of adiposity, cardiovascular risk factors and mortality for a cut-off value of 0.55 obtained a sensitivity of 75.8% and a specificity of 73.3% for men, and a sensitivity of 77.6% and specificity of 56.3% for women.

In addition, several investigations conducted in non-European and non-Hispanic populations also concur on this threshold of WHtR for MetS. Thus, Obeidat et al.[32] in a study on a Jordanian population (n=630, aged 20-70 years) reported a cut-off value of 0.56 in men and 0.52 in women; in India, Rajput et al.,[33] achieved a threshold of 0.52 for men and women (n = 3,042) in all locations (rural or urban areas); and in China, He et al.,[34] in a descriptive study of 1,068 adult subjects, reported a cut-off value for WHtR of 0.5 for men and women alike.

When the NIM-MetS method was applied in this new larger sample of 60,799 workers from the Balearic Islands, the method has showed again the same variables obtained in the original study performed in Cordoba.[15] In the multiple logistic regression, WHtR and BP achieved the highest adjusted OR values. Thus, WHtR was the anthropometric index that best discriminated MetS presence, with an adjusted OR value of 4.4 (3.9-4.9), while SBP obtained an adjusted OR value of 3.8 (3.5-4.1). In addition, the cut-off values obtained for WHtR and for BP are very similar to those of the original method.

Several investigations have confirmed the high predictive ability of WHtR for MetS and CVD. In the systematic review conducted by Ashwell et al.,[35] in which 10 out of the 31 studies analysed the association between anthropometric measurements of central obesity and MetS, WHtR had the highest AUC value 0.76 (men) and 0.75 (women). This contrasted with WC, which obtained an AUC value of 0.75 (equal for men and women) and BMI, with an AUC value of 0.72 (men and women). Similarly, a meta-analysis conducted by Savva et al.,[36] in which 8 out of the 24 studies included compared WHtR (cut-off point 0.5) with BMI (cut-off point of 23 for the Asian population and 25 for the rest) for cardiometabolic risk in an Asian and non-Asian population, and concluded that WHtR showed a stronger association with MetS than with BMI.

Through the present study, the NIM-MetS method has been reproduced, and definitive cut-off values have been proposed for WHtR (0.56) and BP (128-80 mmHg), from which a sensitivity rate of 56.4%, a specificity rate of 94.5%, a validity index of 91.1% and a Youden index of 0.51 are obtained. On the other hand, finally, the long-term ability of MetS to predict CVD has shown to be limited by the dichotomous (binary) and qualitative nature of the classic diagnostic criteria for MetS. An innovative aspect that NIM-MetS brings is to provide a gradient or scale of risk of developing MetS which is divided into four risk levels: Very low risk (probability = 0.4%), low risk (probability = 8.3%), moderate risk (probability = 16.4%) and high risk (probability = 50.5%). In this way, health professionals can

take certain steps depending on the level of risk of MetS and promote a more accurate and early detection of the possible complications associated with CVD and MetS. Along the same lines, there have been several studies using methods based on scores to quantify the amount of risk accumulated by the presence of the components that define the metabolic syndrome (Metabolic Syndrome Severity Score).[37,38]

Limitations

This study presents some limitations that must be acknowledged. First, we must bear in mind that there are different definitions and criteria to determine the presence of MetS. In this study, presence of MetS was ascertained using the NCEP-ATP III definition as a gold standard, which supposes one of the definitions most used and widely accepted by the international community and the WHO. In addition, the study data refers to Caucasian population. Thus, results could not have great applicability to other populations.

Although in the present study NIM-MetS methodology has been tested in a very large sample of workers, the sensitivity found was lower than that obtained in the original study leading to the proposal of the method.[15] This could be related to differences in the study samples, with the workers from the Balearic Islands showing lower prevalence of SMet and obesity and being younger. Although the prevalence of MetS does not affect sensitivity and specificity, this lower prevalence influences PPV and NPV.

In spite of the percentage of participation is high (87.4%), we should take into account that it is not the total target population and, therefore, a bias could have been introduced in the results. Furthermore, participants highly concerned about their health, and thus probably healthier, along with those with a diagnosed disease, could represent the greater proportion of workers attending health examinations because these were not compulsory. This causes bias in the recruitment procedure as, in addition, it is not well-known whether the healthier

workers or the ones with a diagnosed disease are the ones with the greatest interest in the checks. Nor can we ignore the bias of the healthy worker, since those workers with serious illnesses would not be currently active. In addition, it is not well known if the healthiest workers or those with a diagnosed illness have the greatest interest in checks.

Conclusions

The NIM-MetS has proved to be a valid method for the early detection of MetS in a healthy worker population. It is a simple, economical and quick non-invasive test which is easy to apply and interpret in any health care setting (primary health care, hospitals, occupational health) as well as in other settings (education, sport, etc.). WHtR is the best predictor of MetS and its cut-off point can be used for both genders and for different age groups. The clinical decision tree that produces the NIM-MetS uses WHtR (0.56) and BP (128/80 mmHg), and obtains high specificity and diagnostic validity. The NIM-MetS provides a gradient or risk scale which allows a more accurate and earlier detection of CVD in subjects with risk of MetS.

Contributor ship statement

Manuel Romero-Saldana contributed to the conception, design, acquisition and analysis/interpretation of data, drafted the manuscript, critically revised the manuscript and gave his final approval to the text, while also agreeing to be accountable for the integrity and accuracy of all aspects of the work.

Pedro Tauler contributed to the data collection, analysis, critically revised the manuscript, gave his final approval, and agrees to be accountable for the integrity and accuracy of all aspects of the work.

Manuel Vaquero-Abellán contributed to the analysis and interpretation, critically revised the manuscript, gave his final approval, and agrees to be accountable for the integrity and accuracy of all aspects of the work.

Angel A. Lopez-Gonzalez contributed to the data collection, analysis, critically revised the manuscript, gave his final approval, and agrees to be accountable for the integrity and accuracy of all aspects of the work.

Francisco J. Fuentes-Jimenez contributed to the analysis, critically revised the manuscript, gave his final approval, and agrees to be accountable for the integrity and accuracy of all aspects of the work.

Antoni Aguilo contributed to the conception, critically revised the manuscript, gave his final approval, and agrees to be accountable for the integrity and accuracy of all aspects of the work.

Carlos Alvarez-Fernandez contributed to the conception, critically revised the manuscript, gave his final approval, and agrees to be accountable for the integrity and accuracy of all aspects of the work.

Guillermo Molina-Recio contributed to the analysis and interpretation, critically revised the manuscript, gave her final approval and agrees to be accountable for the integrity and accuracy of all aspects of the work.

Miquel Bennasar-Veny contributed to the design, acquisition and analysis/interpretation of data, critically revised the manuscript, gave his final approval, and agrees to be accountable for the integrity and accuracy of all aspects of the work.

Competing interests

None declared.

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Data sharing statement

Extra data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi:10.5061/dryad.cb51t54

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Table 1. Characteristics of the sample according to gender

Variable	Total n=60,799	Men n= 34,827	Women n= 25,972	p
	Mean (95% CI) or n (%)	Mean (95% CI) or n (%)	Mean (95% CI) or n (%)	
Age (years)	40.0 (39.9 – 40.1)	40.4 (40.3 – 40.5)	39.5 (39.3 – 39.6)	<0.001
Smoker (yes)	21,177 (34.8%)	12,746 (36.6%)	8,431 (32.5%)	<0.001
BMI (kg/m^2)	26.1 (26 – 26.1)	26.9 (26.8 – 26.9)	25.0 (25 – 25.1)	<0.001
WC (cm)	82.9 (82.9 – 83.0)	88.6 (88.5 – 88.7)	75.4 (75.3 – 75.5)	<0.001
WHtR	0.49 (0.49 – 0.49)	0.51 (0.50 – 0.51)	0.47 (0.46 – 0.47)	<0.001
ABSI	0.07 (0.07 -0.07)	0.07 (0.07 -0.07)	0.07 (0.07 -0.07)	<0.001
BF (%)	28.9 (28.9 – 29.0)	25.3 (25.3 – 25.4)	33.7 (33.6 – 37.8)	<0.001
SBP (mmHg)	120.8 (120.6 -120.9)	125.4 (125.2 – 125.6)	114.6 (114.4 – 114.8)	<0.001
DBP (mmHg)	73.6 (73.5 – 73.7)	76.0 (75.9 -76.1)	70.4 (70.3 – 70.5)	<0.001
Glucose (mg/dL)	88.3 (88.1- 88.5)	90.6 (90.4 – 90.8)	85.2 (85 – 85.4)	<0.001
Cholesterol (mg/dL)	195.2 (194.9 - 195.5)	196.9 (196.5 -197.3)	193.0 (192.6 – 193.4)	<0.001
HDL-Cholesterol (mg/dL)	52.4 (52.3 - 52.5)	50.5 (50.4 – 50.6)	55.0 (54.9 – 55.1)	<0.001
LDL-Cholesterol (mg/dL)	121.2 (120.9 - 121.5)	121.8 (121.4 – 126.2)	120.5 (120 – 120.9)	<0.001
Triglycerides (mg/dL)	109.3 (108.7 – 109.9)	125.3 (124.4 – 126.2)	88.8 (88.2 – 89.4)	<0.001
MetS (yes)	5,587 (9.0%)	4,097 (11.8%)	1,390 (5.4%)	<0.001

BMI: Body Mass Index; WC: Waist circumference; WHtR: Waist to Height Ratio; ABSI: A body Shape Index; BF (%): Body Fat percentage calculated according to the Deurenberg equation; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MetS: Metabolic syndrome. P<0.05 indicates significant differences between genders

Table 2. Diagnostic test accuracy of NIM-MetS against NCEP-ATP III

STANDARD REFERENCE NCEP APTIIII

		TOTAL			MEN			WOMEN		
		Yes	**No**	**Total**	**Yes**	**No**	**Total**	**Yes**	**No**	**Total**
NIM – MetS (n)	**Yes**	3,001	2,850	5,851	2,433	2,300	4,733	568	550	1,118
	No	2,486	52,462	54,948	1,664	28,430	30,094	822	24,032	24,854
	Total	5,487	55,312	60,799	4,097	30,730	34,827	1,390	24,582	25,972
Efficacy indicators, 95% CI										
Sensitivity		54.7 (53.4 – 56.0)			59.4 (57.9 – 60.9)			40.9 (38.2 – 43.5)		
Specificity		94.9 (94.7 – 95.0)			92.5 (92.2 – 92.8)			97.8 (97.6 – 98.0)		
PPV		51.3 (50 – 52.6)			51.4 (50.0 – 52.8)			50.8 (47.8 – 53.8)		
NPV		95.5 (95 – 95.7)			94.5 (94.2 – 94.7)			96.7 (96.5 – 96.9)		
VI		91.2 (91.0 – 91.5)			88.6 (88.3 – 89.0)			94.7 (94.4 – 95.0)		
LH +		10.6 (10.2 – 11.1)			7.9 (7.6 – 8.3)			18.3 (16.5 – 20.3)		
LH -		0.48 (0.46 – 0.49)			0.44 (0.42 – 0.46)			0.60 (0.58 – 0.63)		
JI		0.50 (0.48 – 0.51)			0.52 (0.50 – 0.53)			0.39 (0.36 – 0.41)		

PPV: Positive Predictive Value; NPV: Negative Predictive Value; VI: Validity Index; LH +: Likelihood ratio positive; LH -: Likelihood ratio negative; JI: Youden Index.

Table 3. Area under the curve (AUC) and cut-off values for WHtR according to gender and age groups

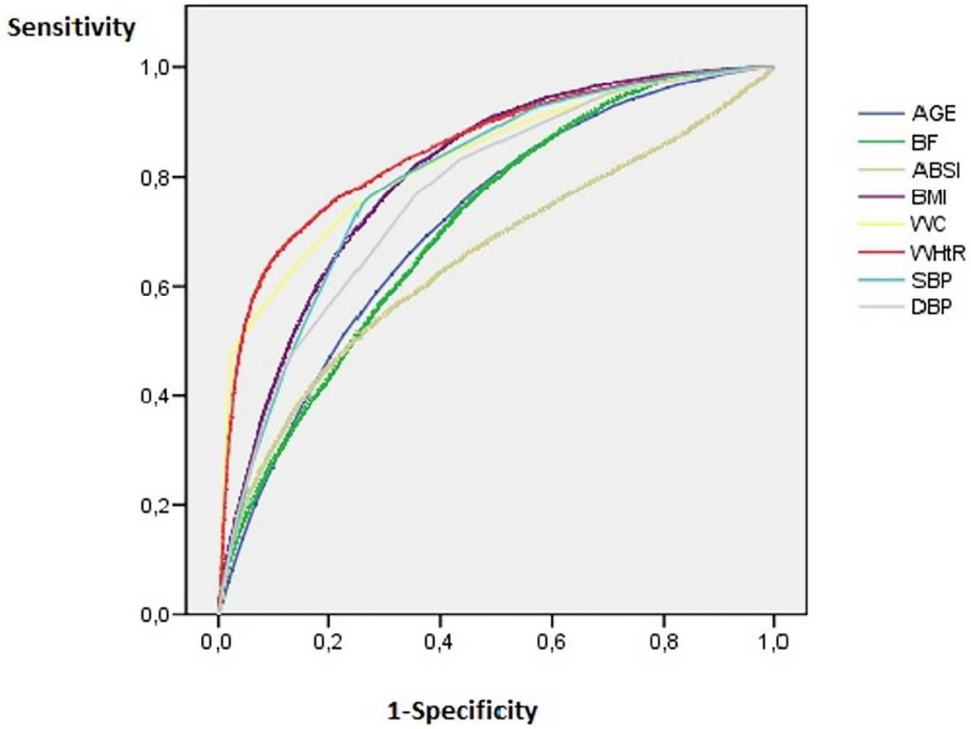
Age group (years)	n	Prevalence of MetS (%)[a]	AUC 95% CI	Cut-off value	Sensitivity (%)	Specificity (%)	JI
			MEN				
20-30	6,825	3.1	0.92 (0.9 – 0.95)	0.55	80.3	93.4	0.74
31-40	11,623	7.5	0.88 (0.86 – 0.89)	0.55	77.4	88.1	0.65
41-50	10,080	14.9	0.82 (0.81 – 0. 83)	0.56	66.4	87.7	0.54
≥51	6,659	23.1	0.75 (0.74 – 0.77)	0.56	58.9	83.0	0.42
Total	34,827	11.8	0.84 (0.83 – 0.85)	0.56	66.7	88.8	0.56
			WOMEN				
20-30	5,715	1.1	0.90 (0.85 – 0.95)	0.51	82.0	84.0	0.74
31-40	8,529	2.7	0.91 (0.89 – 0.93)	0.53	80.3	90.8	0.71
41-50	7,641	6.6	0.91 (0.89 – 0.93)	0.53	80.3	90.8	0.71
≥51	4,087	14.4	0.75 (0.73 – 0.77)	0.55	48.4	90.5	0.39
Total	25,972	5.4	0.85 (0.84 -0.86)	0.53	65.1	88.7	0.54
			TOTAL				
20-30	12,540	2.1	0.92 (0.9 – 0.94)	0.53	84.4	90.1	0.75
31-40	19,792	5.5	0.90 (0.89 – 0.91	0.54	78.2	88.5	0.67
41-50	17,721	11.3	0.83 (0.82 – 0.84)	0.54	69.6	84.3	0.54
≥51	10,746	19.8	0.76 (0.75 – 0.77)	0.56	57.0	85.3	0.42
Total	60,799	9.0	0.85 (0.84 – 0.86)	0.54	68.5	87.0	0.56

a: MetS according to NCEP ATP III criterion; AUC: area under the curve; JI: Youden Index

Table 4. Probabilities of MetS (%) for nodes 3, 4, 5 and 6 in decision trees according to cut-off values of WtHR

WHtR range	BP model	Probabilities of MetS for nodes in the decision tree				Efficacy indicators for diagnostic test accuracy			
Cut-off points	BP	Node 3	Node 4	Node 5	Node 6	Sensitivity (%)	Specificity (%)	VI (%)	JI
0.535	BP[1]	0.3	7.4	10.3	38.4	63.9	89.7	87.5	0.54
	BP[2]	0.5	10.4	12.2	43.3	59.3	92.3	89.3	0.52
	SBP	0.6	10.5	13.7	43.3	57.0	92.6	89.4	0.5
0.540	BP[1]	0.3	7.6	11.5	40.7	62.7	90.9	88.4	0.54
	BP[2]	0.5	10.5	13.5	45.7	57.8	93.2	90.0	0.51
	SBP	0.6	10.7	15.2	45.7	55.6	93.5	90.0	0.49
0.544 [a]	BP[1]	0.4	7.7	12.5	42.8	61.6	91.8	89.1	0.53
	BP[2]	0.5	10.9	14.6	48.0	56.7	93.9	90.5	0.51
	SBP	0.6	10.8	16.4	48.0	54.5	94.1	90.6	0.49
0.550 [b]	BP[1]	0.4	7.9	14.2	46.1	59.6	93.1	90.1	0.53
	BP[2]	0.5	10.9	16.6	51.3	54.7	94.8	91.2	0.46
	SBP	0.7	11.0	18.5	51.4	52.6	95.1	91.2	0.48
0.555	BP[1]	0.4	8.2	15.7	49.1	57.8	94.1	90.8	0.52
	BP[2]	0.6	11.1	18.3	54.4	53.0	95.6	91.7	0.49
	SBP	0.7	11.3	20.3	54.5	51.0	95.8	91.7	0.47
0.560	BP[1]	0.5	8.5	17.0	51.8	55.7	94.9	91.3	0.51
	BP[2]	0.6	11.5	19.9	57.1	51.0	96.2	92.1	0.47
	SBP	0.8	11.6	21.9	57.2	49.1	96.4	92.1	0.46
0.565	BP[1]	0.5	8.8	18.6	54.9	53.4	95.6	91.8	0.49
	BP[2]	0.6	11.9	21.8	60.3	48.8	96.8	92.5	0.46
	SBP	0.8	12.0	23.9	60.4	47.0	96.9	92.4	0.44
0.570	BP[1]	0.5	9.1	19.9	57.4	51.4	96.2	92.2	0.48
	BP[2]	0.7	12.3	23.3	62.8	46.9	97.2	92.7	0.44
	SBP	0.9	12.4	25.5	63.0	45.2	97.4	92.7	0.43

BP: Blood Pressure; BP[1]: Blood pressure ≥128/80 mmHg; BP[2]: Blood pressure ≥128/85 mmHg; SBP: Systolic blood pressure≥128 mmHg; VI: Validity index; JI: Youden Index; a: Cut-off point for WHtR obtained in the total simple (n=60,799); b: Cut-off point proposed by NIM-MetS



	AUC (95% CI)	CP	Sensitivity (%)	Specificity (%)	JI
Age	0.71 (0.71- 0.72)	42.5	69.2	62.5	0.32
WHtR	0.85 (0.84 – 0.86)	0.54	68.5	87.0	0.56
WC	0.83 (0.82 – 0.84)	89.1	72.5	77.6	0.50
BMI	0.8 (0.8 – 0.81)	27.1	78.4	68.3	0.47
ABSI	0.65 (0.64 – 0.66)	0.07	50.4	75.2	0.26
BF%	0.71 (0.7 – 0.72)	29.4	70.9	58.1	0.3
SBP	0.79 (0.79 – 0.8)	127.5	75.8	73.5	0.49
DBP	0.77 (0.76 – 0.78)	78.5	77.3	63.9	0.41

AUC: Area under curve CP: Cut-off point; JI: Youden Index; BMI: Body mass index; WC: Waist circumference; WHtR: Waist to height ratio; ABSI: A Body Shape Index; BF (%): Body Fat calculated according to the Deurenberg equation; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.

Figure 1

96x112mm (300 x 300 DPI)

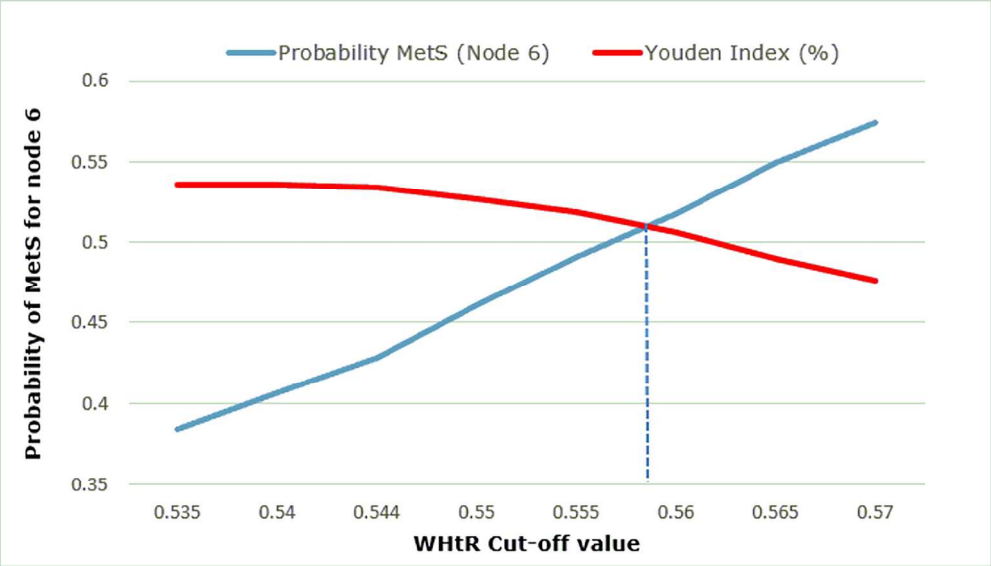


Figure 2

170x98mm (300 x 300 DPI)

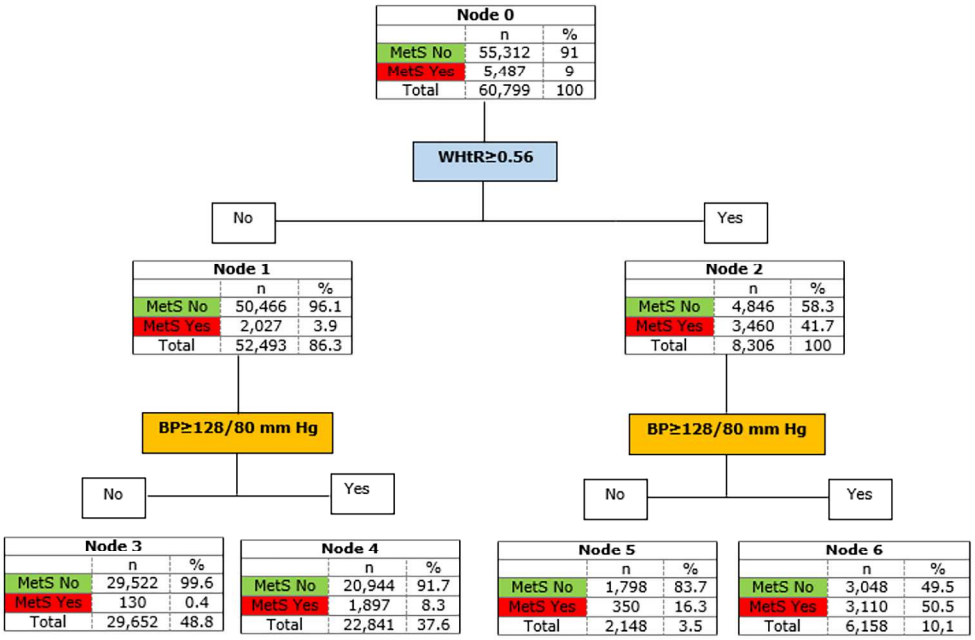


Figure 3

274x183mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Checked in page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6-7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	9
		(*e*) Describe any sensitivity analyses	9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	11
		(c) Consider use of a flow diagram	Not necesary
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11-12
		(b) Indicate number of participants with missing data for each variable of interest	none
Outcome data	15*	Report numbers of outcome events or summary measures	11-12-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted	12-13-14

		estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	13-14
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not indicated
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-14
Discussion			
Key results	18	Summarise key results with reference to study objectives	16-17-18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17-18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section & Topic	No	Item	Checked in page
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	2
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	4
	4	Study objectives and hypotheses	4-5
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	6
Participants	**6**	Eligibility criteria	6
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	6
	8	Where and when potentially eligible participants were identified (setting, location and dates)	6
	9	Whether participants formed a consecutive, random or convenience series	6
Test methods	**10a**	Index test, in sufficient detail to allow replication	7
	10b	Reference standard, in sufficient detail to allow replication	7
	11	Rationale for choosing the reference standard (if alternatives exist)	
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	8
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	8
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	8-9
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	8-9
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	9-10
	15	How indeterminate index test or reference standard results were handled	9-10
	16	How missing data on the index test and reference standard were handled	9-10
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	
	18	Intended sample size and how it was determined	6
RESULTS			
Participants	**19**	Flow of participants, using a diagram	Not indicated
	20	Baseline demographic and clinical characteristics of participants	11
	21a	Distribution of severity of disease in those with the target condition	11-12
	21b	Distribution of alternative diagnoses in those without the target condition	11-12
	22	Time interval and any clinical interventions between index test and reference standard	Not necessary
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	12
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	12
	25	Any adverse events from performing the index test or the reference standard	None
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	17-18
	27	Implications for practice, including the intended use and clinical role of the index test	17-18-19
OTHER INFORMATION			
	28	Registration number and name of registry	
	29	Where the full study protocol can be accessed	
	30	Sources of funding and other support; role of funders	20

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.