Chapter

Anthropometrics in Predicting Cardiovascular Disease Risk: Our Research Work Mathematically Demonstrates that Cardiovascular Sciences Were Always Confused for a Long Time

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Abstract

Cardiovascular diseases (CVD_S) mainly heart disease and stroke are the leading causes of death globaly. Obesity is a major risk factor for myocardial infarction (MI) and CVD. However, how to measure CVD risk with simple baseline anthropometric characteristics? Besides, association of anthropometrics and CVD may present effects of bias, and in evaluating risk, the lack of balance between simple measurements will be particularly prone to the generation of false-positive results. The purpose of this paper is to provide the key concepts for demonstrating association biases for metrics taken from multiple large-scale studies worldwide. Epidemiologically, waist-to-hip ratio (WHR) is a confounding variable with respect to waist circumference (WC) and waist-to-height ratio (WHtR). This is due to different imbalances between hip circumference (HC)-WC and HC-height, respectively, occurring in a protective over-estimation for HC concerning WC and height. Similarly, WC may be a confounding variable with respect to WHtR due to an imbalance in WC-height: This occurs if, and only if, the mean WC > height/2 (WHtR risk cut-off >0.5). This, therefore, over-estimates risk in tallest people and lead to underestimations in the shortest people. Anthropometrically, only WHtR is the only measure that is directly associated to a relative risk volume and yields no biases, and it should therefore be the metric used to compare the anthropometrically-measured causal risk.

Keywords: myocardial infarction, cardiovascular disease, risk prediction, obesity, anthropometric indicator, body composition, bias

1. Introduction

Cardiovascular diseases (CVD_S) mainly heart disease and stroke are the leading causes of death globaly [1]. Obesity is a major risk factor for CVD_S such as coronary

artery disease. However, overweight/obesity are defined as abnormal or excessive fat accumulation measured by the body mass index (BMI), but it may not correspond to the same degree of fatness and metabolic health in different individuals [2]. Thus, accurate estimation of the body composition (BC) as well as body fat distribution are relevant from a public health perspective [3]. Nevertheless, how can the true unhealthy BC and risk be measured with regard to simple baseline anthropometric measurements? In epidemiology, as in real life, not everything that seems accurate at first glance is true in reality. In medical research, false appearances and biases also occur, which can mean that valuable conclusions may turn out to be worthless. Indeed, bias in research occurs when systematic error is introduced into sampling or testing by selecting or encouraging one outcome or answer over others. Therefore, a thorough understanding about biases, and how it affects study results is essential for medical research because association of anthropometrics does not always equate to causation regarding incidents of myocardial infarction (MI) or CVD. Interestingly, this association may present effects of bias rather than reflecting the true putative risk may be responsible for all or much of the epidemiological causality. In non-randomised study designs, baseline differences in the high BC of risk or in the measured risk when comparing between healthy population and MI/CVD cases may introduce systematic bias in results. Similarly, a different BC between groups with similar baseline confounding variables may provide bias if the risk assignment does not account for the covariates that predict the receiving true risk. Thus, not all anthropometrics are optimal for risk assessment. Critical thinking that covers all potential mechanisms of bias is indispensable to prevent incorrect conclusions being drawn, which may have clinical consequences, especially when predicting MI/CVD causal risk.

Conceptually, each anthropometric provides its own biological meaning depending on the part of the BC that can be distinguished, while the notion of equality in the estimate of risk between body measurements may be respected. If not, the lack of a balanced distribution for the simple measurements between healthy and unhealthy cases will be particularly prone to the generation of false-positive results. Regarding this issue, the mathematical relation of equivalence is a key concept for specifying whether two indicators are the same with respect to a given risk. Thus, any indicator will be comparable to other or not, depending on the measured risk. Therefore, a strong association would lead us to infer or not infer a risk, given that the true nature of risk should come from the selective high risk BC instead the mere findings of the statistical association for each metric. In fact, anthropometrically-measured causal risk depends on specific bodily components; our interpretation may not be confused by the association of arithmetic indicators that suggest a supposed risk that is not verified. Thus, criteria for judgement of causal association must be respected, while also recognising that any association may be bogus, indirect o real.

2. Association of anthropometric measures and MI risk

Various previous studies have recognised the association of a raised BMI with MI, as well as a higher association of abdominal obesity measures with MI [4–10]. Despite this, BMI is an important metric that has been proposed to define ideal cardiovascular health and predict CVD risk [11, 12]. However, it is only a surrogate measure of general body fatness and does not provide accurate information about the true high risk BC, unlike waist circumference (WC). Indeed, evidence is accumulating in support of WC as metric linked to visceral adipose tissue, and the only metric among

other simple measurements that predict MI and cardiometabolic risk [4, 7, 9, 13–17]. However, according to the INTERHEART study and others, waist-to-hip ratio (WHR) appeared to have the best predictive value above BMI and WC [4, 18–21]. In addition, results from the UK Biobank have conferred WHR a greater excess risk for MI in women than in men [21].

On the other hand, compound metrics such as waist-to-height ratio (WHtR), whole-body fat percentage (%BF), conicity index, and adiposity measured by technological methods could be better indicators than WC alone to predict cardiovascular events and mortality, even taking consideration of sex differences [5, 14, 20, 22–27]. Furthermore, WHtR and %BF have demonstrated a high level of discrimination in the relationship with a unhealthy BC. WHtR has been more strongly correlated with %BF and adiposity variables in men than it is with WC [24, 27]. WHtR and %BF appear to be strengthened as an anthropometrically valid assessment of biological risk. Thereby, WC and height, and skin folds to a lesser extent, could be taken as basic measurements for evaluating cardiometabolic and MI risk, including cardiovascular mortality, in their relationships with abdominal and relative adiposity [12–16, 20–30]. Complementary, moderate-high endomorphy and high thickness of skinfolds, especially subscapular, have been significantly associated with MI in men [10, 24, 27, 31, 32]. Moreover, patients of both sexes assessed by computed tomography have presented better MI risk prediction as visceral adiposity increases and abdominal subcutaneous area decreases [16, 22].

3. What is new about anthropometrics associated with MI

While overweight/obesity as BMI-measured, enlarged WC, WHR risk cut-off of <1, and WHtR cut-off of ≥0.5 have been verified as baseline characteristics for the association of anthropometrics and MI/CVD worldwide, even accounting for differences in strength of association and by sex [4–10, 12–19, 21–24, 27, 32–37]. Similarly, mathematical inequality between the mean simple body measurements as well as non-equivalent relation in the ratios, ratios of ratios and risk cut-offs may also be implicated (**Table 1**). Thus, data from thousands of MI/CVD cases are collated in **Table 1**, where new anthopometrics have been included as mere mathematical expressions derived from original data, demonstrating the inequality and non-equivalence relations between the corresponding mean simple measurements. After associating anthropometrics and MI/CVD risk, since mathematical inequalities between measurements may be demonstrated in any study population, perspective for epidemiological causality should be shifted accordingly. From evidence reflected in **Table 1**, neither WHR risk cutoff <1 (the mean hip circumference (HC) > WC) nor WC risk cut-off (the mean WC > height/2) will adequately describe the risk, because true risk only occurs at the volume measurement WHtR risk cut-off >0.5, where inequality between WC and height (or height/2) matters too. This is because WHtR mathematically represents a volume function with two independent factors: WC and height. These two measurements are also decisive for estimating %BF [23, 24, 27, 36, 37, 45]. In this sense, mathematical and anthropometric observations in our research work have explained the selection bias for WHR with respect to WC and WHtR and, therefore, have revealed that the risk comparison between healthy and unhealthy cases was not the same [23, 24, 27, 36, 37].

Due to anthropometrically-estimated %BF and mesomorphy presenting a high magnitude of association in MI for men [24, 27, 31], there are still uncertainties

Anthropometric	Men	Women	Association findings**
Weight (kg)	Undefined	Undefined	(–) or weak positive
Height (Ht): (cm)	Undefined (Ht >HC >WC)*	Undefined (Ht >HC >WC)*	(–) or weak inverse
HC (cm)	Undefined (HC >WC >Ht/2)*	Undefined (HC >WC >Ht/2)*	(–) or weak positive/inverse
Height/2 (cm)	Undefined (WC >Ht/2)*	Undefined (WC >Ht/2)*	(–) or weak inverse
HtHR: (Ht/HC)	>**1** (Ht >HC)*	>**1** (Ht >HC)*	(–) or weak inverse
HHt/2R: (HC/(Ht/2))	>**1** (HC >Ht/2)*	>**1** (HC >Ht/2)*	(–) or weak positive/inverse
WC (cm)	>94 (102): (WC >Ht/2)*	>80 (88): (WC >Ht/2)*	Strong-moderate positive
BMI (kg/m²)	>26.5	>25.5	Moderate positive
WHR	≥0.90 <**1** (HC >WC)*	≥0.80 <**1** (HC >WC)*	Strong positive
WHtR	≥**0.5** (Ht >WC >Ht/2)*	≥**0.5** (Ht >WC >Ht/2)*	Strong-moderate positive
WHt/2R: (WC/(Ht/2))	>**1** (WC >Ht/2)*	>**1** (WC >Ht/2)*	Strong-moderate positive
WHR/WHtR	<**2** (WHR <WHtR x 2)*	<**2** (WHR <WHtR x 2)*	Strong positive

*BMI indicates body mass index; CVD, cardiovascular disease; HC, hip circumference; Ht, body height; HHt/2R, hip-to-height/2 ratio; HtHR, height-to-hip ratio; WC, waist circumference; MI, myocardial infarction; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; WHt/2R, waist-to-height/2 ratio. *Regardless of risk cutoff values significant inequality between the mean values of the referenced simple measurements and a non-equivalent relation in the ratios is always found. ** Measures of association such as odds ratios, hazard ratios, Receiver Operating Characteristic curves or other statistical models in all studies were used as appropriate. (–): Null or not association. [a] Ethnically-specific risk cutoffs (either in numerical or in undefined values) are taken into account when reflecting inequality between the simple measurements, and therefore non-equivalent risk in the ratios, ratios of ratios and risk cutoffs. [b] Mathematical inequality between the simple measurements and non-equivalence relations are extracted or extrapoled from the differences between the mean (standard deviation) or median values described in thousands of participants in most studies worldwide. Table was elaborated by the author. From the scientific evidence, new metrics were included.*

Table 1.
Defined and undefined risk cut-off points for the association of anthropometrics and MI/CVD. Imbalance between the mean values of the simple body measurements (in parentheses) where appropriate. Risk cut-off values and mathematical inequality between the corresponding simple measurements and ratios where appropriate too [4–10, 14–30, 32–35, 38–44].

regarding the association between BMI and WHR and their relationships with the true high risk BC. Conceptually, the true risk factor regarding BC derives from %BF, fundamentally the part linked to intra-abdominal fat depots functioning as a neuro-endocrine organ that influence CVD risk [46, 47]. On the other hand, mesomorphy represents relative muscularity, but association with MI is artificial and does not equate causation [10, 24, 31, 48]. Thus, seeing as BMI and WHR are anthropometrically linked to musculoskeletal component, and are more weakly correlated with %BF than other metrics, they have presented an information bias and associated a spurious risk for MI in men [23, 24, 27]. Indeed, it is important to understand the discrepancy observed between the strongest association for WHR, and their worst correlations with measures of general and central adiposity in both sexes [4, 17–19, 21, 23, 27]. The discrepancy between the strength of association for WHR and a lower anthropometric coherence as well as the unbalanced distributions for WC and HC between healthy and cases in both sexes, suggest that there where errors regarding the true risk association. Consequently, a systematic error would be introduced regarding the true risk assignment for WHR and BMI, if, when partially capturing a dimension of spurious risk their data were slanted in an artificial direction towards site of cases. In

contrast, a raised WHtR and %BF have demonstrated anthropometric coherence and balanced distribution for the concrete values of volume by unit of height and body fatness for justifying risk excess. This anthropometric profile could help explain the abundance of MI among individuals with raised visceral fat, irrespective of BMI, HC or mesomorphy rating [10, 23, 24, 27, 31, 48].

4. What is the justification for making our arguments?

4.1 Lessons from anthropometry, mathematics, geometry and epidemiology

Arithmetic value and true risk measured from each anthropometric depends on formulae, unit of measure and body measurements derived from different structural components. Mathematical understanding of some concepts turns out to be key to detecting unhealthy BC and anthropometrically-measured risk. From this perspective, weight, height, height/2, WC and HC represent absolute values without expressing equality for risk as a mathematical object. Consequently, in assessing anthropometrics-associated risk, mathematical relation of equivalence between simple measurements and indicators or ratios to be compared should be recognised by the researchers

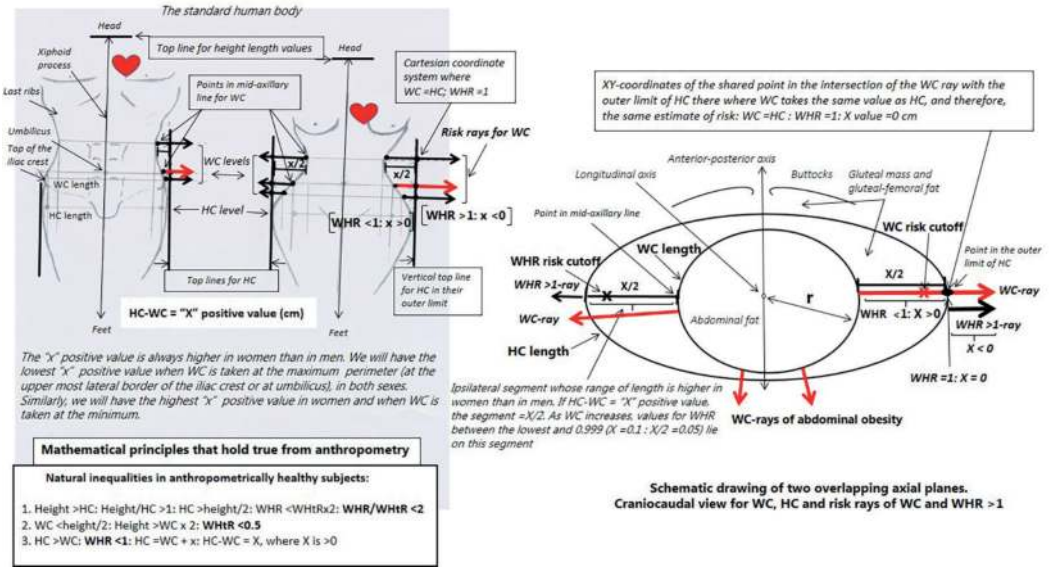

Figure 1.
The standard human body and simple anthropometric measurements. Geometrical lines drawn from anthropometry for understanding metrics and rays of risk for WC and WHR >1. Mathematical principles and anthropometric arguments that hold true in an anthropometrically healthy population. Anthropometrics at baseline would represent mean values per standard deviation for height, height/2, WC, HC, WHR, WHtR and "X" distance being actually valid for any anthropometrically healthy population and ethnicity. On the respective rays of risk for WC (in red colour) and WHR >1 would lie points of increased abdominal obesity representing mean values (SD) for thousands of cases of MI/CVD as well as biological changes pointing towards greater excess risk as WC increases and while height may no condition the whole-risk measured by WC alone. On the ipsilateral segment, which length value is "X" positive (cm)/2 would lie all the points for WHR <1 (including WHR risk cutoff) from the lowest value up to 0.999 (X = 0.1: X/2 = 0.05) just before the outer limit of HC where X = 0. HC indicates hip circumference; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; X, subtracting HC by WC; X/2, ipsilateral segment as horizontal distance between any point of WC in the mid-axillary line and the vertical top line for HC in their outer limit. Footnote: Original drawings built and designed by the author. Dimensions are not to scale. Anthropometric evidence supports the referred mathematical inequalities between the simple measurements in the standard human body.

(**Figure 1**, **Table 1**). Thus, when comparing with anthropometrically healthy subjects and with the evidence of CVD epidemiology, the rationale is as follows.

Muscle, bone, fat and residual mass as different biological components present no differentiation by body weight (unit of mass), and therefore, a higher BMI does not always involve greater body fat excess, at least in normal or overweight people [2, 24, 27]. Weight and height differences between sexes are not recognised by the BMI formula. Thereby, an equal BMI does not mean the same degree of fatness or unhealthy BC. In this sense, the error of estimation for high risk BC or risk may occur in comparing BMI with others, and either by age or by sex.

Height length depends on the bone structure of the adult. In this sense, height never correlates with adiposity [10, 21, 23, 27, 31, 48], and, therefore, it does not account for the true-risk per se. However, height as a volume factor would exert a modulating effect for conditioning the storage and distribution of the body fat as well as the relative volume that it occupies in the three-dimensional abdominal space [24, 27]. Thereby, a significant difference in height between groups and sexes conditions the risk estimated by each concerned anthropometric, and therefore, height as longitudinal dimension also has important implications.

Mathematically, WC and WHtR would be equivalent for the same estimated risk if, and only if, mean WC = height/2. Therefore, WHtR risk cut-off =0.5 is the entity of risk conditioned on WC, but height/2 taking the same value as WC (e.g., 80/160, 84/168, 85/170, 88/176 etc., all =0.5). If not, the error of estimation for both the true high risk BC and risk may occur in comparing WC alone with WHtR, and either by age or by sex. Thus, if the mean WC is >height/2 (WHtR risk cut-off >0.5) (e.g., 80.5/158, 82.6/162, 82.8/162.4, 95.4/187 etc., all =0.51) protective underestimation occurs for height with respect to WC, whether WC alone assigns the risk from a defined risk cut-off.

In another conceptual consideration, evidence supports that there is a higher excess risk of MI/CVD when abdominal obesity increases [13, 14]. However, when comparing between-groups abdominal obesity may be expressed either in cm^2 (two-dimensional area determined from WC length) or in cm^3 (three-dimensional volume of a solid abdominal disk determined from WC and height of the disk = WHtR cm), (**Figures 2** and **3**) [24, 37]. From this new insight, WC and WHtR do not express the same risk when comparing healthy people and MI/CVD cases. This is because WC < height/2 (WHtR <0.5) is a natural inequality. In this way, WC and WHtR refer to the same risk only if the mean WC = height/2 (WHtR risk cut-off =0.5). However, when the mean WC increases above height/2 (WHtR risk cut-off >0.5), the distribution curves of WC and height/2 appear unbalanced between healthy and cases, and only WHtR as an entity of volume may described the risk that is conditional on both WC and height. Otherwise, if we accept WC alone as an anthropometrically-measured causal risk factor, this will lead to an overestimation of risk for WC concerning height, or a protective underestimation of height with respect to WC. It is clear that, if WHtR risk cut-off is >0.5 (the mean WC > height/2), height appears to be inversely associated with the group of cases, and WHtR is the indicator of risk when comparing by ethnicity and sex, but not WC alone. This is because risk is conditional on both WC and height as independent volume factors.

HC length depends on the breadth between both trochanters, the gluteal mass and the gluteal–femoral fat to determine a two-dimensional geometric area on a transverse plane of defined bodily components, but HC neither discriminates between them nor describes cardiometabolic risk. Therefore, it does not account for the true high risk BC or risk [10, 24, 27, 31, 37, 48]. Thus, either the high risk BC or raised %BF is not affected by

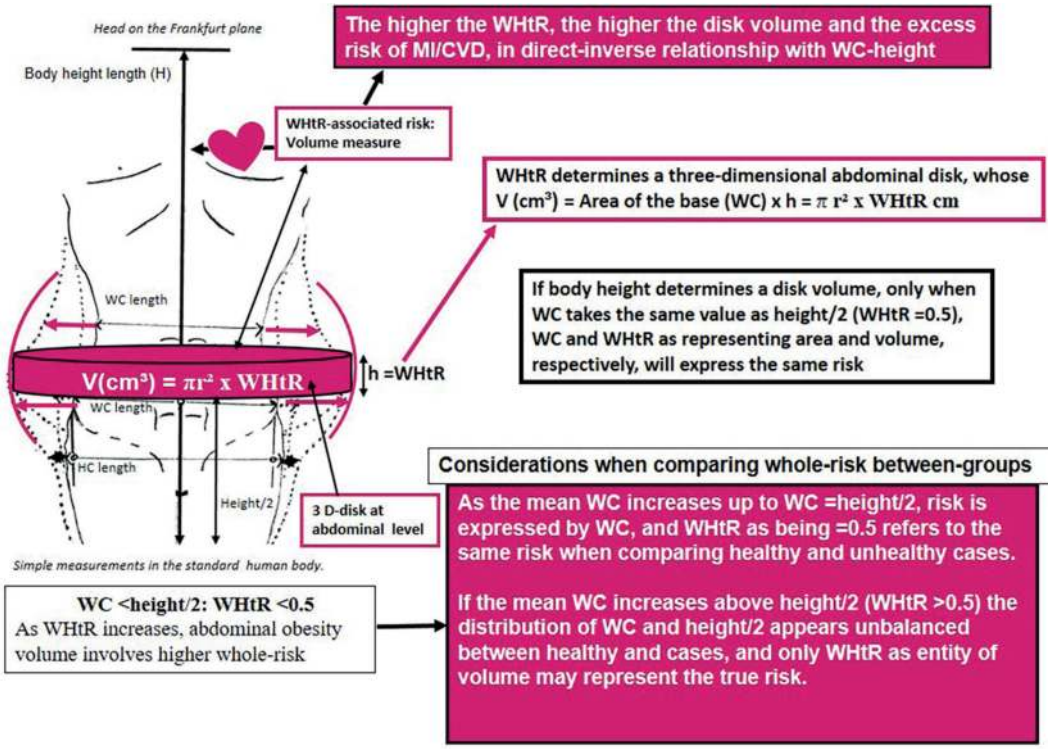

Figure 2.
Anthropometric length measurements in the standard body human and considerations for differencing between volume of a three-dimensional abdominal disk and WC as two-dimensional area. Measurements at baseline would represent mean values per standard deviation for WC, HC, height, height/2 and WHtR being actually valid for any study population and ethnicity. The model of disk for representing volume of an abdominal segment may be applied for both case–control and cohort studies from the respective mean values (SD) and risk cut-offs for WHtR. Anthropometric considerations are explained for understanding volume and excess risk of MI/CVD as WHtR increases. CVD denotes cardiovascular disease; H, body height; height/2, dividing height by 2; h, height of the disk; HC, hip circumference; MI, myocardial infarction, r, radius of the base; V, volume of the disk; WC, waist circumference; WHtR, waist-to-height ratio. Footnote: Original graphical abstract was built and designed by the author.

HC, but vice versa. HC can be modified by physical activity or the ageing process, etc., in both sexes, but this does not justify a direct impact on MI/CVD risk. With modifications in HC, neither WC nor high risk BC and %BF are necessarily affected. In this sense, WC and WHR would be mathematically equivalent for the same estimation of risk if, and only if, the mean HC = WC, and therefore, WHR risk cut-off = 1 being the entity of risk conditional on WC, but HC taking the same value as WC. In this case, subtracting HC by WC we obtain an X value of zero (**Figures 1** and **3**) [36, 37]. If not, the error of estimation for both the true high risk BC and risk may occur in comparing WHR with WC alone, and either by age or by sex. Thus, the mean HC > WC protective overestimation occurs for HC with respect to WC, and WHR <1 may present a risk overestimation by selecting false-positive points as compared to those true-negatives conditional on WC values as the numerator. It is clear that, if WHR risk cut-off is <1 (mean HC > WC: similar to natural inequality), not all subjects in that stratum may present risk because HC as risk factor appears not to be associated with any group when compared. Similarly, if HC > WC (WHR <1: X > 0) is a true premise applicable to a healthy population, the question arises as to how it may be applied to cases of CVD without being a false premise? From an epidemiological viewpoint, effectively only WHR <1 may represent a risk associated to cases when conditioning WC as numerator. This value lies above their

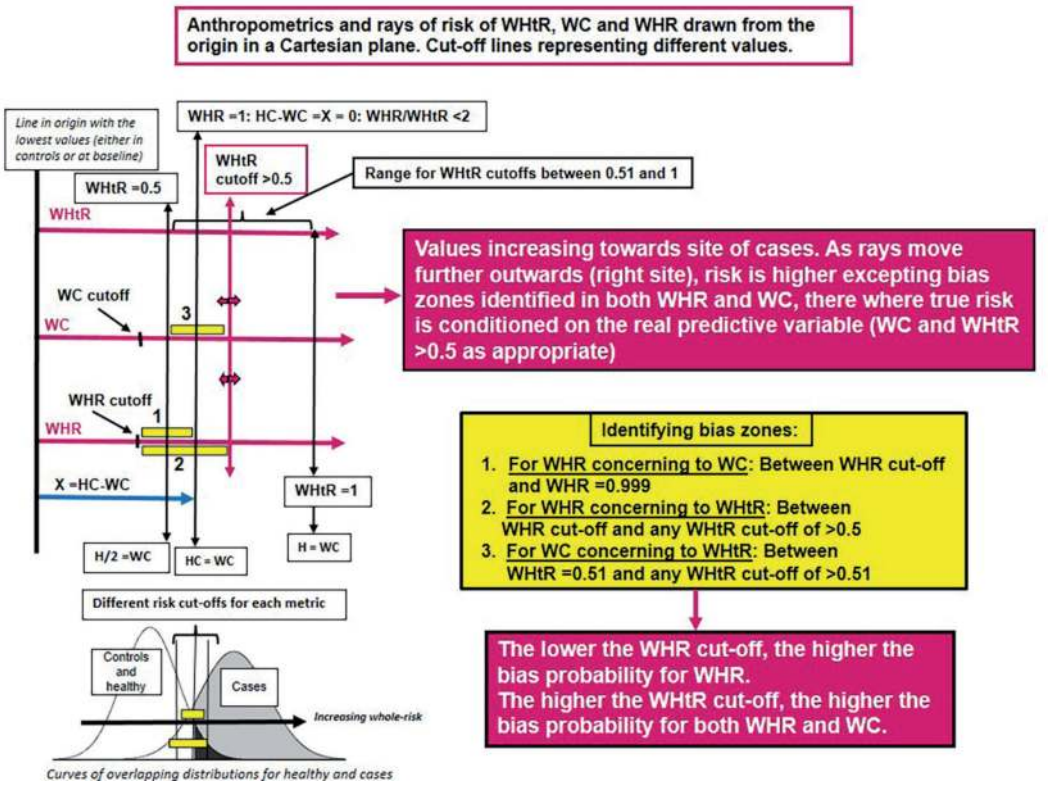

Figure 3.
Number lines in a Cartesian plane for representing values in healthy population and cases of MI/CVD: Metrics-associated risk increases as each anthropometric ray of risk move to the right (site of cases). Subtitled curves of distribution, overlapping area, risk ray and bias zone as appropriate. It is transferable to any study population and ethnicity. All reference values may be represented lying on the respective number lines drawn. We may find the points with the lowest baseline values for WHtR, WC and WHR (healthy/controls or cases) lying on a respective line in the origin. Similarly, risk cut-offs and cutting lines lying where appropriate. The highest baseline values (generally in unhealthy cases) would lie on the arrowhead of the anthropometric rays of risk moving further outwards (right site). Other points would represent mean values per standard deviation for WC, HC, height, height/2, WHR and WHtR in healthy and cases as appropriate. In the respective lines and risk rays drawn in magenta colour would lie points of increased abdominal obesity representing values for thousands of cases of MI/CVD as well as biological changes pointing towards greater excess risk as WC increases and HC and height condition the true risk from WHR and WHtR, respectively. Values for X (between the maximum positive in their origin and zero (WC = HC) would be represented lying on the corresponding partial ray of risk (in blue colour). We have also pointed the theoretical cutting lines for WHtR and WHR there where would occur a balanced distribution of WC-height/2, WC-HC and WC-height mean values (SD) when pooling healthy and unhealthy cases. The model plotted may be applied for both case–control and cohort studies. CVD denotes cardiovascular disease; H, height; HC, hip circumference; MI, myocardial infarction; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; X, subtracting HC by WC. Footnote: Original graphical abstract was built and designed by the author. Dimensions are not to scale.

defined risk cut-off. Obviously, WHR ≥1 (WC ≥ HC: X ≤ 0) will always represent risk associated to group of cases irrespective of HC value (**Figure 1**). Therefore, the true risk assignment for WHR only depends on WC receiving risk as numerator, and besides, WC as the entity of risk compared according to ethnicity and sex, but never WHR alone as an abstract fraction.

WC length depends on specific biological components that determine a two-dimensional geometric area (cm^2) on a transverse plane. Evidence supports WC as the strongest simple metric linked to visceral adiposity that provides a solid estimation of risk [13, 14, 17, 46, 47, 49]. On the other hand, in the standard human body, WC can

be lower than height/2 (WHtR <0.5) without posing any putative risk or protective effect (**Figures 1** and **2**). Only when WC and height/2 are mathematically equivalent (WC = height/2: WHtR = 0.5) is there a notion of equality and balance for the same estimation of risk from WC and WHtR. However, evidence also supports the notion that WHtR >0.5 is strongly associated to cases of MI [15, 18, 21, 23, 27, 37]. When the WHtR risk cut-off is >0.5, equality does not exist between WC and height/2, and only WHtR may be used to draw a valid conclusion for estimating the risk (**Figure 3**, **Table 1**). Thus, if the mean WC > height/2 risk overestimation occurs for WC with respect to height, WC alone will present an overestimation of risk in the tallest people and an underestimation in the shortest. Mathematically, WHtR >0.5 and < 1 is a proper abstract fraction (part/whole) whose decimal value up to 1 (theoretical) tells us the equal parts of WC that we have in height (whole), but never WC (part) referring to the entity of whole-risk as a mathematical object. Quite the opposite is the case; the higher the WHtR (whereas being <1), the higher the risk overestimation for WC as compared to WHtR. Similarly, the higher the WHtR between 0.51 and 0.999, the higher the probability of bias for WC. If WHtR cannot record true risk, WC might capture false risk beyond the true risk of WHtR. Hence, WC might present an error of estimation in women compared to men due to differences in WC and height between both sexes and, therefore, different risks to be compared. Only when the mean WC is lower than height/2 (WHtR risk cut-off <0.5), WC and its risk cut-off would represent the entity of risk without accounting for bias, but only up to WHtR = 0.5 (**Figure 3**). That way, only in unrepresentative, small samples where the mean WC is lower than height/2 or in women where differences between mean WC and height/2 are less important, WC and WHtR would capture similar risk as being close to WHtR = 0.5. However, if WHtR risk cut-off is >0.5 (mean WC > height/2) not all subjects in that stratum will present risk from WC alone because it may not capture true risk, at least without accounting for height. In this regard, if the mean WC > height/2 (WHtR risk cut-off >0.5) is a true premise applicable to MI/CVD cases, how can it be applied to a healthy population without being a false premise? Epidemiologically, those values for WHtR from 0.51 up to any other defined risk cut-off of >0.51, while lying on the overlapping zone of the distribution curves between groups, they may be true-negatives for healthy subjects when conditional on WHtR >0.5 as the true predictive variable, effectively being the mean WC higher than height/2. In this situation, those true-negative points for WHtR always lie before the line of their defined risk cut-off, which is much further on from 0.5 (bias zone for WC, **Figure 3**). Indisputably, if in any study population's WHtR risk cut-off is of >0.5 (mean WC > height/2), the concrete value of this metric while measuring the relative volume and being conditional on both WC and height predicts the received risk, but never WC alone.

The standard human body can have a HC higher than WC without posing any putative risk or protective effect (**Figure 1**). By deduction, HC > WC is an anthropometrically healthy natural inequality, which responds to a linear equation: HC = WC + X, where by subtracting HC from WC we calculate X (>zero) as a unit of length with one decimal digit-tenths; the standard value is higher in women and the middle-aged than in men and elderly subjects, respectively, but higher than zero in all cases. Mathematically, WHR <1 is a proper abstract fraction whose decimal value ranged from hundredths up to 1, which states that equal parts of WC in HC, but it shows no anthropometric consistency or true risk beyond that of WC or X distance. It is clear that WHR <1 is simply a way of representing size (part/whole) that is not a whole number or entity of whole-risk as a mathematical object, unlike WC or X. In this sense, WHR <1 might represent a higher risk than WC and X, when HC has the importance of being overestimated as a protective factor with respect to WC

and, therefore, creating bias for WHR. This is because fractions of equal value do not refer to the same risk and the sensitivity of WHR (hundredths) is different from X (tenths). It is clear that between two consecutive values of WHR <1 we have 10 of X (e.g., between 0.95 and 0.96. we have from 5 up to 4.1 for X, but not all referring to the same risk as it is 0.95, which misclassifies risk). Thus, the higher the positive value of X (e.g., in women, middle-aged people, athletes), the higher the probability of bias for WHR when compared to WC, and if values of WC (numerator) and X as true-negatives below their respective risk cut-offs receive no true risk, WHR may effectively capture false-positive points in the stratum of <1. "From a proper abstract fraction, if WHR risk cut-off is of <1, WC turns out to be the entity of risk to be compared, but never WHR performing better than WC, at least while understanding maths and biases" [37].

Anthropometrically, in any study population, from the lowest baseline up to the highest values there is a direct correlation between cardiometabolic risk for WC and WHtR indicating the corresponding risk cut-offs. As WC and WHtR increase, the respective risk cut-offs and points with greater excess risk move further outwards lying on their geometric rays. However, WC may only represent risk when WHtR = 0.5 and the mean WC and height/2 are balanced in their data distribution (**Figure 3**). Similarly, WC alone may represent risk with respect to WHR when the WC cut-off lies before the line where WHR = 1. When the WHR risk cut-off is ≥1 (improper fraction), WC and WHR express the same risk. On the contrary, while WHtR may demonstrate a risk cut-off between 0.51 and 0.999 (<1), neither WC nor WHR will represent risk due to overlapping and bias zones where false-positive points might be selected from both with respect to WHtR, which would receive no risk up to their risk cut-off lying on their ray of risk further outwards (site of cases), (**Figure 3**). Indisputably, the risk points from WHR and WC in bias zones before the WHtR risk cut-off will never capture the true risk while not being true positives lying on their respective rays of risk after the same WHtR risk cut-off. The risk captured by WHR and WC in the identified bias zones will always be false, at least partially.

Epidemiologically, neither height nor HC correlate to cardiometabolic risk. Hence, in predicting MI/CVD risk, HC and height may only be conditional risks for WHR and WHtR as area and volume factors, respectively. HC never appears to take the same cut-off value as height (the mean height is always higher than HC and HC > height/2). WC hardly reaches the same cut-off value as height or HC (mathematically it is always fulfilled as the mean height > HC > WC. The mean HC > WC > height/2, see **Table 1**). In addition, as WC increases, WHR >1 (whole/part) may also draw a similar correlation of risk up to the highest WC values because it directly depends on WC as a total area of risk, irrespective of HC (**Figure 1**). Nevertheless, WHR <1 (part/whole) draws neither ray nor greater excess risk, at least between their risk cut-offs and the 0.999 value where a higher or lesser bias occurs as HC increases or decreases and WC does not move in its respective ray of risk. On the other hand, only WHtR as a relative volume allows a clear indication of risk to be recognised up to value of 1, which theoretically would represent the unity of risk corresponding to the total volume where WC would take the same value as height (in a balanced distribution). In this approach, we will always find the point for WHtR = 0.5 before the line for WHR = 1, and the WHtR risk cut-off lies much more outwards (in the site of cases) than WC and WHR. Thereby, the curves of distribution and overlapping zones explain that, in capturing risk, WHtR presents much more sensitivity (true-positive fraction) than WC or WHR. This is because true-negative values conditioned on the WHtR risk

cut-off are not selected as false-positive ones, unlike WC and WHR between their respective risk cut-offs and the end of the bias zones (**Figure 3**).

Anatomically, HC is also higher than height/2 and lower than height (height/HC >1; HC/(height/2) >1) (**Figure 1**). Hence, there would be no equivalent relation between WHR and WHtR risk cut-offs to compare the same risk if the first is lower than the second × 2 (WHR/WHtR <2). According to this premise, WHtR ≥0.5 will always detect risk before WHR ≥1 (see **Figure 3**). Since the balanced distribution between WC and height/2 on the one hand, and between WC and HC on the other hand, may only be found on the risk cut-offs of WHtR =0.5 and WHR =1, respectively, both indices will never capture the same risk because it is anthropometrically impossible and epidemiologically false (**Table 1**). Therefore, bias will occur for WHR with respect to WHtR due to an unbalancing of HC and height/2 values between healthy and unhealthy cases (**Figures 1** and **3**). If WHR risk cut-off is lower than WHtR × 2 and WC does not move, WHR-associated risk above WHtR would be a

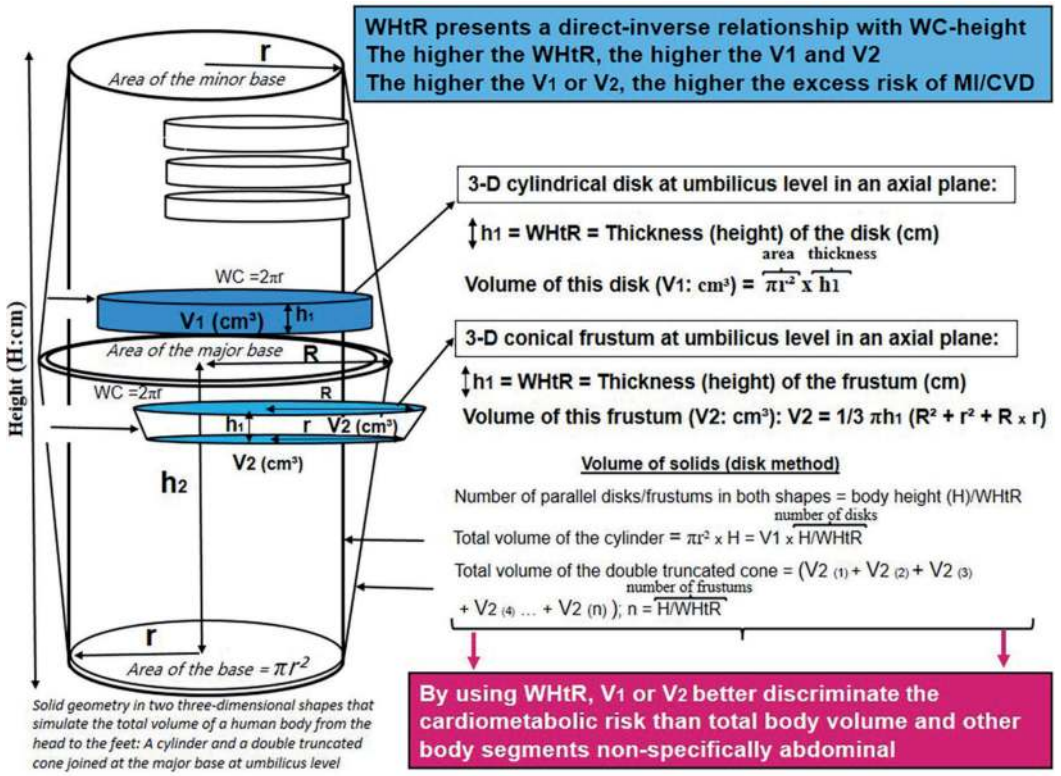

Figure 4.
Lessons from geometry: Volume of solids. Geometric model representing the human body as a solid cylinder or two truncated cones joined together at their major bases. Geometry formulas and explanations for understanding the meaning of WHtR when comparing cardiometabolic risk between healthy population and cases of MI/CVD. Geometric values at baseline would represent the mean values per standard deviation for WC, radius, heights and WHtR being actually valid for any study population and ethnicity. The model may be applied for both case–control and cohort studies from the respective mean values (SD) and risk cut-offs for WHtR. "Volume" refers to the amount of three-dimensional space that bodily components occupy in relation to their mass and density. Volume is determined by geometry formulas. The base of the cylinder and the major base of the truncated cones have a length or perimeter equal to WC as appropriate. Dividing H by WHtR we get the total number of disks that fit into each three-dimensional shape. CVD denotes cardiovascular disease; H, total height corresponding to that of the cylinder or double truncated cone; h_1, height or thickness of each disk or frustum; h_2, height of a single truncated cone (H/2); MI, myocardial infarction, R or r, radius of each base as appropriate; V_1, volume of the cylindrical disk; V_2, volume of the conical frustum; WC, waist circumference; WHtR, waist-to-height ratio.

false-positive due a protective overestimation for HC concerning height, either by age or by sex. "From a mathematical conception, ..., if ratio of the risk cut-offs between WHR and WHtR is of <2 (WHR <WHtR x 2), WHtR turns out to be the entity of risk to be compared, but never WHR performing better than WHtR, at least while understanding maths and biases" [37].

From geometry, the concrete volume of a three-dimensional disk or frustum (e.g., at umbilicus level) may be quantified from the WHtR. Simulating a cylinder or truncated cone, the volume of this disk will depend on area of the base$_{(s)}$ (πr^2, where WC =2πr: r = WC/2π) and their geometrical height (thickness of the disk = WHtR cm) [36, 37]. Geometrically, the human body as a solid from the head to the feet would have several disks, so that number of disks = body height (H)/WHtR, and the sum of the volume of all the disks would give us the total volume of the body. The total body volume would be the theoretical unity of risk where WC = height: WHtR =1: number of disks =1 (**Figure 4**). Obviously, only from this hypothetical situation WHtR ≥1 (improper fraction where the mean WC ≥ height) will always represent risk associated to group of cases irrespective of heiht value, and WC and WHtR ≥1 refering to the same risk. Thereby, an epidemiologically real WHtR gives us the corresponding relative volume (cm^3) that we have by unit of height or disk in a direct-inverse relationship with WC-height. The higher the WHtR, the higher the volume of the disk. On the other hand, although WC values do not change, the disk volume may be modulated by body height towards a higher or lesser amount of three-dimensional space that risk components occupy and, therefore, modifying their cardiometabolic effect. Epidemiologically, WHtR is important because it captures risk above the WC area, at least when height may have significant differences between groups to be compared and with a WHtR risk cut-off >0.5 and < 1. In this approach, the area and volume from WC and WHtR, respectively, would not be comparable. "From a proper abstract fraction, if WHtR risk cut-off is of >0.5 and <1, the value of this metric is the entity of risk to be compared, but WC never performs better than WHtR, at least while understanding maths and biases" [37].

5. Novel findings in medical research and implications for an anthropometrically correct MI/CVD risk assessment

It is well known BMI depends on weight and it strongly depends on metabolically healthy musculoskeletal components and body fat mass, especially subcutaneous, without discriminating the unhealthy intra-abdominal fat and their volume [2, 14, 23, 24, 37, 48]. Why to choose BMI to assess MI/CVD risk if it captures metabolically contradictory components? The consequence of this chimera is that to describe individuals' risks based on BMI is unfounded and potentially misleading. Accordingly, the concepts of ideal anthropometric health and BMI-classified obesity should not be considered synonymous or interchangeable, unless we accept misclassification and paradoxical information for biological risk assessment. BMI fails to discriminate between harmful body fat and healthy components and is an inappropriate formula to assess the association between excess fat mass and MI/CVD. Besides, while a part of the musculoskeletal component (mesomorphy) may be associated with MI, as %BF increases, a part of the association for BMI would capture a false risk and, therefore, information bias would occur for the true high risk BC in both sexes. The excessive body weight in individuals who have a high BMI and normal %BF (e.g., individuals/athletes with high mesomorphy rating) would indicate a score of spurious risk, but

never performing better than WC [24, 27, 37]. With respect to WHR, it is well known that it has demonstrated the highest predictive abilities for MI risk [4, 13, 17–21, 23]. Nevertheless, WHR may present bias with respect to WC when the risk assignment for both does not refer to the same risk, therefore reducing the quality of the comparison [24, 36, 37].

It is noteworthy that WC and HC only may coincide at the same estimation of risk when WC takes the same value as HC (WHR =1; X = 0, see **Figure 1**). Any WHR value of <1 (X > 0) demonstrates no cardiometabolic risk beyond that of WC alone or X. WHR as a proper fraction (<1) will never represent the entity of risk, and any risk-code selected for WHR between their risk cut-off values of <1 and 0.999 will be biased if WC or X receives no risk-code. There would only be a true risk for WHR with respect to WC when WC or X predicts the true risk from their defined risk cut-offs. If not, WHR may select true-negative values as false-positive ones when they merely represent protective overestimation for HC concerning WC and X.

Mathematically, between any WHR risk cut-off <1 (e.g., 0.95) and 0.999, we could always find different individuals and an infinite number of proper fractions whose decimal values receive a risk-code, but that do not refer to the same high risk BC as measured from the WC or X risk cut-off. This discovery arises from rigorous data analysis in the measurements for WC and HC, and where misclassification occurs for WHR-associated risk [23, 24, 36, 37]. As an example, 93.1/98 vs. 93.9/98 vs. 95/100, etc., =0.95: X between 5 and 4.1; 93/95.9 vs. 94.1/96.9 vs. 98/100.9, etc., =0.97: X between 3 and 2.1; 93.8/93.9 vs. 94.2/95 vs. 99/100 etc., =0.99: X between 1 and 0.1. Broadly, there would be five values for WHR between 0.95 and 0.99, and infinite fractions for values of X between 5 and 0.1; HC > WC in all and a WC risk cut-off ≥94.4 in each set. Equal values for WHR (e.g., between 0.82 and 0.999; X between 18 and 0.1) may be transferred to broader populations where the mean values for WC and HC were higher or lower than in the example. In any situation, WC and X values that depend on their own risk cut-offs would reflect different risk-codes in each fraction while WHR would support a unique value for the risk, but any mean value of WHR <1 precludes the same estimation of risk for WC and HC (HC ≠ WC), making the validity of WHR beyond that of WC alone anthropometrically impossible. These observations may help to explain a higher bias for WHR in predicting MI/CVD risk in women because the X positive value is always higher in women than in men. In fact, HC > WC at the baseline involves a positive X value, and the higher the X value, the higher the bias occurs by selecting a higher number of proper fractions and false-positives, so that the protective effect for HC would always be overestimated. Similarly, a higher bias for WHR would occur when the WC is taken at the minimum level vs. the maximum (e.g., at the umbilicus) due to a longer range between the lowest and 0.999 value (see **Figure 1**). "From a proper abstract fraction, if WHR risk cut-off is of <1 all WHR-associated risk above WC as being mathematically incorrect and anthropometrically unjustified provides epidemiological false inferences" [37].

In another mathematical consideration, our research has also revealed that WHR and WHtR contrast by suggesting the same true risk if HC and height present a relationship of height/HC =2. This ratio would occur if and only if WHR/WHtR = 2 (e.g., 0.90/0.45, 0.95/0.475, 1/0.5, 1.2/0.6 etc., HC = height/2 in all). This also appears anthropologically unlikely and selection bias occurred for WHR with respect to WHtR due to the protective overestimation for HC regarding height [23, 37].

As mentioned above, WC and WHtR may only be comparable if the equivalent relationship between WC and height refers to same estimation of risk for both (WC = height/2: WHtR risk cut-off =0.5). If not, between 0.51 and any WHtR

risk cut-off up to 1 (e.g., >0.55), we could always find different individuals and an infinite number of fractions receiving the same binary code for WHtR (no risk), but not referring to the same risk-code from the WC risk cut-off (see **Figure 3**). As an example, 82.8/162.4 vs. 88.6/174 vs. 80.6/158 vs. 95.4/187 etc., =0.51; 95.2/178.2 vs. 90/168 vs. 83/156, etc., =0.53; 96.7/178 vs. 92.5/168.2 vs. 98.8/179.6, etc., =0.55. Broadly, there would be no risk-code for WHtR ≤0.55 when the WC represents different risk-codes if their risk cut-offs were > 84 or > 95 on each set, and WC > height/2 in all. Thereby, the higher the WHtR, the higher the risk overestimation for WC occurs by selecting false-positive points as compared to those true-negatives below the WHtR risk cut-off. Equal values for WHtR (e.g., between 0.51 and 0.65) may be transferred to other populations where the mean values for WC and height were higher or lower than in the example. In any situation, WC values depending on their own risk cut-off would reflect different risk-codes into each fraction while WHtR would support a unique, continuous code (no risk) up to their own risk cut-off value. Hence, WC might present bias with respect to WHtR when the risk for both metrics does not refer to the same high risk BC, when compared either in men or in women. Thus, WC might capture risk if there are no differences in height between healthy and unhealthy cases (WHtR risk cut-off close to 0.5). In contrast, the risk captured from WC would be not equivalent when the mean height (WHtR risk cut-off much higher than 0.5) determines a significantly higher relative volume in cases, and therefore a different high risk BC when compared to healthy people (see **Figures 2** and **3**). Regarding this observation, the risk association for WC and WHtR will be equivalent if, and only if, the WHtR risk cut-off is very close to 0.5, but any value >0.5 precludes the same estimation of risk for WC and height (WC ≠ height/2), making the validity of WC alone beyond that of WHtR anthropometrically impossible. Thereby, "when WHtR risk cut-off is of >0.5 and <1 all WC-associated risk above WHtR ... provides epidemiological false inferences" [37].

In another sense, a different cardiometabolic effect among visceral and extra-abdominal fat has been argued when using WC to measure the total abdominal adipose tissue. However, there is evidence that the higher the intra-abdominal fat, the higher the WC value, irrespective of subcutaneous extra-abdominal fat [13–15, 22]. From the Framingham study, visceral fat has been strongly associated with a metabolic risk profile and MI in both sexes and technological studies have also observed that the ratio visceral fat/subcutaneous extra-abdominal fat presented a direct association with MI while subcutaneous area presented the inverse [12, 14, 16, 22, 37, 50]. The anthropometric explanation would be because, as intra-abdominal fat increases, subcutaneous adipose tissue of the extra-abdominal space suffers the mechanical effect of compression, which decreases their relative thickness and volume (tight fat) [37]. Moreover, it is noteworthy that %BF measured by DEXA strongly depends on WC and height rather than BMI in adult individuals [45]. In addition, MI men present high mesomorphy and low ectomorphy ratings, and %BF is more strongly correlated with WHtR than it is with WC (intra-abdominal + subcutaneous area). Therefore, WC does not necessarily refer to risk for an accurate comparison but considering it for a higher relative volume by unit of height, closely linked to a low ectomorphy [10, 24, 27, 31, 48]. Thereby, sophisticated volumetric imaging methods have demonstrated differences in the association of visceral and subcutaneous fat with an adverse metabolic risk profile in both sexes [50].

A novel insight in research, for the first time we have used a propensity score method to address selection biases in balancing the distribution of covariates between anthropometrically healthy subjects and MI cases [36]. It is well known in

observational studies, treatment (or exposure) selection is often influenced by subject characteristics [51–53]. As a result, baseline characteristics of treated (or exposed) subjects often differ systematically from those of untreated (or unexposed) subjects. Therefore, one must account for systematic differences in baseline characteristics between treated and untreated (exposed or unexposed) subjects when estimating the effect of treatment (or exposure) on outcomes [53]. Based on our idea of how to reduce the effects of confounding in non-randomised anthropometric studies, we have applied the cited method. Thus, the conditional distribution of risk between groups (healthy and unhealthy cases) should be the same when observed baseline characteristics do not present standardised differences [37, 53]. Thereby, similar baseline characteristics for WHR and WC may provide bias in outcomes of both, if the risk assignment in both does not account for the covariates that predict the receiving true risk, WC as numerator and WHtR as measure volume, respectively. In this sense, as a result, risk assignment for WHR and WC may be systematically biased if values between WC, HC, height/2 and height show no balanced distribution and, therefore, the concerned metrics may not be directly comparable (see **Figure 3** and **Table 1**). Consequently, if the mathematical equivalence between covariates and propensity scores for metrics is not explored, it will be impossible to ensure a balanced distribution of risk between anthropometrics and groups. In agreement with the stratification method, all subjects who have (nearly) similar baseline characteristics and, therefore, similar propensity scores would have the same probability (nonzero) to receive a risk-code, making the risk assignment strongly ignorable [53]. Comparing the similarity of healthy and unhealthy cases in the same strata should begin with a comparison of the means or medians of the simple covariates and the distribution of their categorical counterparts between groups. If, after conditioning on the simple measurements, there remain systematic differences between means or medians, this would be an indication that the propensity score model has not been correctly specified for unbalancing the distribution of the measurements and the risk assignment. Thus, from our research, we have anthropometrically and mathematically demonstrated an association bias of WHR for unbalancing HC with respect to WC and height values in MI men [36, 37]. Besides, results from other larger studies [4–9, 14–22, 28–30, 32–35, 38–44] may be transferred to our analysis as appropriate. In revealing inequality between the simple measurements and risk cut-offs for metrics, our conclusions are not coincidental due to identifying biases and checking the lack of external validity. In brief, we have demonstrated association biases that are extendible to all previous studies and we have proposed the premises to avoid it.

6. Discussion

The anthropometric robustness of BMI and WHR as a link to the true risk of the BC and MI/CVD is unclear and diffuse. Conceptually, each of these provides its own meaning without a verifiable associated risk beyond that of WC. Nevertheless, only a rigorous interpretation removing bias could avoid confusing or paradoxical information, independently focused on the number of lifestyle factors and other established risk factors that influence ideal cardiovascular health [11].

It is well known that BMI has significant association with MI in both sexes, but not the best, and unimportant differences were found when compared by sex [4, 17–19, 21]. From the UK Biobank results, the ratio of women-to-men's hazard ratios for incident MI for the comparison between BMI and WC demonstrated a higher hazard ratio of

association for WC in women, and no difference in men. Only WC and WHR, but not BMI and WHtR, were significantly associated with the risk of MI in women compared to men. Moreover, measures of central adiposity, particularly WHR as compared to BMI, showed a higher hazard ratio in women than in men [21]. However, when exploring the association between anthropometrics and obesity, novel findings have explained the reasons why both BMI and WHR are not optimal indicators in predicting MI risk, at least in men [23, 24, 27]. Thereby, it can be reasonably assumed that, since the musculoskeletal component may be artificially or indirectly associated to MI, BMI fails to reveal the true high risk BC by underestimating visceral fat volume and overestimating risk from the mesomorphy component. Thus, in two individuals with mesomorphy dominant and different high risk BC, the same BMI would underestimate the higher body fat volume in one of them. This observation means that BMI has the importance of producing a greater impact and bias in men due to it capturing a dimension of spurious risk beyond that of women. On this basis, from the UK Biobank, the comparison between BMI and WC by sex presented bias. This is because both metrics cannot refer to the same high risk BC when comparing men and women, and WC without accounting for the whole-risk (a 1-SD WHtR was >0.5 and < 1 in both sexes) [21, 37].

To our knowledge, body weight and HC have showed low predictive ability for MI and never justifying true biological plausibility for the risk. On the other hand, height and ectomorphy has been inversely associated to MI with a higher relative risk, although not necessarily referring to a causal relationship [10, 23, 24, 31, 48]. It is clear then that WC would be the only one among the simple measurements for reflecting both the cardiometabolic risk and the highest association discriminative for MI in both sexes [4, 7, 9, 12–21, 23, 24]. Besides, as %BF increases in vivo, the body fat storage is homogeneously distributed and WC, rather than BMI, becomes the best clinical expression of a body fat volume increase. Nevertheless, compound indexes such as WHR, conicity and WHtR have always captured a higher dimension of risk [4, 7, 9, 12, 16–19, 21, 23, 24, 27].

Surprisingly, most studies predicting MI/CVD risk always used a WHR cut-off <1 and/0r WHR/WHtR <2 in both sexes and different ethnicities while selection biases were never discussed [4, 5, 7, 13, 15, 17–19, 21, 28–30, 32, 35, 38–44, 54]. Why, when WHR <1, has the causal relationship between HC and adverse MI/CVD outcomes not clearly been elucidated? From the INTERHEART study [4], the median WHR in the overall population was 0.93 in cases and 0.91 in controls with a significant difference between both values, and therefore for the X distance, so the risk comparison was done without balancing between HC and WC. Besides, WC was obtained at the narrowest point (the longest X distance), and WHtR as entity of risk was not explored. On the other hand, the follow-up in the CONOR study [17] found, for WHR and WC, an association stronger in women and middle-aged than in men and elderly participants, respectively. However, the higher value of X for middle-aged (X = 21) and elderly women (X = 18) with respect to male counterparts (X = 11 and 8, respectively) was not kept in mind, and therefore, biases occurred with respect to WC and X in the risk comparison for unbalancing the mean HC and WC. Additionally, WC would appear to be found with classification bias for the risk in women compared to men if height was not accounted for in the data analysis and WHtR as an entity of risk was not well compared. Similarly, from the UK Biobank study [21], a 1-SD WHR was significantly associated with a higher hazard ratio of MI in women than in men, and with a corresponding women-to-men ratio of hazard ratios of 1.15. Nevertheless, the mean (SD) of WHR was <1 in both sexes (0.82: X = 18 in women, 0.93: X = 7 in men), so the false premise accepted in the risk assignment up to 0.999 value provided

a selection bias for WHR when compared to WC or X. Thereby, having a baseline characteristic of WHR <1 either in healthy population or in cases, a different high risk BC as measured by WC and X will provide a higher WHR-associated risk due to the protective overestimation for HC where equal numbers of WHR <1 predict false-positives when accounting for an imbalance of the mean HC and WC or X. Besides, in data distribution and hazard ratios, WHR in the top was always <1 when WHtR in the bottom was >0.45–0.5 and < 1 in both sexes (WHR/WHtR <2), so the risk comparison between both indices was biased and demonstrated a protective overestimation for HC concerning height. Additionally, the strength of association for WC was significantly higher in women than in men while the hazard ratio for WHtR was similar in both sexes (1.34 in women, 1.33 in men). By deduction, height differences were higher in men than in women in occurring similar risk assignments for WC and WHtR in women (hazard ratio of 1.35 and 1.34, respectively), but not in men (hazard ratio of 1.28 and 1.33, respectively). This is because the mean WC and height demonstrated a different relationship, and WC and WHtR was not compared for the same risk [37]. Indeed, the mean (SD) of WHtR at the baseline in women (0.52 ± 0.1) was closer to 0.5 than that of men (0.55 ± 0.1) [21]. This means that, in the stratum between 0.5 and 0.52, WC and WHtR captured a similar dimension of risk in women due to a lower probability of selecting false-positives, while in a higher range up to 0.55, only WHtR captured the highest risk, as it happened in men. Thereby, height differences between women and men involve less chance of bias for WC in women when compared to WHtR, and WHtR more accurately predicts risk in men than WC [21]. By contrast, in the follow up of a Swedish cohort, WC presented less statistical significance for a recurrent MI in the female group [38]. However, the risk the WHtR measured was not explored and, therefore the risk comparison between sexes could not be referred to the same high risk BC and relative volume.

On the other hand, since short-stature has been associated with MI, the WC associated risk that is geometrically-derived from a two-dimensional area will be overestimated in taller individuals with respect to shorter people, including sex differences. In contrast, WHtR has the importance of corresponding to a relative volume where intra-abdominal risk components occupy all the space except for small peripheral-subcutaneous area, which is less deleterious [24, 37, 46, 47]. Unequivocally, WHtR gives us a relative risk volume and the higher the WHtR, the higher the risk. Besides, WHtR yields no bias with respect to others and it may capture a dimension of risk above WC. Obviously, this only happens when WHtR risk cut-off moves too far towards an excess of 0.5, as proven in men [21, 23, 24, 27]. It is also anthropometrically and mathematically demonstrable in most studies (**Table 1**).

In another consideration, some studies have signed a trend towards higher risk of MI as HC decreased (narrow hip) in a relationship with sarcopenia and deficiencies in physical activity [4, 19]. However, despite different values of HC either in the UK, Sweden, Norway, Spain or even in infarcted populations worldwide, studies have always found a WHR risk cut-off <1 and HC never takes the same value as WC [4, 18–21, 23]. On the other hand, HC-adjusted WC has demonstrated the strongest association with coronary disease and cardiovascular mortality [41–44, 53]. Nevertheless, by entering both WC and HC as independent markers of future CVD risk, the causal association for HC-adjusted WC in analytic models also appears to be wrong due to selection bias for the risk. The key lies in the discriminatory risk cut-offs for WC and HC, which reflect different sensitivity and specificity as well as different coherence and biological plausibility from each one. When using HC-adjusted WC, whether considering HC as a protective factor in a WHR risk cut-off of <1 (mean

HC > WC: X > 0) [39–42, 53], this argument becomes a false premise, because we will always find points of spurious risk in any WHR-associated risk above the WC, and therefore draw false conclusions for causation. It would occur even when X values are 0.1: WHR =0.999 (**Figures 1** and **3**). Hence, anthropometric risk evaluation is not subsumable by combining WC and HC data at the same level of equality (WC = HC instead of HC = WC + X), either for WHR <1 or HC-adjusted WC. That way, the paired comparison of two different biological factors would adulterate the associated joint risk and the real effect of HC, which takes a protective role falsely assigned. Then (and only then), when WC takes the same value as HC (risk equivalence) there will be the same (x, y) coordinates in the shared point where WC = HC: WHR = 1: X = 0, and, therefore, the same estimation of risk for WC and HC (**Figure 1**). In the same way, noting that anthropometrically healthy women significantly present lower WHR than men (higher X distance), a higher bias for WHR in predicting MI/CVD risk in women may be explained due to a higher selection of abstract fractions and spurious risk points where HC does not account for the same estimation of risk as WC. Similarly, higher bias would occur when the WC is taken at the minimum perimeter (both sexes), due to a higher X length (**Figure 1**). In this approach, the higher X value, the higher bias may occur. Thus, a higher HC in middle-aged people, physically active subjects or in women with higher gluteal–femoral fat deposits never justify a protective effect that influence MI/CVD, at least anthropometrically and while balancing the mean values of WC, HC, and X in any correct comparison between healthy and unhealthy cases including sex differences.

To our knowledge, using stratification for matching the selection bias of WHR has been demonstrated in men. This was because the same WHR risk-code (yes) on the same matched fractions between 0.95 and 0.999 always found different risk-codes for WC (yes/not) when conditioned on both WC < HC and WC receiving a true risk above their risk cut-off [36, 37].

In agreement with our observations, the strata between the WHR risk cut-off and 0.999 on the one hand, and from 0.51 up to any other WHtR risk cut-off of >0.5 on the other hand, usually coincide on the overlapping areas of the distributions for WHR and WHtR between healthy populations and MI/CVD cases. Thus, for the same binary code of no risk (true-negatives) between 0.51 and any other WHtR risk cut-off of >0.5, we could find the same WHtR value for different fractions from WC and height. However, WC might produce false-positives above their own risk cut-off if conditioned on WC > height/2 and WHtR received no risk (bias zone for WC as explained above). When unbalancing HC vs. WC and height mean values, or the mean WC vs. height/2 false-positive points for WHR and WC, respectively, might be selected for biasing any associated risk above WHtR. Besides, evidence states that, in any study population, HC and height/2 always present different mean values (HC > height/2: WHR/WHtR <2), so a risk assignment for WHR and WHtR always shows an imbalance for overestimating the protective effect of HC with respect to height, and therefore, comparing different risk [4–10, 14–30, 32–35, 38–40], (**Table 1**).

From a syllogistic approach, whether in any study population WHR (risk cut-off <1) shows a higher magnitude of association than WC (the first false major premise for a causal risk), while the mean HC is higher than WC (the second true minor premise), any WHR-associated risk above WC will occur for unbalancing the distribution of WC and HC as covariates. This fact determines false risk assignment for WHR (association bias) with respect to WC, which induces a false inference as the conclusion for causation. In no case WHR <1 would risk be captured above the WC because HC > WC is a natural inequality associated with a healthy population. Similarly, a WHtR risk cut-off >0.5 occurs, the

WC shows higher magnitude of association than WHtR (the first false major premise for a causal risk) and when the mean WC > height/2 (the second true minor premise), any WC-associated risk beyond that of WHtR will occur for unbalancing the distribution of WC and height/2 as covariates. Thus, WC that captures a false risk (association bias) with respect to WHtR would induce a false inference as the conclusion for causation. In no case can WC alone capture the risk above WHtR because WC < height/2 is a natural inequality associated with an anthropometrically healthy population, and only up to a WHtR risk cut-off =0.5 (mean WC = height/2) would WC and WHtR capture the same risk. With the same premise, if any WHR risk cut-off is lower than that of WHtR × 2, and being the mean HC > height/2, any WHR-associated risk beyond that of the WHtR will occur for unbalancing the distribution of HC and height/2 as covariates, but WHR never captures the risk above WHtR. To clarify this, apply the results of the studies referenced in **Table 1** on **Figure 3** and once the simple measurements and their mathematical inequalities in the standard human body are well known, see **Figure 1**).

As a philosophically and anthropometrically correct reflection, not all subjects are at risk as according to their WHR measurement, and with similar baseline characteristics between their risk cut-off of <1 and 0.999 or twice the WHtR value that refer to the same risk as measured from WC or WHtR risk cut-off, respectively (bias zone for WHR). Similarly, not all subjects at risk according to their WC measurement, and with similar baseline characteristics for WC alone above their risk cut-off refer to the same risk as measured from WHtR between 0.51 and any other real risk cut-off >0.5 (bias zone for WC), (**Figure 3**).

Epidemiologically, while a shorter stature may be significantly associated to cases of MI/CVD (WHtR risk cut-off >0.5) and the mean values of HC higher than both WC and height/2 (WHR <1: WHR/WHtR <2: HC > WC > height/2, see **Table 1**), WHtR will always capture the highest dimension of risk above WC and WHR. This is because WHtR as a three-dimensional volume measure would always capture higher a biological risk than WC as a two-dimensional area. Similarly, when balanced distribution between the simple measurements may be checked and the risk may be conditioned on the real predictive variables (WC or WHtR >0.5 as appropriate) [36, 37], WHtR becomes the gold standard for risk assessment. It is geometrically clear. The same values of risk for WC between different individuals refer to a similar risk from WHtR as relative volume if the mean WC is ≤height/2 (WHtR ≤0.5 and unimportant differences for height), but never occur when individuals present a mean WHtR of >0.5 (significant differences for height). Thus, WHtR should be used as the optimal metric when making an anthropometrically and mathematically correct risk prediction, irrespective of the strength of association for other metrics in different studies. In such studies, a spurious risk might be artificially slanted towards the group of cases in the rest of compared metrics when specifically defined or universally categorised risk cut-offs were used [4–10, 14–30, 32–35, 38–44, 49, 54, 55].

Our demonstrations are a touchstone on the risk associated with WHR and WC from many studies, so universal recommendations made on the issues relating to WHR and WC alone for determining abdominal obesity and substantially increased risk of metabolic complications may turn out to be fallacious or at least have information bias [13, 14, 56]. Validity for both WHR and WC depends on the degree for measuring the risk. However, when having a WHR risk cut-off <1 as an abstract fraction or WC alone as a two-dimensional area, it will be impossible to discriminate the risk and relative volume, unlike WHtR, which is a more faithful measure. Thus, a true description of risk for WHR <1 requires of a categorical syllogism, where the risk derives from an affirmative proposition for the WC value as a numerator. On the

other hand, any association of risk for WC alone above WHtR will be a false conclusion, if the WHtR risk cut-off is of >0.5 and < 1. Since a part of the assigned risk for WHR and WC may be spurious, the conclusion for the risk will be in error due to a fallacious argument. Similarly, the assumption of risk for categorised risk cut-offs for overweight/obesity when not measuring the true high risk BC nor abdominal obesity volume will be a misleading proposition, which will provide a false conclusion for the associated real risk, or at least provide a conclusion with paradoxical information and bias. Therefore, in any study population, the risk captured by each metric depends on itself, its sensitivity and specificity, consistency, coherence, plausibility and anthropometric validity, rather than on its strength of association with respect to others, at least while predicting risk with simple measurements, where mathematical relationships of inequality provide imbalance and biases for the causal risk association.

In summary, BMI and WC will never refer to the same risk and high risk BC. Regarding that insight, while technological methods are clinically impracticable, to predict MI/CVD risk, WC should be the anthropometric reference for assessing the true high risk BC and risk beyond that of BMI.

It is worthy to note that the universally categorised risk cut-offs for metrics such as overweight/obesity [2], WHR ≥0.90 in men and ≥ 0.85 in women (<1 in both) [14], WC >94 (102) in men and > 80 (88) in women [13, 14, 56], and WHtR >0.5 and < 1 in both sexes, may provide confounding and association biases for causal risk. This occurs when the mathematical relationships are unbalanced between the simple measurements of healthy and unhealthy cases, and a spurious risk assignment being slanted in direction to the group of cases in the confounding metrics. At the same time, in the overlapping areas of the confounding metrics, subjects with similar baseline values must present different risk assignments when conditional on both imbalances between simple measurements and the real predictive variables [37]. Thus, regardless of WC, HC and height should be controlled in data analyses to preclude a different–equal risk assignment between subjects who have equal–different high risk BC and risk. Accordingly, a higher strength of association for WHR or WC with respect to WHtR does not mean higher risk, but association biases where both the high risk BC and relative volume were not well compared. In other words, WHR-associated risk above WC and WC-associated risk beyond that of WHtR were always a bias error, which is evidence that posed issues for the cardiovascular sciences for a long time due to the research process itself. Thus, when ignoring biases in research, false inferences could be drawn to predict MI/CVD risk in both sexes. On the contrary, only WHtR-associated risk above WC and WHR will hold true. Thereby, by identifying and removing biases in research, WHtR will always provide equality and balance between healthy populations and MI/CVD cases to be used as an entity of risk, while also having the importance of being cheap, accessible and easy to measure. Therefore, an appropriate ethnically-based and sex-specific WHtR risk cut-off would be the easiest and most definitive anthropometric tool to meet the best epidemiological criteria for the judgement of causal associations and to identify individuals at risk of MI/CVD. Broadly, it would occur while the degree of adiposity/overweight/obesity still has the importance of accumulating a homogenously distributed body fat volume. A continuous process of accumulating body fat over time provides changes in body shape and a higher degree of adiposity, even with fat flaps that would involve a higher risk and volume excess non-homogeneously distributed and, therefore, non-fully measurable from WC and height. In any case, a high degree of fatness will always keep a high correlation with WHtR, %BF and components of risk of the somatotype [10, 24, 27, 31, 45, 48].

Lastly, after reviewing thousands of cases of MI/CVD, our findings have both internal and external validity, and therefore, they determine the generalisability to any ethnically-based or sex-specific population because they mathematically and epidemiologically satisfy our observations. On this issue, bias and causal associations in observational research must be well known [51–53], and overall, to avoid categorising as risk the value of each metric if their risk cut-off was not well verified and balanced with respect to others and specifically defined and checked in each study population. We also believe that an evolution of findings based on a balanced weighing of potentials for false-positive biases can produce scientific knowledge for the advancement of medical and cardiovascular sciences.

7. Conclusion

Association biases for anthropometrics in predicting MI/CVD risk in both sexes have been demonstrated in anthropometric and mathematical terms. Regardless of BMI, which demonstrates either paradoxical or non-optimal MI/CVD risk prediction in most studies, WHR-associated risk can lead to misleading evidence derived from a generalised mathematical misconception, which overestimates the protective effect of HC concerning WC and height. Until our discoveries by using matching in the overlapping zones between healthy population and cases, no other research has demonstrated biases by assigning spurious risk to true-negative values.

Epidemiologically, in the association of MI/CVD risk, WHR always appears to be a confounding variable with respect to WC and WHtR, due to differences in both the mean X value (HC–WC) and HC – height/2, respectively, either between groups or by sex. This is because there is always a WHR risk cut-off of <1 (mean HC > WC: natural inequality) and WHR/WHtR of <2 (mean HC > height/2: natural inequality). This, therefore, creates a protective overestimation for HC concerning WC and height. Similarly, WC may be a confounding variable with respect to WHtR due to differences for the mean WC and height/2, comparing either by group or by sex. This occurs if, and only if, the WHtR risk cut-off is >0.5 (mean WC > height/2), therefore creating an overestimation of risk for WC with respect to height in the tallest people and an underestimation of risk in the shortest, without accounting for a relative volume by unit of height.

Anthropometrically, the true risk exclusively derives from enlarged WC and abdominal obesity volume. However, accounting for body height as a volume modulator factor rends HC irrelevant or clinically useless, either in women or in men. Any association of MI/CVD causal risk for WHR beyond that of WC and WHtR becomes mathematically biased, anthropometrically inconsistent, biologically less plausible and epidemiologically false. WHtR as a proxy of adiposity and relative volume measure yields no bias and is biologically more plausible and consistent; it may capture a dimension of risk above WC as a two-dimensional transverse area. This only happens when height has an inverse association and the WHtR risk cut-off is >0.5. Thereby, in predicting MI/CVD risk, WHtR is the optimal anthropometric, rather than WC, WHR and BMI. Thus, quoting my own thinking: "Statistics confused medical science and cardiology, but mathematics does not fool the heart". Hence, researchers have the responsibility to design and conduct studies in a way that makes them capable of balancing the simple body measurements, ratios, ratios of ratios and risk cut-offs, as well as the high risk BC and true risk when predicting anthropometrically-measured

causal risk. Once the association biases for anthropometrics have been revealed, the worldwide focus of clinicians and scientists must shift.

8. Recommendation

After decades spent using anthropometrics in medical research and health sciences, our relevant and novel findings with Cartesian demonstrations should be extended to the broader scientific community for the knowledge gained regarding adiposity/overweight/obesity and CVD risk prediction. Many investigations continue to be conducted without consideration of biases, with some studies even spending public resources to obtain unclear or even false conclusions. It is time to avoid such biases in research, as well as in clinical practice.

On the issue relating to anthropometric measures and CVD causal risk, by using non-optimal metrics such as BMI and WHR or even WC alone, public health goals may be impacted by inaccuracies and biased information, especially when tackling prevention and control programmes and gauging CVD risk. It is important to ensure accuracy when measuring each anthropometric characteristic, as well as their relationship as a risk factor for CVD. Thus, monitoring ideal cardiovascular health by measuring body weight (in BMI) or HC (in WHR) will always be less accurate than using abdominal volume measure indirectly obtained from WC and height (in WHtR). Clinical and cardiological protocols should be changed because using misleading metrics will lead to the science remaining anchored in the past and without advancement in the application of the scientific knowledge.

Conflict of interest

The author declares no conflict of interest.

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