Editorial

Body Mass Index, Waist-to-Height Ratio, Cardiometabolic Risk Factors and Diseases in a New Obesity Classification Proposal

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Abstract: In this mini-hot topic issue, methods of body composition analysis are reviewed, a new shape chart based on waist-to-height ratio is presented and a new obesity classification system is proposed. Anthropometric indices are surrogate measures of body fat and are cost-free, practical and easy to interpret for health care providers and lay people. The answer to the question of “the best anthropometric index” varies according to study design, geographic area, characteristics of the study population and the outcome assessed. Recent studies suggest using measures of general obesity and abdominal obesity for assessment of excess body fat. The use of waist-to-height ratio as a global anthropometric index for children and adults is suggested in this mini-hot topic. Anthropometric indices have a good performance in predicting health risks in epidemiologic studies, but by themselves have limited use in treatment decisions of individual obese patients. Body mass index is strongly correlated with total body adipose tissue mass and is a measure of general obesity. Current classification of obesity is based on body mass index, an anthropometric index that does not inform about body fat distribution, is not a powerful discriminator of cardiometabolic risk factors and does not convey information about the presence of risk factors or co-morbidities. Therefore, a new obesity classification system is needed. I suggest this should be based on body mass index, waist-to-height ratio and obesity associated risk factors and diseases. Future studies should focus on seeing how the proposed obesity classification system works in different populations.

Keywords: Obesity, body weights and measures, body mass index, waist to height ratio, anthropometry, obesity classification.

INTRODUCTION

Excess body fat is associated with disorders of several organ systems including, but not limited to cardiovascular, gastrointestinal, respiratory, reproductive, musculoskeletal and cutaneous systems [1]. Individuals with a body mass index (BMI) ≥30 kg/m² have a high mortality rate [2]. Central (android) obesity is associated with more adverse health outcomes than peripheral (gynoid) obesity [1]. Therefore, the determination of the quantity and the distribution of excess fat are important. In this mini-hot topic, Ayvaz and Çimen [3] review methods of body composition and indicate that accurate determination of body composition can be achieved by hydrodensitometry (underwater weighting) or dual energy X-ray absorptiometry (DEXA) among several methods that are available or in-development. Unfortunately, these two methods are not widely available in every health care facility and can be time-consuming and costly. DEXA requires exposure to X-rays. Medical personnel are needed to perform DEXA or underwater weighting. Bioelectrical impedance, an acceptable alternative to underwater weighting and DEXA [4, 5] is also not widely available and there is an initial cost for purchasing the bioelectrical impedance analyzer. Anthropometric indices have been shown to be surrogate measures of body fat and are cost-free, practical and easy to interpret for health care providers and lay people. Body mass index is the most frequently used anthropometric index and has been recommended by the World Health Organization (WHO) to classify obesity [6]. Regulatory bodies use BMI as an outcome measure for the evaluation process of weight loss drugs. As BMI does not give information about the distribution of body fat, the use of alternatives has been suggested. Waist-to-hip ratio (WHr) was used in the first definition of the metabolic syndrome by the WHO [7], but the use of waist circumference (WC) has been recommended by International Diabetes Federation, the United States National Heart, Lung, and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society and International Association for the Study of Obesity in a joint statement that redefines the metabolic syndrome [8]. However, although the above mentioned major health organizations agreed on a single set of cut points for blood pressure, triglyceride, HDL-C and glucose components, they could not do this for waist circumference due to ethnic variation between waist circumference and cardiometabolic risk [9]. The identification of national or regional cut points for waist circumference was therefore suggested [8]. The use of waist-to-height ratio (WHtR) may circumvent the problematic issue of different cut-off values for different populations. In this mini-hot topic, Ashwell [10] suggests WHtR as a global anthropometric index to estimate cardiometabolic risk and recommends the cut-off value of 0.5 for “Consider Action” and the
cut-off value of 0.6 for “Take Action” steps for adults. For children, the WHtR cut-off point of 0.5 is proposed as “Take Action” strategy.

Why do we Need Anthropometric Indices?

Anthropometric indices are helpful in two settings: 1) in the care of patients, 2) in scientific studies that assess the burden of obesity. A health-conscious question for any layperson is “Is my weight right for me?” or in other words “What should my normal weight be?” The answer to this question comes from the relationship between weight and height, as for instance in the BMI formula. As a first step in the clinical care of an overweight patient, an assessment should be made to determine if the patient is indeed overweight. If so, the excess weight should be quantified and the distribution of body fat should be determined. Then the patient and the health care provider should decide upon a target weight after a diligent and cost-effective search for possible underlying secondary causes of obesity and the associated co-morbidities. Body composition analysis is helpful in the initial evaluation and in the assessment of response to weight-reducing intervention. As serial body composition analyses by underwater weighting or DEXA are impractical or not widely available, serial measurements of anthropometric indices are in common practice. A sub-study of the Diabetes Prevention Program showed that estimation of visceral fat by computed tomography (CT) was not better than anthropometric indices in predicting the risk of diabetes in overweight subjects with impaired glucose tolerance and no anthropometric index was superior to the other [11].

In my opinion weight, not BMI, WC, WHpR or WHtR is the most important focus for subjects who come to clinic for weight loss. Health care providers should first assess the degree of excess weight. Obviously, this is best accomplished by taking the patient’s weight, not a surrogate marker. A judgment about body fat distribution could be made by obtaining WC, WHpR or WHtR. Eyeballing can be an alternative, but I think it is not a precise method for follow-up. Previous weight and its fluctuations are important part of past medical history in individuals who seek weight loss treatment. Patients are likely to remember prior weights at certain points in their life-time, like the weight when in high school, at military service, marriage, prior to pregnancy, at delivery etc, but nobody can remember their past WHpR or WHtR, unless it is documented in the medical record. Another important aspect of weight management is setting goals. Loss of 10% of body weight has been recommended for obese subjects [1]. The goal should be understandable and acceptable by the patient. Target body weight, not a target anthropometric index will be an easily understood primary goal by lay people. Waist circumference could be a secondary target. As waist circumference is one of the components of the current definition of the metabolic syndrome, it should be measured, documented and followed during the course of weight loss treatment. Again in my opinion, body weight is the major focus in the communication of weight loss progress between the patient and the health care provider. Except for the waist circumference, other anthropometric indices are ratios and the resultant numbers when losing weight are much smaller than the numbers in weight. In conclusion, I stress that anthropometric indices have limited value in day-to-day clinical practice in the outpatient clinical setting.

The use of anthropometric indices in scientific studies is well established. In all epidemiologic studies I know, quantification of obesity and/or determination of body fat distribution by BMI or other anthropometric indices are used to document the relation between obesity and adverse health outcomes. Data from epidemiologic studies enabled major health authorities to advocate cut-off points for BMI, WHpR and WC for routine clinical practice and for general public [6, 7, 12, 13].

The Deficiencies or Limitations of Anthropometric Indices

The use of anthropometric indices is recommended by major health organizations in various guidelines [6, 7, 12, 13]. In this mini-hot topic, Ashwell and coworkers summarize the history of anthropometric indices in medicine and discuss their strengths and weaknesses [10]. The following section aims to give selected examples pointing to deficiencies or limitations of anthropometric indices.

Body Mass Index

BMI is the ratio of weight in kilograms to the square of height in meters [6]. BMI could misclassify muscular athletic subjects as obese, because it does not differentiate adipose tissue from muscular tissue and assumes that increased body weight is due to increased adiposity at all times. BMI does not inform about the distribution of fat in the body. The evidence behind BMI is based on its J-shaped relationship with all-cause mortality [6]. But, recent data challenge the J-shaped relationship and indicate that overweight subjects with a BMI<=25 and <30 kg/m^2 do not have an increased total mortality rate compared to subjects with a BMI>=18.5 and <25 kg/m^2. Only obese subjects (BMI>=30 kg/m^2) have an increased risk of death [14]. A systematic review that evaluated the association between obesity and mortality showed that subjects with previously diagnosed coronary artery disease who are overweight or obese did not have an increased total mortality or cardiovascular mortality rate [15]. Also severely obese (BMI>=35 kg/m^2) coronary artery disease patients did not have an increased total mortality rate, but only had a high cardiovascular mortality rate [15]. This observation was called “obesity paradox” and the authors questioned the utility of BMI in the evaluation of obesity in patients with established coronary artery disease [16].

Waist-to-Hip Ratio

When patients lose weight, WHpR will remain the same or change trivially because both WC and hip circumference will change in the same direction. The value of WHpR as a screening tool is not firmly established. A meta-analysis of prospective studies did not find WHpR superior to WC in predicting future development of CVD events [17]. In addition, another meta-analysis did not find WHpR superior to BMI and WC in predicting future diabetes mellitus [18]. In the European Prospective Investigation into Cancer and Nutrition Study (EPIC), WHpR had a lower association with all-cause mortality than WC and WHtR [2]. From a pooled data analysis of two cohort studies, Schneider et al. reported
that WHpR was not a significant predictor of cardiovascular mortality and all-cause mortality [19].

**Waist Circumference**

WC is a predictor of total mortality, diabetes and cardiovascular disease (CVD) [12, 20]. Both BMI and WC are strongly correlated with total body adipose tissue mass with a correlation coefficient (r)=0.80 [21]. WC is a better correlate of intra-abdominal adipose tissue (r=0.77-0.79) than BMI (r=0.59-0.69) [21]. An elevated WC points to central obesity, an important piece of information that cannot be obtained by calculating BMI. Measurement of WC cannot determine the contributions of subcutaneous abdominal adipose tissue and intra-abdominal adipose tissue to central obesity. The estimation of abdominal fat compartments requires magnetic resonance imaging or CT [11]. The use of WC as a screening tool assumes that a 186 cm tall man with a WC of 104 cm have the same cardiometabolic risk as a 170 cm tall man with a WC of 104 cm, considering all classical cardiovascular risk factors, like age, smoking habit, blood pressure and lipids are equal. A proposal to use waist circumference as a measure of abdominal obesity assumes people with the same waist circumference have the same cardiometabolic risk regardless of height. But, it has been shown that height has an inverse association with cardiovascular disease mortality and total mortality [22, 23]. WHR of a 186 cm tall man with a WC of 104 cm is 0.56 and this individual is on the yellow area of the Ashwell® Shape Chart that is published in this mini-hot topic issue [10] and needs to “Consider Action” for weight management. WHR of a 170 cm tall man with a WC of 104 cm is 0.61 and this individual is on the red area of the Ashwell® Shape Chart, has a higher degree of abdominal obesity and needs to “Take Action” for weight loss.

**Waist-to-Height Ratio**

In this mini-hot topic, Ashwell and Browning [24] urge to use “WHtR” as the standard abbreviation for waist-to-height ratio. There are some studies reporting WHtR as not the best anthropometric index to predict cardiometabolic risk. In the San Antonio Heart Study, WHtR was not better than WC in predicting new development of diabetes in 1730 participants after 7.4 years of follow-up [25]. A meta-analysis evaluated anthropometric indices for discrimination of cardiometabolic risk factors and reported that WHtR is the best discriminator of hypertension, diabetes and dyslipidemia in both sexes [26].

Alternative anthropometric indices have also been evaluated. Hip circumference is an index of muscle mass and has been suggested to reflect exercise status and insulin sensitivity [27]. A large hip circumference has been found to be associated with a lower rate of all-cause mortality and a lower rate of combined CVD and diabetes incidence after 24 years of follow-up in a Swedish female cohort [27]. In contrast, another large-scale prospective study found no association between hip circumference and total mortality [2]. Sagittal abdominal diameter has been found to be significantly correlated with cardiometabolic risk factors, but it was not better than WC, WHpR, WHtR and BMI in risk assessment [28].

**Which Anthropometric Index is the Best?**

The answer to the question of “which is the best anthropometric index?” is not straightforward. In Tehran Lipid and Glucose Study, there was no difference between central obesity variables in predicting CVD in males, but in females WHpR and WHtR were better than WC and BMI [29]. In another paper from the same country, BMI or WHpR predicted the onset of diabetes mellitus after 3.6 years of follow-up in subjects aged less than 60 years. In subjects who are more than 60 years old, WC was the only independent predictor of diabetes [30]. Two other studies from Iran reported that WHtR was the best predictor of future development of diabetes mellitus in men and women [31, 32]. Gelber et al. [33] examined the relationship of anthropometric indices to incident CVD in two prospective studies, the Physicians’ Health Study and the Women’s Health Study, and found that WHtR was the best with minor differences than other indices. The authors concluded that although WHtR demonstrated statistically the best model fit and the strongest association with CVD, there was no clinically meaningful difference among anthropometric indices in prediction of future development of CVD [33]. It is evident that the answer to “the best anthropometric index” varies according to study design, geographic area, study population, age of the participants and outcome assessed. As obesity is associated with a wide range of morbidities, the outcome parameter to find the best anthropometric index should be all-cause (total) mortality. The largest prospective study that compared anthropometric indices for all-cause mortality is EPIC [2]. EPIC was conducted in nine European countries with 359387 participants and with a mean follow-up of 9.7 years. Models for WC, WHpR and WHtR were adjusted for BMI and other variables (height, age at recruitment, study center, smoking status, education level, alcohol consumption and physical activity). The relative risk of death in subjects with the highest quintile of WC compared to the lowest quintile was 2.05 (95% confidence interval [CI], 1.80 to 2.33) and 1.78 (%95 CI, 1.56-2.04) in men and women respectively. For the highest quintile of WHpR, relative risks were 1.68 (%95 CI, 1.53 to 1.84) and 1.51 (%95 CI, 1.37 to 1.66) in men and women respectively [2]. For the highest quintile of WHtR, relative risks were 2.22 (%95 CI, 1.94 to 2.55) and 2.03 (%95 CI, 1.76 to 2.34) in men and women respectively [34]. WHtR had the highest relative risk for total mortality but the CIs of WHtR and WC were overlapping. The CI of WHtR was clearly higher than the CI of WHpR. EPIC authors suggested using both general adiposity and abdominal adiposity measures to assess future risk of death [2]. EPIC data shows that the answer to the question of “the best anthropometric index” is BMI plus WC or BMI plus WHtR [2, 34]. This view is also supported by others [20, 35, 36]. Lee et al. compared the discriminatory power of BMI, WC, WHpR and WHtR for hypertension, diabetes and dyslipidemia in a meta-analysis that included nine cross-sectional and one longitudinal study [26]. Area under the curve from receiver operating characteristic curve analysis of each anthropometric index was pooled using a random-effects model to determine the index that best discriminates each studied cardiometabolic risk factor. The area under the curve of WHtR was the highest in both males and females [26].
Waist-to-Height Ratio in a Proposed Obesity Classification

From a practical point of view, the use of a single anthropometric index instead of two is attractive for the medical community and lay people. But practicality changes from one person to another. Lay people may find the use of two measures complicated and less tempting. From the reasons Ashwell and Hsieh [37] delineated, the use of WHtR as a global anthropometric index is justified. These reasons are: 1) WHtR is more sensitive than BMI as an early warning of health risks. 2) WHtR is cheaper and easier to measure and calculate than BMI. 3) A cut-off point of WHtR=0.50 indicates increased risk for men and women. 4) A cut-off point of WHtR=0.50 indicates increased risk for people in different ethnic groups. 5) WHtR may allow the same cut-off point values for children and adults. 6) WHtR cut-off values can be converted into a consumer-friendly chart [37]. Published in this mini-hot topic The Ashwell® Shape Chart is the only chart that promotes the use of WHtR by the public and health care providers. The suitability of WHtR in global risk assessment should be embraced by major health authorities like WHO, International Diabetes Federation, World Hearth Federation, the United States National Heart, Lung, and Blood Institute and International Association for the Study of Obesity and the following public health message should be emphasized: "Keep your waist circumference to less than half your height" as suggested by Ashwell in this mini-hot topic [24].

Combined Use of Body Mass Index, Waist-to-Height Ratio, Obesity Associated Risk Factors and Diseases in a Proposed Obesity Classification

Current classification of obesity is based on BMI and do not inform about the associated risk factors, co-morbidities, prognosis and implications for treatment. Therefore, a new clinical classification of obesity is needed. Sharma and Kushner [38] laid down the following reasons for adoption of a new clinical obesity staging system:

1. Anthropometric indices are surrogate measures of body fat and have limited guidance in treatment decisions in individual patients [38]. As Ashwell noted in this mini-hot topic [10], Ancel Keys was one of the first to propose using BMI had indicated that BMI was inappropriate for individual diagnosis.

2. Anthropometric indices do not give information on quality of life, functionality, mobility, prognostic factors and psychological well-being [38].

3. Anthropometric indices do not give information about future risk of coronary artery disease [38]. Framingham risk score, a tool to predict future risk of coronary heart disease does not include any anthropometric index [13].

4. Anthropometric indices are not powerful discriminators of cardiometabolic risk factors. In our previous study [39], the area under the receiver operating characteristics curves of anthropometric indices for hypertension, diabetes mellitus, dyslipidemia and metabolic syndrome ranged between 0.46 and 0.78, mostly clustering between 0.60 and 0.70, suggesting that the use of anthropometric indices is slightly better than flipping a coin to discriminate the presence or absence of a cardiometabolic risk factor. The evaluation of an overweight patient cannot avoid the measurement of blood pressure, fasting glucose

Table 1. Proposed Classification of Obesity

<table>
<thead>
<tr>
<th>Class</th>
<th>Name</th>
<th>Anthropometric index</th>
<th>Stage</th>
<th>Co-morbidities</th>
<th>Management†</th>
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</thead>
<tbody>
<tr>
<td>-1</td>
<td>Underweight</td>
<td>BMI&lt;18.5† or WHtR&lt;0.4</td>
<td>0, 1, 2</td>
<td>Any</td>
<td>None</td>
</tr>
<tr>
<td>0</td>
<td>Normal weight</td>
<td>BMI≥18.5 to &lt;25 or WHtR≥0.4 to &lt;0.5</td>
<td>0, 1, 2</td>
<td>Any</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Overweight</td>
<td>BMI≥25 to &lt;30 or WHtR≥0.5 to &lt;0.6</td>
<td>0</td>
<td>None</td>
<td>Prevent further weight gain.</td>
</tr>
<tr>
<td>1</td>
<td>Overweight</td>
<td>BMI≥25 to &lt;30 or WHtR≥0.5 to &lt;0.6</td>
<td>1</td>
<td>Obesity associated risk factor</td>
<td>Weight loss treatment by diet, exercise and behavioral modification options.</td>
</tr>
<tr>
<td>1</td>
<td>Overweight</td>
<td>BMI≥25 to &lt;30 or WHtR≥0.5 to &lt;0.6</td>
<td>2</td>
<td>Obesity associated disease</td>
<td>Weight loss treatment by diet, exercise and behavioral modification options. Weight loss drugs are an option if BMI≥27.</td>
</tr>
<tr>
<td>2</td>
<td>Obesity</td>
<td>BMI≥30 or WHtR≥0.6</td>
<td>0</td>
<td>None</td>
<td>Weight loss treatment by diet, exercise and behavioral modification options. Weight loss drugs are an option.</td>
</tr>
<tr>
<td>2</td>
<td>Obesity</td>
<td>BMI≥30 or WHtR≥0.6</td>
<td>1</td>
<td>Obesity associated risk factor</td>
<td>Weight loss treatment by diet, exercise and behavioral modification options. Weight loss drugs are an option.</td>
</tr>
<tr>
<td>2</td>
<td>Obesity</td>
<td>BMI≥30 or WHtR≥0.6</td>
<td>2</td>
<td>Obesity associated disease</td>
<td>Weight loss treatment by diet, exercise and behavioral modification options. Weight loss drugs are an option. Bariatric surgery is an option if BMI≥35 and other treatments fail.</td>
</tr>
<tr>
<td>3</td>
<td>Morbid Obesity</td>
<td>BMI≥40 and WHtR≥0.6</td>
<td>0, 1, 2</td>
<td>Any</td>
<td>Weight loss treatment by diet, exercise and behavioral modification options. Weight loss drugs are an option. Bariatric surgery is an option if other treatments fail.</td>
</tr>
</tbody>
</table>

The column refers to proposed action for weight management, obesity associated risk factors and diseases should be treated individually. †represented as kg/m². BMI: body mass index. WHtR: waist-to-height ratio. Obesity associated risk factor: borderline hypertension, impaired fasting glucose, impaired glucose tolerance, low HDL-C, high LDL-C, high triglycerides or metabolic syndrome. Obesity associated disease: cardiovascular diseases, diabetes mellitus, essential hypertension, nonalcoholic steatohepatitis, obesity hypoventilation syndrome, obstructive sleep apnea or polycystic ovarian syndrome. Obesity associated risk factors and diseases are conditions that respond favorably to weight loss treatment.
and lipids. I believe the use of anthropometric indices as an only tool to predict cardiometabolic risk is unthinkable. Current management guidelines [6-8, 13] require the measurement of cardiometabolic risk factors, implying a secondary role for anthropometric indices.

Considering above reasons, the current BMI based classification of obesity can be replaced with a new classification system that includes an anthropometric index that gives information about centralized fat distribution, obesity associated cardiometabolic risk factors and obesity associated diseases. The system should only include risk factors and diseases that respond favorably to weight loss. Although obesity is associated with a range of derangements in multiple organ systems, only some of those have been shown to respond to weight management. The proposed classification system for obesity is shown in Table I. It can be considered as a different version of the classification system that Sharma and Kushner published [38]. Two anthropometric indices that are surrogate markers of general (BMI) and abdominal obesity (WHtR) are proposed in the new classification. Obtaining two measurements, one for generalized obesity and one for abdominal obesity does not entail any extra cost, will take some seconds more from the health care providers’ busy time and can be easily instituted in every health care delivery point. Then a staging system that informs about the presence or absence of obesity associated risk factors and diseases are incorporated into the proposed obesity classification system. Either class and stage numbers or names can categorize an individual. For example “class 2 stage 1 obesity” or “obesity with associated risk factors” would denote someone with a BMI≥30 kg/m² or WHtR≥0.6 with either borderline hypertension, impaired fasting glucose, impaired glucose tolerance, metabolic syndrome, low HDL-C, high triglycerides or high LDL-C. Management should intensify as subjects move from a lower to a higher class of obesity.

FOCUS FOR FUTURE STUDIES

Future studies should no longer attempt to find the best anthropometric index to predict total mortality or cardiometabolic risk. As reviewed above, the answer changes according to various settings and outcomes. Future studies should use prospective data and investigate the applicability, reliability and validity of the proposed obesity classification system. Better versions of the proposed classification system can be developed and are welcome. The proposed classification system can improve when other obesity associated risk factors or diseases are discovered and are shown to respond to weight loss.

CONCLUSION

The answer to the question of “the best anthropometric index” varies according to study design, geographic area, characteristics of the study population and the outcome assessed. Recent studies suggest using measures of general obesity and abdominal obesity for assessment of excess body fat. BMI has been suggested by the WHO to evaluate general obesity. The use of WHtR as a global anthropometric index to estimate cardiometabolic risk has been suggested and Ashwell recommends the cut-off value of 0.5 for “Consider Action” and the cut-off value of 0.6 for “Take Action” steps for adults. For children, the WHtR cut-off point of 0.5 is proposed as “Take Action” strategy [10]. Current classification of obesity is based on body mass index, a measure that is strongly correlated with total body adipose tissue mass but do not inform about fat distribution. A new classification system of obesity based on body mass index, waist-to-height ratio and obesity associated risk factors and diseases has been suggested in this mini-hot topic. Future studies should not attempt to find the best anthropometric index, but should focus on improving the definition of obesity.

ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>DEXA</td>
<td>Dual energy X-ray absorptiometry</td>
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<tr>
<td>EPIC</td>
<td>European Prospective Investigation into Cancer and Nutrition</td>
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<tr>
<td>r</td>
<td>Correlation coefficient</td>
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<tr>
<td>WC</td>
<td>Waist circumference</td>
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<td>WHpR</td>
<td>Waist-to-hip ratio</td>
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<tr>
<td>WHtR</td>
<td>Waist-to-height ratio</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</table>

REFERENCES

Waist-to-Height Ratio in a Proposed Obesity Classification


Mukuddem-Petersen J, Snijder MB, van Dam RM, et al. Sagittal abdominal diameter: no advantage compared with other anthropometric measures as a correlate of components of the metabolic syndrome in elderly from the Hoorn Study. Am J Clin Nutr 2006; 84: 995-1002.


