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Original Article

Cardiometabolic risk stratification using a novel obesity phenotyping system based on body adiposity and waist circumference

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ABSTRACT

Background: The estimation of obesity-associated cardiometabolic risk does not usually take into account body composition or the distribution of adiposity. The aim of the present study was to assess the clinical usefulness of a novel obesity phenotyping system based on the combination of actual body fat percentage (BF%) and waist circumference (WC) according to the cardiometabolic risk estimation.

Methods: A classification matrix combining BF% and WC as measures of both amount and distribution of adiposity establishing nine body phenotypes (3 BF% x 3 WC) was developed. Individuals were grouped in five different cardiometabolic risk phenotypes. We conducted a validation study in a large cohort of White subjects from both genders representing a wide range of ages and adiposity (n = 12,754; 65 % females, aged 18–88 years).

Results: The five risk groups using the matrix combination of BF% and WC exhibited a robust linear distribution regarding cardiometabolic risk, estimated by the Metabolic Syndrome Severity Score, showing a continuous increase between groups with significant differences ($P < 0.001$) among them, as well as in other cardiometabolic risk factors. An additional 24 % of patients at very high risk was detected with the new classification system proposed ($P < 0.001$) as compared to an equivalent matrix using BMI and WC instead of BF% and WC.

Conclusions: A more detailed phenotyping should be a priority in the diagnosis and management of patients with obesity. Our classification system allows to gradually estimate the cardiometabolic risk according to BF% and WC, thus representing a novel and useful tool for both research and clinical practice.

1. Introduction

Over the past decades, obesity has been increasingly prevalent throughout the world. Between 1975 and 2014, the prevalence of obesity in adults, defined as a body mass index (BMI) ≥30 kg/m^2, increased from 6.4 % to 14.9 % in women and from 3.2 % to 10.8 % in men [1]. According to medical definitions, obesity is a condition marked by an increase in adipose tissue that is relevant enough to exert a negative impact on health [2] having a multifactorial origin [3]. Excess adiposity is linked to higher rates of morbidity and mortality due to the increment in the development of comorbidities such as type 2 diabetes (T2D), cardiovascular disease, non-alcoholic fatty liver disease, sleep apnea, and some types of cancer [4,5].

Patient-specific combinations of lifestyle interventions, anti-obesity drugs, and bariatric surgical procedures are the most habitual treatment strategies for obesity [6,7]. However, in the time of personalized medicine and with the focus on precision nutrition for the treatment of the patients living with obesity, all obesities (i.e. patients with the same BMI-based classification of "obesity", but with substantial differences on adiposity distribution, cardiometabolic risk, etc.) cannot be managed

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with the same approach [8,9]. In this line, the first step for a personalized treatment must be a detailed phenotyping of the patients with obesity. Body mass index (BMI) has been the most extensively used tool for the diagnosis of obesity. However, it is well known that BMI exhibits notable inaccuracies and misclassifies patients with obesity, while actual body fat percentage (BF%) estimation helps to better determine the obesity-associated cardiometabolic risk [10–12]. In addition, BMI does not take into account the amount and distribution of body fat, which can differ among people with the same BMI. In this sense, adipose tissue distribution in addition to the amount of adiposity also provides crucial information to get a more accurate prediction of a given patient's cardiometabolic risk [13,14]. In this sense, patient stratification according to BMI and waist circumference (WC) simultaneously allows a better prediction of cardiometabolic risk [15–17] or even the establishment of specific cardiometabolic risk phenotypes using the combination of BMI and WC to define a kind of "matrix" [18,19]. Although the cardiometabolic risk predicted using this method is more accurate than using BMI or WC alone, it still has the same limitations as the BMI [20].

Since an accurate classification system for phenotyping the obesities is of paramount importance [21], we have recently put forward the combination of BF% and WC as a novel and practical tool for the estimation of obesity-associated cardiometabolic risk. We hypothesized that the proposed grading system better identifies the cardiometabolic risk than other classifications. This emerging grading system can be useful both in the clinical setting and for research purposes, providing a more accurate identification of the increased risk associated with both excess fat and harmful adiposity distribution [20].

2. Materials and methods

2.1. Study design

We studied a cohort of 12,754 mainly White subjects (8,265 females/4,489 males), aged 18–88 years including patients and volunteers visiting the Department of Endocrinology & Nutrition of the Clínica Universidad de Navarra. The sample included consecutive subjects with body composition determination by air displacement plethysmography (ADP) between May 2003 and June 2019. The experimental design was approved, from an ethical and scientific standpoint, by the Hospital's Ethical Committee responsible for research (Protocols 067/2003, 030/2006, 081/2009, 169/2014, and 117/2018) and the study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all subjects.

2.2. Anthropometric measurements

Anthropometry, body composition analyses and blood sampling were performed on the same morning in fasting conditions. Height, weight and WC were measured wearing a swimming suit as previously described [11,22]. BMI was calculated dividing the weight in kg by the square of height in m. Systolic (SBP) and diastolic (DBP) blood pressures were determined after a 5-minute rest in the semi-sitting position with a sphygmomanometer. Blood pressure was determined at least 3 times at the right upper arm as previously described and the average was used in the analyses [23].

2.3. Body composition

Body density was determined by ADP (Bod-Pod®, COSMED, Albano Laziale, Italy). Data for calculation of BF% by this plethysmographic method has been reported to agree closely with the traditional gold standard hydrodensitometry underwater weighing [24]. It uses the pressure-volume relationship to estimate volume and density and has been shown to predict fat mass and fat-free mass more accurately than DEXA and bioimpedance (BIA) [24,25]. BF% was estimated from body density using the Siri equation. In order to show that the proposed classification system is also valid with other devices to measure BF% or even with prediction equations, we repeated the group distribution analysis after the estimation of BF% with the *Clínica Universidad de Navarra-Body Adiposity Estimator* (CUN-BAE) [22] in the whole sample or after measuring BF with BIA (Tanita BC-420MA, Tanita Corp., Tokyo, Japan) in a separate cohort of 693 individuals.

2.4. Laboratory procedures

Plasma biochemistry was analyzed as previously described [10,12,14,26,27]. Briefly, plasma and serum samples were collected in the morning after overnight fasting. Plasma glucose was determined using an analyzer (Modular P800, Roche, Basel, Switzerland). Insulin was measured by a commercial assay (Immulite®, Diagnostic Products, Los Angeles, CA, USA). Total cholesterol and triglyceride concentrations were determined by enzymatic spectrophotometric methods (Roche). HDL-cholesterol was measured by a colorimetric method in a Beckman Synchron® CX analyzer (Beckman Instruments, Bucks, UK). LDL-cholesterol was estimated by using the Friedewald formula. White blood cells (WBC) number was quantified using an automated cell counter (Beckman Coulter, Fullerton, CA, USA). Uric acid was measured by enzymatic tests (Roche). The quantitative insulin sensitivity check index (QUICKI) was calculated as indirect measure of insulin sensitivity [23]. The Metabolic Syndrome Severity Score (MetSSS) was calculated as previously described [28]. In 2,725 patients from the whole cohort an oral glucose tolerance test (OGTT) was performed to rule out the presence of T2D. Normoglycemia (NG), impaired glucose tolerance (IGT) and T2D were defined following the criteria of the American Diabetes Association [29].

2.5. Classification matrix according to BF% and WC

A classification matrix combining the actual adiposity expressed as BF% and WC as a measure of distribution establishing nine body phenotypes (3 BF% x 3 WC) was developed. The cut-off points were those defined by the WHO as increased or high cardiometabolic risk for WC (80 and 88 cm in females, and 94 and 102 cm in males, respectively) [17,30] and the most frequently used for defining overweight and obesity according to BF% (30.0 and 35.0 % in females, and 20.0 and 25.0 % in males, respectively)[10,11,31-35]. Individuals were grouped in five different risk phenotypes, following a traffic light-like classification system (green: no risk; yellow: slightly increased risk; orange: increased risk; dark orange: high risk and red: very high risk) according to the predicted risk. We decided to use the WC instead of the waist-to-hip ratio (WHR), since the WC has been shown to be a better estimator of visceral adipose tissue than the WHR [20,36,37]. In addition, the WC presented a lower collinearity with BF% (0.59, $P < 0.001$) than the waist-to-height ratio (WHtR) (0.72, $P < 0.001$), suggesting that WC is more unrelated to BF% than WHtR. Moreover, we believe that, for practical reasons, it is easier to use the WC than the WHR or the WHtR in clinical practice.

2.6. Statistical analysis

Data are presented as mean ± standard deviation (SD). Differences between groups were analyzed by unpaired Student's *t* tests, ANOVA followed by Bonferroni's tests or ANCOVA with sex and age as covariates, as appropriate. Differences in distributions were computed by chi-square test. The calculations were performed by SPSS version 23 (Chicago, IL, USA) and GraphPad Prism 8 (La Jolla, CA, USA). *P* values lower than 0.05 were considered statistically significant.

3. Results

Anthropometric and biochemical characteristics of the subjects included in the cohort study are presented in Table S1. The sample of

12,754 subjects had a mean age of 46 ± 14 years and was mainly composed by women (65 %). This cohort included 2,090 (16 %) people with normal weight (NW), 3,506 (28 %) subjects with overweight, while 56 % of the individuals (7,158) were classified as with obesity, according to BMI. Therefore, the studied cohort included a wide range of age, BMI and BF% representing a broad spectrum of the population (Table S2). The differences regarding sex in the whole sample are shown in Table S1.

Distribution of the 12,754 subjects according to the combination of BF% and WC segregated by sex with the cut-off points used for establishing the matrix is shown in Fig. 1A. The number of subjects in the 9 groups segregated by sex is shown in Fig. 1B. According to the five different risk phenotypes classification, we found 862 (7 %) in the green group (absence of risk); 622 (5 %) in the yellow group (slightly increased risk); 990 (8 %) in the orange group (increased risk); 1,744 (13 %) in the dark orange group (high risk) and 8,536 (67 %) in the red group (very high risk) (Fig. S1). Following a similar classification system but using the combination of BMI and WC 6,869 (54 %) individuals are classified in the "equivalent" red group (Fig. S2). It must be highlighted that with the classification system that combines BMI and WC, 13 % fewer patients of the whole cohort are classified in the higher risk group, which represents that the system combining BF% and WC allows to detect many more patients at very high risk (67% vs 54 %). Therefore, considering only those at very high risk, 24 % more of patients are detected with the combination of BF% and WC (Fig. 2), revealing the marked difference ($P < 0.001$) between the BF%-WC matrix as opposed

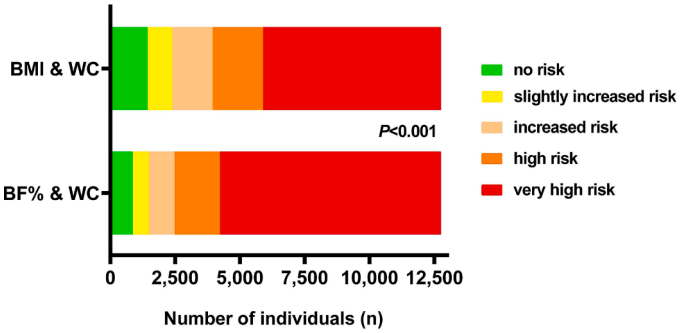

Fig. 2. Comparison of the distribution of the 12,754 individuals according to the combination of body mass index (BMI) and waist circumference (WC) (top) and body fat percentage (BF%) and WC (bottom) in relation to the 5-phenotypes new classification system proposed. Differences in distribution were computed by chi-square test. The traffic light-like colors classification system is indicated.

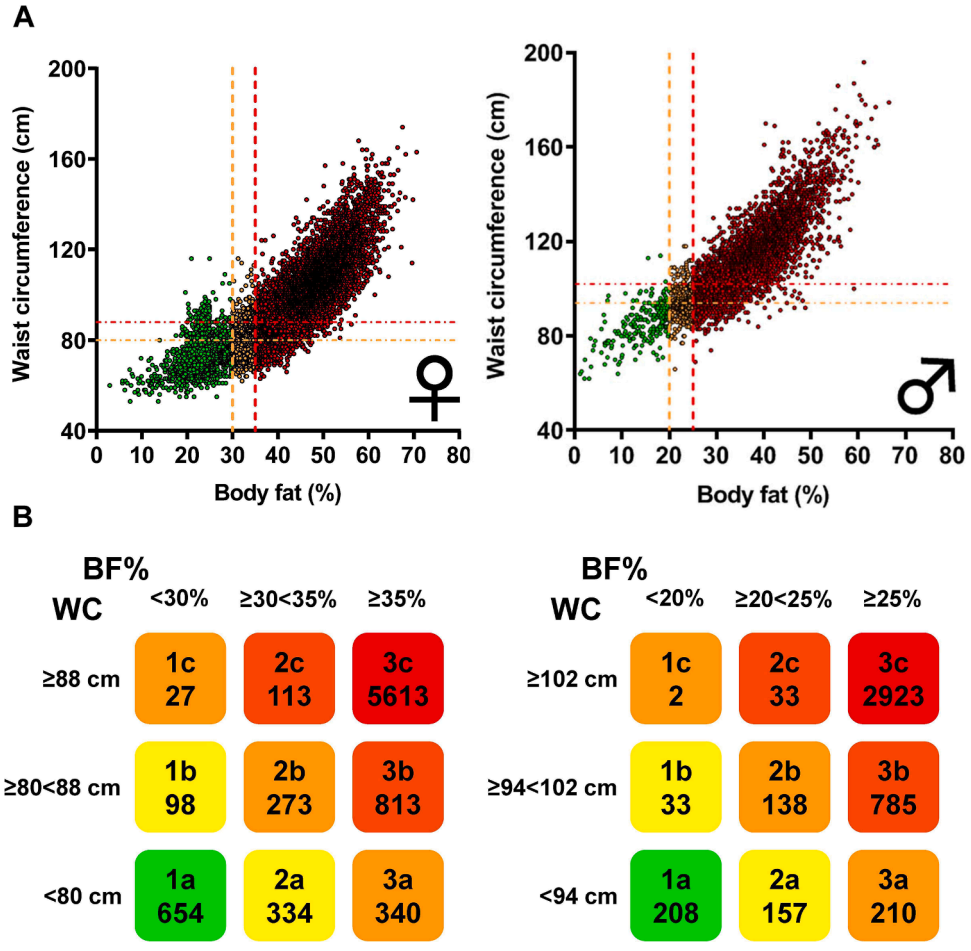

Fig. 1. Distribution of the 12,754 individuals, according to the combination of body fat percentage (BF%) and waist circumference (WC) segregated by sex. A) Graphical distribution of BF% and WC in 8,265 females (left) and 4,489 males (right). Vertical dashed lines indicate cut-offs for defining overweight and obesity according to BF% (30.0 and 35.0 % in females, and 20.0 and 25.0 % in males, respectively); while horizontal lines indicate cut-offs for defining increased or high cardiometabolic risk (80 and 88 cm in females, and 94 and 102 cm in males, respectively) according to WC. Colors denote normal weight/underweight (green), overweight (orange) or obesity (red) according to BF%. B) Matrix classification according to BF% and WC cut-off points of females (left) and males (right) defining five different risk phenotypes, following a traffic light-like colors classification system (green: absence of risk; yellow: slightly increased risk; orange: increased risk; dark orange: high risk and red: very high risk), according to the predicted cardiometabolic risk. The number of subjects in each of the nine squares is indicated. BF%, body fat percentage; WC, waist circumference.

to the BMI-WC one. The distribution by sex (Fig. S3A) shows a higher number of females in the green and yellow groups and a more abundant representation of males in the dark orange and red groups (83% vs 79 %, $P < 0.001$ for the global distribution). The age distribution showed that as age increases, the number of individuals in the highest risk groups increases, particularly in the red group ($P < 0.001$ for the global frequency distribution). The five risk group of the BF%-WC matrix combination exhibited a robust linear distribution in anthropometric and body composition values (Fig. S4). Moreover, the cardiometabolic risk, estimated by the MetSSS showed also a continuous increase between groups with significant differences ($P < 0.001$) among them (Fig. 3) as well as in other cardiometabolic risk factors (Fig. 4). Moreover, from the patients in whom an OGTT was carried out to rule out the presence of diabetes 74 % of those classified as with NG was classified in the red group, as compared to 85 % in the IGT group and 92 % in the T2D group ($P < 0.001$ for the global frequency distribution) (Fig S5). Interestingly, to highlight the differences in risk estimation obtained by using the different matrices, we analyzed risk groups distribution regarding BF% and WC in the green (lower cardiometabolic risk) group by BMI and WC. From the 1,433 individuals in the green group by BMI and WC, 790, 346 and 297 were classified in the green, yellow and orange groups by BF% and WC, respectively, exhibiting between them increased cardiometabolic risk, assessed by the MetSSS (Fig. 5) and other cardiometabolic variables (Table S3). However, at the other edge, in the red group by BMI and WC we found a very low misclassification rate, resulting that from the 6,869 individuals in that group, 35 subjects corresponded to the dark orange group and 3 to the orange group according to BF% and WC (data not shown).

Being aware that ADP or other body composition techniques are not always available in clinical routine, we aimed to show that the proposed classification system may be also used with BF% measured or estimated with other tools. In this sense, we re-classified the 12,754 individuals included in our study using BF% estimated by using the CUN-BAE equation. The distribution in the different cardiometabolic risk groups was practically superimposed with the results obtained with the actual ADP data (Fig S6 and S8). In the same line, although in a much smaller separate cohort of 693 subjects with BF% measured by BIA, we also got a very similar global distribution in the cardiometabolic risk groups (Fig S7 and S8).

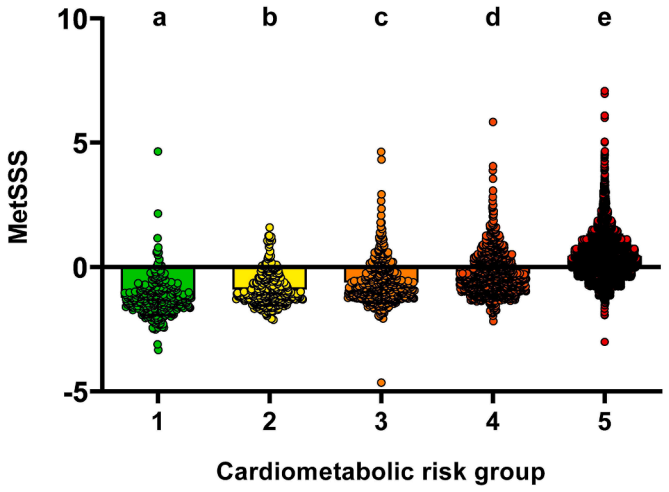

Fig. 3. Metabolic syndrome severity score (MetSSS) in the subjects of the cohort classified according to the traffic light-like colors classification system based on the matrix according to BF% and WC. The number of subjects in each group was 352, 310, 494, 1,005 and 4,724. Bars are the mean ± SD. Statistical differences between groups were analyzed by ANCOVA with sex and age as covariates. Different lowercase letters indicate significant differences among groups at the level of $P < 0.001$.

4. Discussion

The main objective of the present study was to analyze the clinical usefulness of a new classification system for obesity phenotyping taking into account actual BF% and WC as indicators of total amount and distribution of adiposity [20]. We herein show that the use of our phenotyping system better stratifies patients according to their increasing cardiometabolic risk providing a useful tool for both epidemiological studies and routine clinical diagnostics.

In the era of personalized medicine, an accurate phenotyping and a precise estimation of cardiometabolic risk should be a priority in the diagnosis and management of patients with overweight or obesity. In most studies regarding obesity, BMI is the most frequently used classification method. However, it is well known that BMI has high specificity but very low sensitivity for diagnosing obesity if we look at the BF%, which ultimately defines obesity [11,33,35]. In addition, besides not being a good proxy of adiposity, BMI does not inform about adipose tissue distribution or the amount of visceral adiposity, which is more closely associated to obesity complications than the subcutaneous depot [17].

The classification of patients in terms of their adiposity is usually done based on quantity (BMI) or distribution (for example, according to WC). Studies stratifying the patients according to both amount and distribution are scarce. It has been shown that the combination of BMI and WC may help to predict global and regional adiposity [38] and cardiometabolic risk [39,40] better than BMI or WC alone. In the same line, the combination of BMI and WC or WHR may predict mortality more precisely than BMI or WC/WHR alone [15,16].

With the aim of stratifying the patients in adiposity categories several studies have proposed a “matrix” combining BMI and WC [40, 41] showing that the combination is more strongly related to cardiovascular risk factors than BMI or WC individually. Interestingly, some studies have used this matrix to compare the ability of the WHtR to identify patients at risk, showing that the WHtR is superior to identify more people at “early health risk” [18,19,42]. Other studies have analyzed the combination of BMI and other proxies of adiposity distribution such as WHR or WHtR, suggesting that they may be useful in routine screening for cardiovascular risk [43,44]. However, these studies still have the well-described limitations of BMI (very useful in epidemiological studies, but highly imprecise estimating BF% at the individual level), so it would be better to perform patient phenotyping based on direct estimation of BF% instead of BMI. Although the BMI is still the predominant anthropometric tool used for the classification of overweight/obesity, we believe that a paradigm change for a better diagnosis of the patients with overweight or obesity is needed [8,20]. On the other hand, the WC has been reported to be a better estimator of visceral adipose tissue than the WHR and exhibits a lower collinearity with BF% than the WHtR. These observations, together with the fact that the WC is easier to handle in clinical practice made us choose the WC as a proxy of visceral adiposity.

Using the phenotyping system proposed in the present study a 5-group gradual staging of the patients according to their cardiometabolic risk is clearly defined as evidenced by the MetSSS and the other cardiometabolic risk factors. A 7 %, 5 %, 8 %, 13 % and 67 % of the patients were allocated in the green, yellow, orange, dark-orange and red risk groups, respectively. Although 67 % of the patients in the red group may seem disproportionate, it must be taken into account that 84 % and 92 % of our cohort exhibited overweight or obesity defined by BMI or BF%, respectively, being mostly a sample of people seeking medical advice. The proportions of people located in each group in the general population remain to be determined. It should be noted that a significantly higher number of patients at risk is detected using this system as compared to the combination of BMI and WC. This is especially striking in the green group by BMI and WC, where a high rate of incorrectly classified individuals is found, with these incorrectly classified subjects showing an increased cardiometabolic profile. As far as we

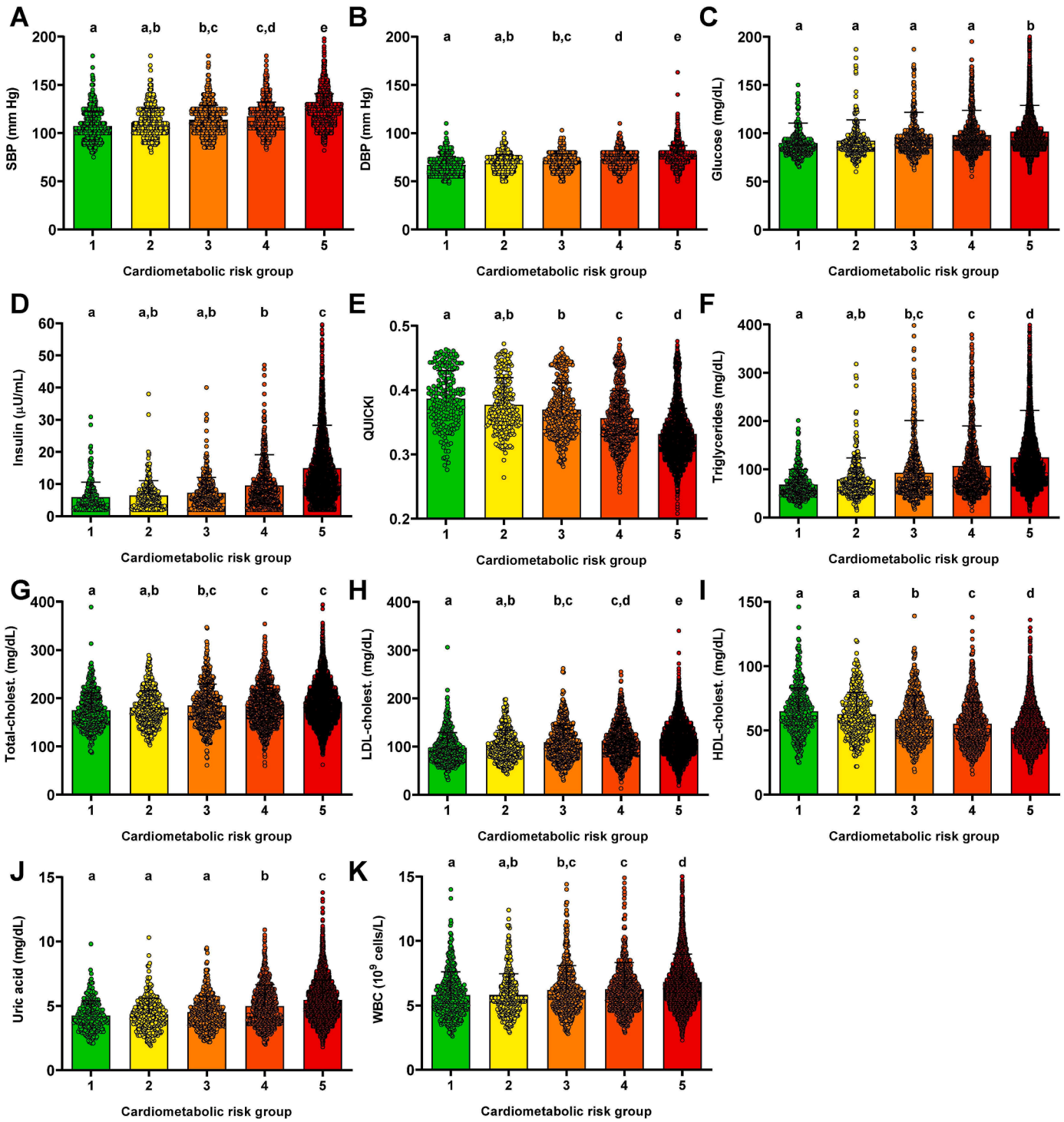

Fig. 4. Markers of cardiometabolic risk in the subjects of the cohort classified according to the traffic light-like colors classification system based on the matrix according to BF% and WC. Comparison of (A) systolic blood pressure (SBP) (number of subjects in each group 737, 551, 864, 1,570 and 7,756), (B) diastolic blood pressure (DBP) (737, 551, 864, 1,570 and 7,756), (C) fasting plasma glucose (456, 396, 640, 1,200 and 6,104), (D) insulin concentrations (201, 234, 395, 844 and 4,593), (E) quantitative insulin sensitivity check (QUICKI) (198, 233, 392, 837 and 4,536), (F) triglyceride levels (480, 391, 656, 1,258 and 5,795), (G) total cholesterol (481, 392, 660, 1,260 and 5,805), (H) LDL-cholesterol (459, 381, 636, 1,222 and 5,647), (I) HDL-cholesterol (470, 387, 644, 1244 and 5,762), (J) uric acid (266, 282, 457, 913 and 5,298) and (K) white blood cells count (WBC) (458, 329, 564, 1,094 and 5,614). Bars are the mean ± SD. Statistical differences between groups were analyzed by ANCOVA with sex and age as covariates. Different lowercase letters indicate significant differences among groups at the level of $P < 0.05$.

know, there are no similar studies combining BF% and WC or other measures of adiposity distribution.

The present study has some limitations. First, it was conducted in White individuals and the validity of our phenotyping system needs to be determined for other ethnicities. Second, the study was limited to adults (>18 y) and it would be interesting to extend it to children and adolescents [45]. A recent study has been published in school-aged children that suggest that similar approaches may improve the estimation of cardiovascular risk [46]. Third, our study is cross-sectional. The clinical usefulness of our classification system in prospective studies

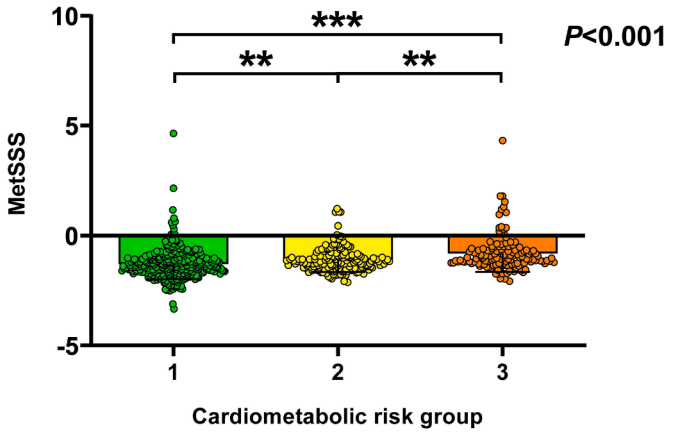

Fig. 5. Metabolic syndrome severity score (MetSSS) in the subjects of the cohort classified as "absence of risk" (green) with the body mass index and waist circumference (WC) matrix ($n = 1{,}433$), according to the traffic light-like colors classification system of the matrix body fat percentage and WC. The number of subjects in each group was 314, 164 and 132. Bars are the mean ± SD. Statistical differences between groups were analyzed by ANCOVA with sex and age as covariates followed by Bonferroni's tests. $^{**}P < 0.01$ and $^{***}P < 0.001$.

needs to be assessed. Fourth, we have not taken into account smoking or the medication taken by the patients, considering only biochemical and clinical variables. And fifth and final, WC is an indirect estimation of visceral adipose tissue. However, the correlation of WC with visceral adipose tissue determined by image techniques is higher than the correlation of BMI with BF%. Our study has several strengths. First, the proposed classification system has been validated in a large sample ($n = 12{,}754$) including subjects from both genders encompassing a wide range of body adiposity and ages (18–88 y). Second, actual BF% data have been measured by ADP, a highly precise technique. In this sense, it has to be stressed that since not all clinicians have access to ADP, other body compositions techniques/estimations such as BIA or the CUN-BAE, or other body adiposity estimators, can be used to apply the classification system, as shown in the present study. Data obtained with these formulas correlate better with the actual BF% than the BMI [22,47].

5. Conclusion

In summary, since not all obesity phenotypes are equal and may be treated in the same way a refined phenotyping should be a priority in the diagnosis and management of patients with obesity. In this sense, the classification system proposed in the present study allows to gradually estimate the individuals' cardiometabolic risk according to their total body fat amount and distribution, representing a novel and promising useful tool for both clinical practice and research purposes.

CRediT authorship contribution statement

J.G.-A. and G.F. and designed the study and obtained the funds, analyzed and interpreted the data and drafted the manuscript. **J.G.-A., V.C., B.R., L.S.-G., R.M., A.R., S.B., M.A.-A., P.Y.-E., L.O., C.M.P., C. S., J.E., and G.F.** provided study materials/data, critical input and revised the article for important intellectual content. All authors read and approved the final version of the article. **J.G.-A. and G.F.** are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Data availability

The data that support the findings of this study are available upon reasonable request.

Declaration of competing interest

No potential conflicts of interest relevant to this article were reported.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2024.02.027.

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