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RESEARCH ARTICLE

Anthropometrics and Myocardial Infarction Risk: A Misleading Evidence Was Accepted by Cardiovascular Sciences When Errors of Bias Were Overlooked Worldwide. When Should We End Discussion about the Optimal Metric?

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ABSTRACT

Despite the impact of the COVID-19 pandemic, myocardial infarction remains the leading cause of cardiovascular deaths in Europe. Body mass index (BMI)-defined obesity is a major risk factor for myocardial infarction. However, in the association of anthropometrics and myocardial infarction, the lack of balance between the simple body measurements when comparing healthy and unhealthy cases has demonstrated that affects the outcome. Thus, regardless of association strength of anthropometrics, other criteria to judge the biological causality must be investigated.

We aim to assess different studies worldwide to understand the key concepts to demonstrate association biases for anthropometrics when predicting myocardial infarction risk. In this approach, natural mathematical inequalities between simple measurements in healthy subjects were investigated. Weight, height, height/2, waist circumference and hip circumference mathematically represent absolute values that do not express mathematically equality for the true risk. That way, the mathematical concept of fraction or ratio in anthropometrics such as BMI, waist-to-hip ratio (WHR) or waist-to-height ratio (WHtR) plays an important role. Thus, some anthropometrics may be seen as confounding variables when measuring high-risk body composition. Weight is a confounding factor without indicating a high-risk body composition, meaning that BMI is not fully predictive. WHR is a confounding variable concerning waist and WHtR due to imbalances between the mean hip–waist and hip–height, respectively, which indicates a protective overestimation for hip concerning waist and height. Waist measure may be a confounding variable concerning WHtR due to an imbalance in the mean waist–height. This occurs if, and only if, WHtR risk cut-off is >0.5 and if height is ignored as volume factor, therefore creating an overestimation of risk for waist circumference in the tallest people and underestimation in the shortest. Mathematically/anthropometrically, only WHtR-associated risk above BMI, waist and WHR holds true while considering it as a relative risk volume linked to a causal pathway of higher cardiometabolic risk.

In conclusion, WHtR is the only metric that is directly associated to a risk volume and having more biological plausibility. It should be used to assess the anthropometrically-measured myocardial infarction risk, once the imbalances between measurements and association biases are recognised.

Keywords: myocardial infarction, cardiovascular disease, risk prediction, obesity, anthropometric indicator, body composition, waist-to-height ratio, bias.

1. INTRODUCTION

Despite the impact of the COVID-19 pandemic, each year cardiovascular disease (CVD) causes 3.9 million deaths in Europe and over 1.8 million deaths in the European Union. Myocardial infarction (MI) remains the leading cause of cardiovascular deaths in Europe, highlighting the need for further reductions in risk factors[1]. Body mass index (BMI)-defined obesity is a major risk factor for CVD including MI, and is the metric most often used for cardiovascular health promotion and disease reduction[2]. However, obesity is defined as abnormal or excessive fat accumulation, but it may not correspond to the same degree of fatness and metabolic health in different individuals[3]. Thus, an accurate estimation of the body composition (BC) as well as body fat distribution will be more relevant from a scientific perspective, an aspect that has been endorsed by the American Heart Association[4]. In light of this, how can the high-risk BC and true risk for any type of CVD be measured by using simple baseline anthropometric characteristics? In cardiovascular research, biases also occur, which can mean that valuable conclusions may turn out to be worthless. Then, in medical research, it is important to estimate the causal risk of an exposure factor on subject-important outcomes because the association of anthropometrics does not always equate to causation regarding incidents of MI. The causal risk can be estimated in observational studies, which can often present numerous inherent shortcomings. The major limitation in using observational data to estimate causal effects is the confounding factors[5]. Traditionally, these confounding factors can be adjusted with multivariate models. However, the distribution of anthropometrics as confounding factors may be different between healthy and unhealthy subjects, and model extrapolation can be erroneous. Furthermore, the causal effect estimated with regression models can vary depending on different specifications and assumptions of the model[5].

On the other hand, exposure selection is often influenced by subject characteristics. As a result, baseline characteristics of exposed subjects often differ systematically from those of unexposed subjects. Therefore, one must account for systematic differences in baseline anthropometric characteristics between exposed and unexposed subjects when estimating the effect of exposure on outcomes[6]. The propensity score method may be employed in observational studies to resolve imbalance issues in the anthropometric characteristics between groups. Initially, the confounding factor status is used as the dependent variable and regressed on covariates with the logistic regression model. Thus, the conditional distribution of risk between groups should be the same when the observed baseline characteristics do not present standardised differences[6]. Thereby, similar characteristics for confounding anthropometrics may produce bias in outcomes, if the risk assignment does not account for the covariates that predict the true risk. As a result, risk assignment for anthropometrics such as BMI, waist-to-hip ratio (WHR) or even waist circumference (WC) alone may be systematically biased if the values between the concerned simple measurements do not represent risk equivalence or balanced distribution, and, therefore, the metrics may not be directly comparable. Consequently, if the mathematical equivalence between covariates and propensity scores for anthropometrics are not explored, it will be impossible to ensure a balanced distribution of risk between anthropometrics and groups. Therefore, comparing the anthropometric similarity of healthy and unhealthy cases in a single stratum should begin with a comparison of the means or medians of the simple covariates and the distributions of their categorical counterparts between groups. If, after conditioning on the covariates, there remain systematic differences between means or medians, this would indicate that the propensity score model has not been correctly specified due to unbalancing the distribution of the covariates, and therefore, the true risk assignment[6].

Interestingly, the association of anthropometrics may present effects of bias. Systematic bias may be introduced in results when comparing the baseline differences in high-risk BC or in the measured true risk between groups. Thus, regardless of the strength of association, other criteria for the judgment of causal association – such as biological plausibility, consistency, coherence and specificity – must be respected, keeping in mind that any association may be spurious, indirect or real[7]. To avoid selection bias, all participants, either in the exposed or unexposed groups, must be similar in all important respects except for exposure or disease. Likewise, all anthropometrics may not be optimal for true risk assessment, at least without assessing the simple measurements as covariates and conditioning the risk on the true and predictive variable. Thereby, a lack of balanced distribution for simple measurements or comparing for different high-risk BC are particularly prone to the generation of false-positive results. The mathematical relationship between measurements and the risk equivalence between metrics are key concepts when

specifying whether two indicators are equal regarding a given risk. In fact, anthropometrically-measured risk essentially depends on a high-risk BC. Our interpretation may not be confused by the strength of association of arithmetic indicators that suggest or assume a supposed unverified risk, and where some confounding factor is not an intermediate link in the chain of causation between anthropometric and outcome for the risk association.

2. ANTHROPOMETRIC MEASURES IN PREDICTING MI RISK

Our research work is focused on previous observational studies where measures of association – such as odds ratios, hazard ratios, receiver operating characteristic curves or other statistical models – were used as appropriate, either in case-control or cohort studies [8–21]. Similarly, multivariable analysis with regression models were used where appropriate. Either universally categorised or defined risk cut-offs for anthropometrics were pre-set or calculated by using means (SD), tertiles, quartiles, quintiles or sensitivity/specificity in all comparisons.

Evidence supports that WC is linked to visceral adipose tissue. By deduction, WC is the best simple body measurement that predicts cardiometabolic and MI risk[8,9,11–26]. In addition, an enlarged WC in normal-weight people may indicate a higher MI risk because WC is an indicator of abdominal fat, which is associated with cardiometabolic risk, mortality and recurrent CVD[22,26–29]. However, from the INTERHEART study, WHR appeared to have the best predictive value ahead of BMI and WC[8,13,15,17,19]. Moreover, results from the UK Biobank found that WHR presented a greater excess risk of MI in women than in men[19]. Alternatively, 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 with sex differences[21,25,30–39]. Furthermore, WHtR has been more strongly correlated with %BF and adiposity variables in men than it is with WC[31,32]. Thereby, combining WC and height as volume factors and variables for estimating %BF would constitute an easy measurement for evaluating MI risk, including cardiovascular mortality[18,19,21,31–39].

It is important to note that patients of both sexes assessed by computed tomography have presented better MI risk prediction when visceral adiposity increases and abdominal subcutaneous area decreases[25,30].

Epidemiologically, general obesity, enlarged WC, WHR risk cut-off of <1 and WHtR cut-off ≥ 0.5 have been verified as baseline characteristics for the assessment of MI risk worldwide, even accounting for differences in strength of association and by sex[8–21,31–33]. Similarly, mathematical inequalities between the mean simple measurements, as well as non-equivalent relationships in the ratios, ratios of ratios and risk cut-offs, also may be implicated (Table 1). Thus, data from thousands of MI cases were collated in Table 1, where new metrics have been included as mere mathematical expressions derived from original data, demonstrating the inequality and non-equivalent relationships between the corresponding mean simple measurements. After associating anthropometrics and MI in any study population, the perspective for epidemiological causality should be shifted accordingly since mathematical inequalities and unbalanced distributions between simple measurements may be demonstrated.

Table 1. Risk cut-off points for the association of anthropometrics and MI. Imbalance between the mean values of the simple body measurements where appropriate. Risk cut-off values and mathematical inequality between the corresponding simple measurements and ratios where appropriate. (References: 8-21, 31-33, 46, 47, 49-51).

Anthropometric	Men	Women	Association findings**
Weight (kg)	Undefined (W >(Ht-100)*	Undefined (W >(Ht-100)*	(-) or weak positive
Height (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 (<30)	>25.5 (<30)	Moderate positive
Weight/(Ht-100)	**>1**	**>1**	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
Somatotype (mesomorphy rating)	>4.9	-	Strong positive

BMI indicates body mass index; HC, hip circumference; Ht, body height; HHt/2R, hip-to-height/2 ratio; HtHR, height-to-hip ratio; MI, myocardial infarction; W, body weight; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; WHt/2R, waist-to-height/2 ratio.
*Regardless of risk cut-off values significant inequality between the mean values of the referenced simple measurements and a non-equivalent relationship in the ratios (numerator over denominator) is always ** Measures of association such as odds ratios, hazard ratios, receiver operating characteristic curves or other statistical models were used as appropriate. Means (SD) or medians, tertiles, quartiles, quintiles, sensitivity/specificity and universally categorised or defined risk cut-off points were used in all the comparisons where appropriate (-): Null or not association.
a. Ethnically-specific risk cut-offs (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 cut-offs.
b. Mathematical inequality between the simple measurements and non-equivalent relationships are extracted or extrapoled from the differences between the mean (SD) values described in thousands of participants in most studies worldwide. Source: This table was elaborated and updated by the author, who have the copyright. New metrics mathematically derived from the scientific evidence were included.

3. PRIOR MATHEMATICAL AND ANTHROPOMETRIC CONSIDERATIONS

The standard human body is comprised of different structural components. Not all simple anthropometric measurements are fully valid for estimating the causal risk of MI. Natural mathematical inequalities between the simple body measurements in anthropometrically healthy subjects are evidence from the epidemiological kinanthropometry (Figure 1). From this perspective, weight, height, height/2, WC and hip circumference (HC) represent absolute values with different mathematical relationships between them and without expressing equality for the true risk as a mathematical object. Consequently, in assessing risk association, the mathematical relationships between the simple measurements and the ratios, ratios of ratios or compared risk cut-offs should be recognised (Figure 1 and Table 1). Therefore, an accurate interpretation should be performed on the epidemiological findings for the association of anthropometrics and MI risk after recording the measurement values in anthropometrically healthy subjects[8–21,31–33].

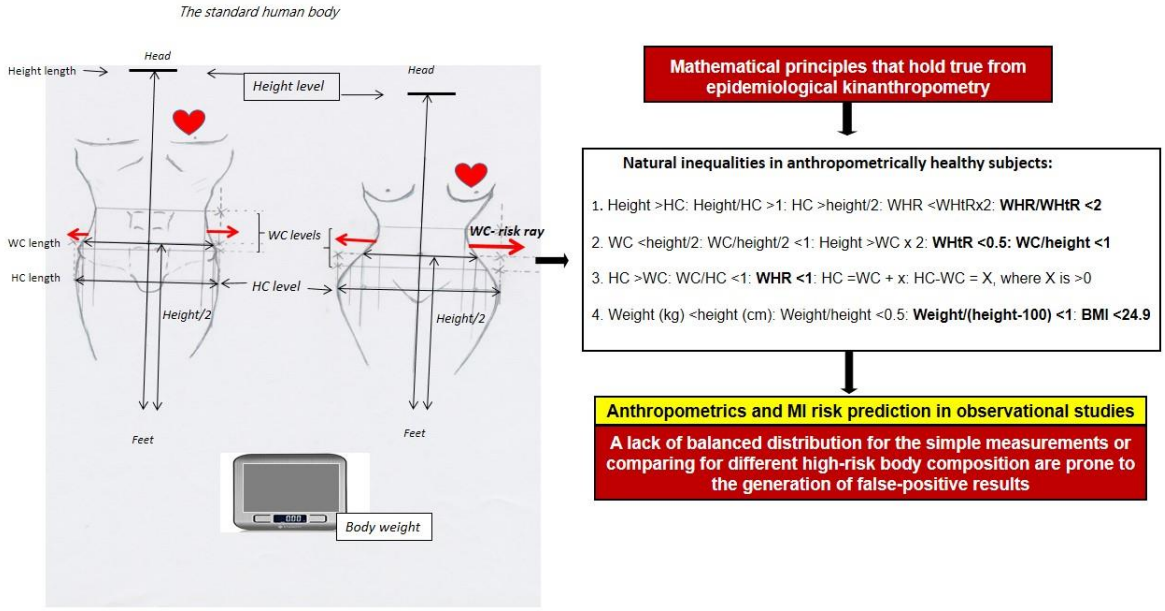

Figure 1. The standard human body and simple anthropometric measurements. Geometrical line drawn for understanding ray of risk for WC as abdominal obesity increases. Mathematical expression that hold true in any anthropometrically healthy population. A key issue in observational studies is framed.
Anthropometrics at baseline would represent absolute mean values per standard deviation for body weight (kg), height (cm), BMI (kg/m²) height/2 (cm), WC (cm), HC (cm), WHR, WHtR, rest of the ratios and X value (cm), being actually valid for any anthropometrically healthy population and ethnicity. On the respective ray of risk for WC (in red color) would lie points of increased abdominal obesity representing biological changes pointing towards greater excess risk of myocardial infarction as WC increases and while height may no condition the true risk measured by WC alone. BMI indicates body mass index, HC, hip circumference; MI, myocardial infarction; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; X, subtracting HC by WC.
* Anthropological and epidemiological evidence support that referred mathematical inequalities between the simple measurements in a standard human body hold true.
Source: The original graphical abstract was investigated and built by the author. Dimensions are not to scale.

Some mathematical inequalities between simple measurements in the human body are central to the comparison of healthy and MI cases. This is because the lack of balanced distribution between the measurements is prone to the generation of selection biases. Similarly, anthropometric ratios between simple measurements often are numerical fractions where mathematical understanding is essential. In this sense, value of the numerator (N) and denominator (D) matter, and ratios with a value of <1 (D>N) are proper abstract fractions where only N is a cardinal number representing a quantity, while D is used in a nominal way[40]. Thus, N and D are different, even though they are represented in the same way. Hence, an anthropometric ratio, while being a proper fraction, is simply a way of representing a size (part/whole) that is not a whole number or quantity of whole-risk. In each fraction, N represents the number of equal parts (or percentage), and D represents the number of parts that the whole (100% or the unity) is divided into. But, each fraction never represents the same whole as that measured by N. On the contrary, when N≥D (improper fraction: ratio with a value of ≥1), N and the fraction represent the same whole with respect to the concerned measurements in the fraction. In anthropometric ratios of ≥1, the simple measurement as N and the ratio as fraction represent the same whole and mathematically depend on N. In this situation, the ratio and N alone as the numerator represent the same whole. But, this does not signify the highest risk BC, which may depend on another predictive variable that is much more capable of capturing the highest true risk.
In this approach, a deep reflection is necessary. Most of the universally used anthropometrics represent fractions (see Figure 1). Similarly, in the risk cut-offs for the association with MI we find imbalances between the simple measurements as well as proper or improper fractions in the different anthropometric ratios (see Table 1). Consequently, association findings for each metric and causality for the true risk are not interchangeable. A thorough interpretation must be performed after collating the mathematical inequalities in the epidemiological findings, to

understand the biases of causal association in universally used metrics (Figure 2).

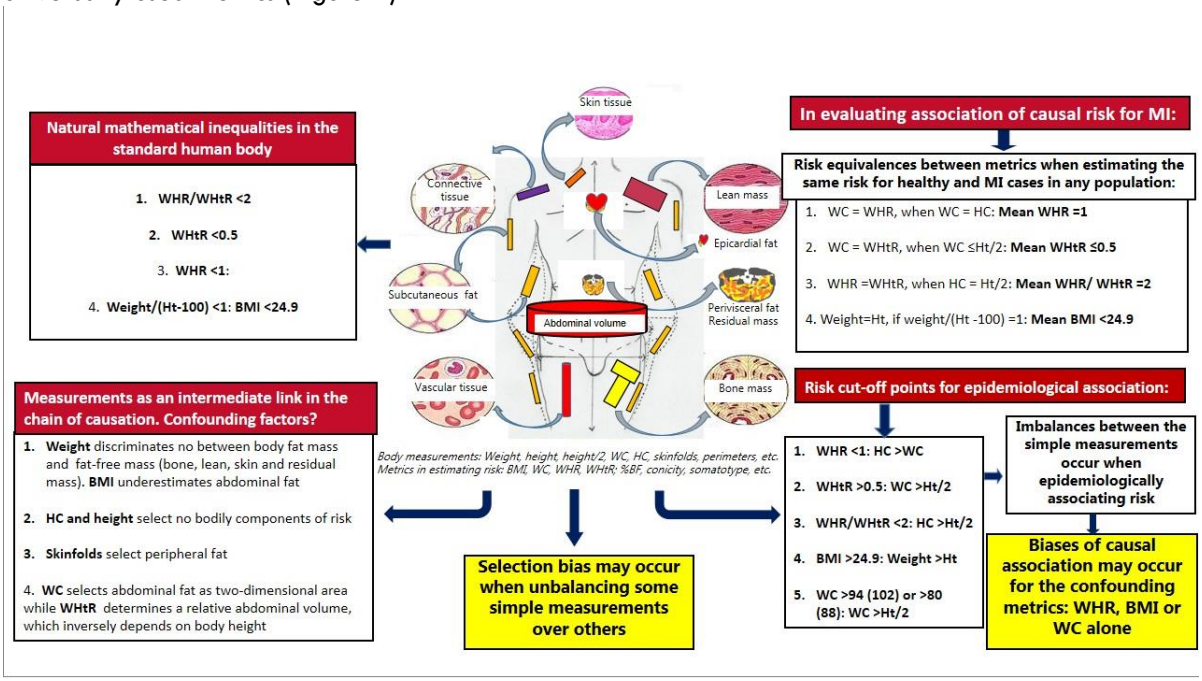

Figure 2. Body composition, bodily components distribution and simple measurements in the human body. Mathematical expressions for understanding inequalities between measurements and risk equivalences between metrics as well as the risk cut-offs for the epidemiological association with MI are framed. Association biases for unbalancing the simple measurements in the risk cut-offs of the main metrics are identified.
BMI indicates body mass index in kg/m², HC, hip circumference in cm; Ht, body height in cm; MI, myocardial infarction; WC, waist circumference in cm; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.
Source: The original graphical abstract was elaborated and built by the author. Dimensions are not to scale. Distribution of components in the human body is a mere representation.

BMI is a metric that relates weight and height through a universal formula (weight (kg)/height (m²). It was developed numerous years ago (in the 19th century) and has not been updated by the current knowledge in science and technology. Nevertheless, dividing weight (kg) by height minus 100 (cm) in all anthropometrically healthy subjects, we obtain a proper abstract fraction (part/whole), where the normal value is <1 (BMI <24.9 kg/m²: the upper limit for a normal weight)[3], (Figure 1). Only when weight is ≥ (height minus 100), we obtain an improper fraction (whole/part) and a value of numerator over denominator ≥1. Any BMI risk cut-off in a recognised degree of overweight/obesity (>24.9) will always be an improper abstract fraction in direct relationship with weight gain[3]. However, in this situation, it is only possible to say that both BMI and weight as numerator represent the same whole, exclusively depending on weight, but never referring to the highest risk BC, which anthropometrically depends on other specific variables that predict the true risk and demonstrate a stronger association than BMI (see Table 1). Thereby, BMI behaves as a confounding index, where the high-risk BC and true risk may not be fully explained by weight in kg and height in m² as numerator and denominator, respectively.

WHR relates WC and HC regarding two parallel dimensions. However, WHR <1 is a proper abstract fraction that describes the equal parts of WC that we have in HC (part/whole), but it shows no consistency or true risk beyond that of WC. This is because WHR <1 is not a whole number or entity of whole-risk as a mathematical object, unlike WC. Only when WHR is ≥1, WC as numerator and WHR represent the same whole. However, the WHR risk cut-off for the association with MI always appear to be found <1 and having a strong association (see Table 1). In this epidemiological situation, an imbalance between the mean WC and HC values when comparing healthy and MI cases justifies a selection bias by protective overestimation of HC with respect to WC, and indicates a higher probability of bias in women[38,39]. Thereby, WHR behaves as a confounding variable, where the high-risk BC and true risk may not be explained by WHR in isolation.

From another perspective, the standard human body usually has a HC higher than height/2 and lower than height (height/HC >1; HC/(height/2) >1), (Figure 1). Hence, there would be no equivalence relation between the WHR risk cut-

off and WHtR when comparing the same true risk, if the first is lower than the second × 2 (WHR/WHtR <2)[31,38,39] (see Table 1). Since the balanced distribution between WC and height/2 and between WC and HC may only be found with risk cut-offs of WHtR =0.5 and WHR =1, respectively, both indices will never indicate the same true risk. Furthermore, it is anthropometrically impossible and epidemiologically spurious[38,39]. Mathematically, WHR and WHtR indicate different risks, if HC and height do not present a relationship of height/HC =2: HC =height/2, which is anthropologically unlikely. Therefore, a selection bias occurs for WHR with respect to WHtR, due to the protective overestimation for HC with regard to height[31,38,39]. It is clear that, if the WHR risk cut-off is lower than WHtR × 2 and WC does not change, then any WHR-associated risk above WHtR would be spurious[39].

Among the simple anthropometric measurements, WC is the only one that measures the abdominal fat including the intra-abdominal fat component. Additionally, WHtR <1 mathematically is also a proper fraction (part/whole) where WC as the numerator and WHtR would never represent the same whole. Only when a hypothetical WHtR risk cut-off is ≥1 (i.e., epidemiologically impossible) and mathematically WC/height = whole/part, WC and WHtR would refer to the same whole, exclusively depending on WC. On the other hand, in anthropometrically healthy subjects WHtR is always <0.5 and the mean WC <height/2 (WC/ (height/2) <1). In this approach, only when balancing measurements and the mean WC =height/2: WC/ (height/2) =1: WHtR risk cut-off ≤0.5 (Figure 2), may we find a risk equivalence between WC and WHtR, and both metrics would express the same whole[38, 39]. Nevertheless, this epidemiological situation is not realistic and most observational studies describe a WHtR risk cut-off >0.5 (mean WC >height/2), (see table 1). Moreover, WC determines a two-dimensional area measurable in cm^2 while WHtR represents the volume (cm^3) of an abdominal disk, where thickness or height of the disk is in WHtR cm (or a multiple of this)[38,39,46]. Thereby, WHtR as relative volume measure will always capture the highest true risk above WC. Thus, if the WHtR risk cut-off is >0.5 and <1, any WC-associated risk beyond that of WHtR would be a false one due to a risk overestimation for WC concerning height[39]. It suggests that individuals with the same enlarged WC and different WHtR may present the same abdominal area but have a different abdominal volume and MI risk. That way, WC may behave as a confounding variable, where WC in isolation may not explain the high-risk BC and all true risk, at least without mathematically accounting for height as volume factor.

4. ANTHROPOMETRICS AND CAUSAL RISK ASSOCIATION FOR MI

Based on the epidemiological evidence, neither a WHR risk cut-off <1 (mean HC >WC) nor a WC risk cut-off when being the mean WC >height/2 (WHtR >0.5) will capture the true high-risk BC because a WHtR risk cut-off >0.5 becomes a volume measure and the entity of true risk. It is at this point when the inequality between WC and height (or height/2) is also significant (Figure 3). This is because WHtR mathematically represents a volume function accounting for two independent factors: WC and height[38,39]. As mentioned above, if, and only if, a WHtR risk cut-off is ≥1 (improper fraction), WC alone as a numerator may indicate the highest true risk of an abdominal area measured without accounting for the height factor. However, this is an anthropological chimera, and furthermore is epidemiologically unrealistic.

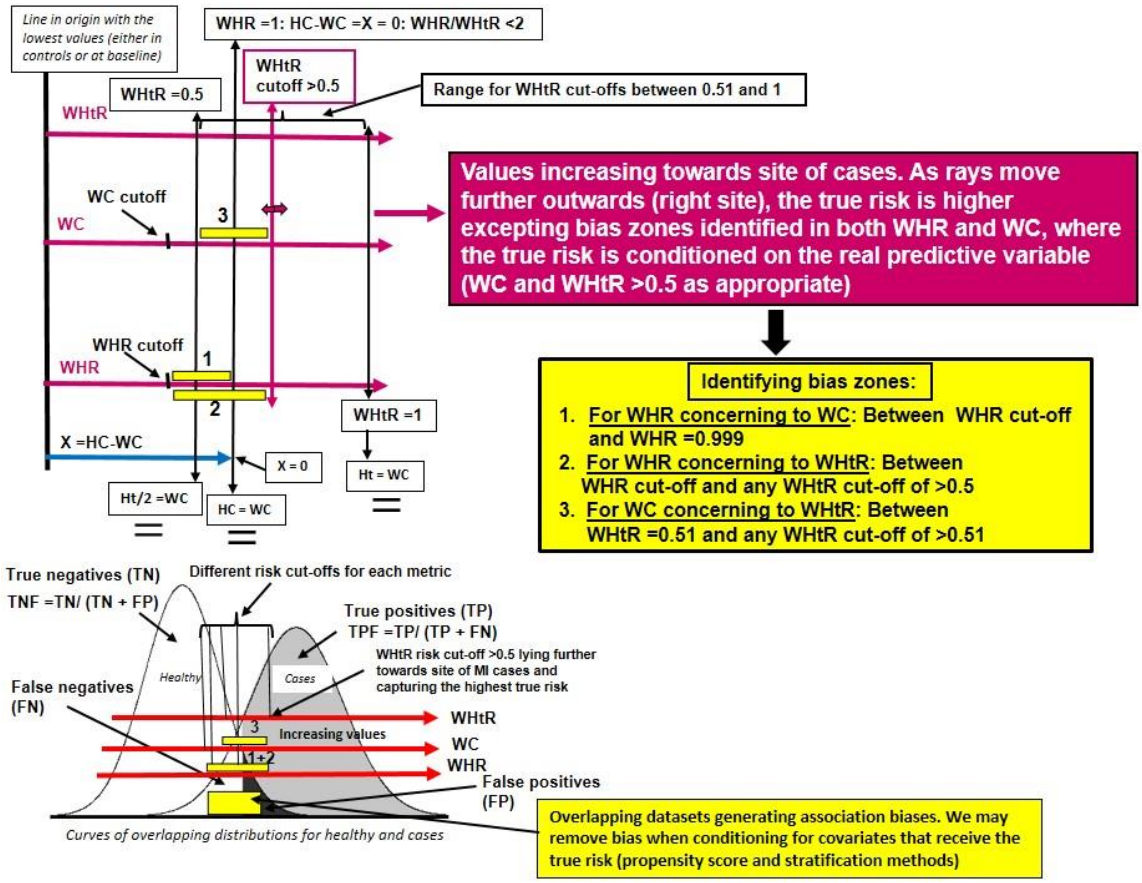

Figure 3. Number lines and anthropometric rays of risk in a Cartesian plane for representing values in healthy population and cases of MI: Metrics-associated risk increases as each ray of risk move to the right (site of cases). Cut-off lines representing different values where appropriate. Subtitled curves of distribution, overlapping area, risk rays and bias zones where appropriate. It is transferable to any study population and ethnicity.
All reference values may be represented lying on the drawn number lines. We may find the points with the lowest baseline values for WHtR, WC and WHR (healthy/controls or unhealthy 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 an arrowhead of the 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 MI cases as appropriate. On the respective risk rays drawn in magenta color would lie points of increased abdominal obesity representing values for thousands of cases of MI 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 (from the maximum positive in their origin up to zero (WC = HC) would be represented lying on the corresponding partial ray of risk (in blue color). 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. HC denotes hip circumference; Ht, body height; MI, myocardial infarction; TNF, true negative fraction; TPF, true positive fraction (sensitivity), WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; X, subtracting HC by WC; =, balanced distribution between concerned simple measurements. Source: The original graphical abstract was designed and built by the author, who has the copyright. Dimensions are not to scale.

In addition, WC and height have also been validated by dual-energy X-ray absorptiometry as the two most significant simple measurements for estimating anthropometrically-measured %BF[41]. In this regarding, WHtR and %BF increasingly seem to be the most important metrics in predicting MI risk, especially in men[31,32,38,39]. Thus, a raised WHtR and %BF have demonstrated anthropometric coherence and describe a balanced distribution for the concrete values of volume by unit of height and body fatness, respectively. Both increased metrics justify MI risk excess. This anthropometric profile could help explain the abundance of MI among individuals with raised visceral fat, irrespective of BMI, HC or weight.

Conceptually, the causal risk derives from the high-risk BC and pathophysiological properties of visceral fat deposits. In this sense, there is evidence to suggest that perivisceral fat deposits (including epicardial fat) that function as a neuroendocrine organ are a causal pathway for

understanding the components of the BC that influence CVD[42–44]. Thus, WC has demonstrated a higher correlation with WHtR than WHR or BMI[13,19,31–33,39]. However, WHR has usually presented a stronger statistical association than WC and WHtR, although those said discrepancies were never discussed before (see Table 1). It is well known that a high-risk BC does not depend on HC, but vice versa. Besides, HC has always presented weak or null association findings[8,15,19,31,33,38,39]. Indeed, after checking that HC is irrelevant with regard to the cardiometabolic risk, the mathematical and anthropometric demonstrations in our research have explained the selection bias for WHR with respect to WC and WHtR, and therefore, revealed that the risk comparison between healthy and MI cases was never the same[31,38,39] (see Figure 3). This is because WC and HC values were always unbalanced in their data distribution, and baseline differences between both values and their intrinsic risk were always ignored, either by age or by sex[39]. In this sense, HC turns to be a confounding factor. In fact, for the first time in predicting MI risk, an assignment of spurious risk for WHR has been demonstrated in men despite it reflecting the highest association[38]. In addition, an association bias of WHR with respect to WC and WHtR mathematically may be demonstrated in any study population[39]. Similarly, the mathematical and anthropometric reasons have been explained as to why WC may never capture higher true risk than WHtR, and both WHR and WC may always present identified bias zones if the WHtR risk cut-off is >0.5 (and <1) due to the selection of true negative values as false-positive ones[39]. This is because WHtR may present a higher true positive fraction than WC and WHR, and preclude to select many false-positives due to quantifying a higher relative volume as WHtR increases (Figure 3)[38,39].

Regarding BMI, most studies have demonstrated a moderate association to MI (Table 1). It is in consonance with a weaker association for weight and height than for WC, with weight being an overall poor predictor for MI[31,33,39,45,46]. Additionally, a BMI risk cut-off >24.9 only means that weight and BMI represent the same whole, but do not necessarily refer to the true BC of risk or whole-burden of specific cardiometabolic risk. In this line, since BMI captures total body mass (kg) and height does not correlate with body fat, neither peripheral nor intra-abdominal fat (lower density and higher volume) will be the main factor expressed by this index. This is because the densities for musculoskeletal and body fat components are different, and BMI will always express the unit of mass as a numerator, but never measuring a volume index nor correctly estimating the metabolically unhealthy intra-abdominal fat[39,45,46]. In this sense, in identifying high-risk BC, weight is a confounding factor, at least while WHtR is >0.5 and any calculated BMI risk cut-off reflects moderate levels of overweight[3] (see Table 1).

Anthropometrically, BMI and WHR appear to be strongly linked to the musculoskeletal component, and more weakly correlated with WC and %BF than WHtR[13,19,31,32,46]. Thus, either BMI or WHR have always reflected an information bias about the true risk, and a misleading evidence would be accepted if the BC was not correctly interpreted when weight and HC behave as confounding factors, making the associated true risk more difficult to identify[31,32,38,39,46].

It is important to note, general obesity adversely influences MI by worsening CVD risk factors. However, after reviewing epidemiology, we warned some key observations. Since weight factor is less sensitive in capturing high-risk BC, it is clear that abdominal obesity measured by WHtR is detected earlier than obesity measured by the current BMI criteria (BMI ≥30 kg/m^2). This statement is based on epidemiological distribution curves of the main anthropometrics, where abdominal obesity metrics such as WHR, WC or WHtR capture associated risk before the general obesity criterion. This is because any BMI risk cut-off is always found to be below that of 30 kg/m^2. In this sense, while body fat is accumulating over time, an increase in the abdominal volume and BC of risk may be detected before BMI reaches the degree of general obesity.

5. DISCUSSION

We examined previous literature on the association of anthropometrics with thousands of MI cases worldwide. Our research mathematically and anthropometrically demonstrates that a misleading evidence has confused the cardiovascular sciences when errors of bias and other criteria for judgment of causal association were overlooked.

The anthropometric robustness of linking BMI and WHR to the high-risk BC and MI risk is unclear and diffuse. Besides, both indices may present information bias about the individual risk. Conceptually, each of them provides its own meaning without a verifiable associated causal risk beyond that of WC. Nevertheless, only a rigorous interpretation of removing bias and applying biological plausibility criteria could avoid confusing or paradoxical conclusions, independently of other non-anthropometric risk factors that influence MI risk.

On the other hand, in observational studies, along with measures of statistically significant association, it is necessary to look for the presence of selection and information bias as well as confounding factors[7]. For the first time in predicting MI risk, association biases for some metrics have been demonstrated, and confounding factors such as HC and weight have presented a poor discriminatory power that would affect the real outcome for WHR and BMI, respectively[31–33,38,39,46]. By contrast, height does not correlate with adiposity measures[19, 31] and it may not be directly involved in the causal pathway. Nevertheless, the real outcome for WC in isolation may be affected, if the height factor turns to be ignored when estimating the true risk[31,32,38,39,46]. Hence, in evaluating outcome of association for any metric, it is essential to recognise the mathematical relationships between simple measurements and metrics and the anthropometric consistency for the true risk as well as the biological plausibility.

After reviewing most of the studies, BMI has demonstrated a moderate association with MI; however, this is always below that of WHR and WC[8,13,15,17,19,31,32,46]. Moreover, BMI has presented an inverse association with mortality in subjects with MI, and presents a U-shaped association with the nadir among overweight or obese subjects, which has been termed the obesity paradox [29,47,48]. Nevertheless, evidence supports the suggestion that BMI strongly depends on a metabolically healthy musculoskeletal component and body fat mass, especially of the subcutaneous, without distinguishing the metabolically unhealthy intra-abdominal fat[32,33,39,41–46]. Why should BMI be chosen to assess MI risk if the weight factor captures metabolically contradictory components? The consequence of this chimera is that to describe individuals at risk based on BMI is unfounded and potentially misleading. Accordingly, the concepts of cardiovascular health and BMI-classified obesity should not be considered synonymous or interchangeable, otherwise we accept misclassification and paradoxical information[39,46]. It is clear that, while a part of the healthy component of the weight and mesomorphy rating may be artificially associated to MI without being a pathophysiological causal pathway, as %BF increases (higher relative volume), a part of the BMI-associated risk may be spurious and, therefore, falsely correlated either with age or with sex[32,39,45,46]. The excessive body weight in individuals who have a moderate–high BMI and normal %BF would indicate a score of spurious risk, but this would never indicated a worse degree of health, unless their baseline characteristics of true risk change over time.

Conceptually, BMI neither distinguishes bodily components (body fat and fat-free mass) nor distinguishes the distribution of subcutaneous and perivisceral fat. In addition, BMI fails to reveal the true BC of risk due to an underestimation of the abdominal fat volume and by assigning spurious risk to a part of the mesomorphy component[39,45,46]. Besides, body weight as a confounding factor makes BMI less sensitive to changes in measures of abdominal obesity or increases in lean mass. Thus, in two overweight-mesomorphic individuals with different intra-abdominal fat contents, the same BMI would underestimate the higher fat volume in one of them. This observation means that BMI produces greater impact and bias in men due to it capturing a dimension of spurious risk beyond that of women[39].

A matter of further consideration is how accept the obesity paradox without defining the structural risk component to measure or other nutritional risk criteria? [49]. The obesity paradox would not be real, but an inaccurate choice of the metric, which does not take into account other nutritional control criteria and the main causal link for the risk (the visceral fat) [42–44]. Besides, in the universalised U-shape, mortality in underweight (by malnutrition status and low lean muscle mass) and normal weight subjects is not interchangeable with the chain of causation by increased BMI and outcome. It is clear that very high BMI values provide a better description of body fat excess and, therefore, higher health risk. However, fat and protein stores as well as nutrition status and preserved muscle mass after MI affect health and survival with different impacts. Regardless of BMI, the higher the abdominal fat volume and WC, the higher the true risk and mortality, at least over a time of effect continued after MI [20,29]. In this line, body weight and WC as absolute simple measurements have never demonstrated a similar level of predictive risk[8,9,11–26,31,33,45,46], and any BMI risk cut-off >24.9<30 versus WHtR >0.5 mathematically will never express the same concept and high-risk BC when compared. Therefore, BMI as a continuous numerical variable never meets the criteria to be an optimal metric above WC, WHR, WHtR and %BF, either by capturing spurious risk or showing a weaker–moderate association than those[8–21,31–33,39,45,46]. In this sense, there will be a misleading assumption of risk for categorised risk cut-offs of overweight/obesity when the true high-risk BC or abdominal obesity volume are not measured, which will provide a false conclusion for the associated real risk, or at least it will produce

paradoxical and biased information. This is because weight loss or weight gain do not exclusively affect the unhealthy bodily components that influence nutritional status and health risks. BMI was originally described without accounting for pathophysiological properties of the adiposity visceral[42–44]. In addition, all the calculated BMI risk cut-off points statistically are in overweight range when collating association with MI (see Table 1). Thereby, the overlapping area in the BMI distribution curves always coincides in a range where BMI is a confounding variable, and therefore, the assignment of risk in that stratum may be spurious if it is not conditioned on a balanced distribution for weight and height and another more predictive covariate receiving the true risk[6]. Consequently, if our observation is not explored with a valid method such propensity score, it will be impossible to ensure an equal assignment of true risk between subjects who have similar BMI values.

In most studies, WHR had the best predictive value among other indices [8,13–15,17,19,21,31,45,50,51,52]. Surprisingly, the WHR cut-off was always <1 and/or WHR/WHtR <2 in both sexes while selection biases were never discussed[39]. Why was the presence of biases not looked for when the WHR risk cut-off is <1 (proper fraction), and therefore, never referring to the whole-risk as a mathematical object? Why, when WHR <1 was the causal relationship between HC and adverse MI outcomes not clearly elucidated? Why were the mean values for HC and height (or height/2) as mathematical objects in all comparisons overlooked? When unbalancing measurements and accepting imbalances in the risk cut-offs, selection bias may occur in the causal association. Mathematically and anthropometrically, an association bias of WHR with respect to WC and WHtR have been demonstrated in men, and besides, it may be explained with Cartesian demonstrations in both sexes[31,38,39] (see Figure 3). Indisputably, the imbalance between measurements when comparing healthy and MI cases provides an overestimation or underestimation of some measurements over others. Thus, when the WHR cut-off is <1 and WHR/WHtR <2, we find a protective overestimation for HC with respect to WC and height, respectively. Otherwise, only if the WHR risk cut-off is ≥1 and WHR/WHtR ≥2 would we obtain balance and, therefore, the same estimation of risk for WC with respect to HC, and for height with respect to HC, respectively[39] (see Figure 2). Unfortunately, this epidemiological situation is unrealistic and it only would occur in unrepresentative population samples.

To our knowledge, mathematical inequalities between the simple measurements in the anthropometrically healthy subjects were ignored (WC ≠ HC ≠height; WC ≠height/2 ≠HC; WHR ≠WHtR x 2) and, therefore, the statistical association for the causal risk was always biased. This is because baseline values for WC, HC and height neither conceptually nor anthropometrically involve the same causal risk. Besides, epidemiologically, we always find a mean HC >WC >height/2, and WHR/WHtR <2, so the mean HC in any risk cut-off is always higher and lower than WC and height, respectively. Similarly, in most observational studies, the mean WC is always higher than height/2 (WHtR cut-off ≥0.5) (see Table 1). We would always assign a protective overestimation for HC with respect to WC and height, as well as a risk overestimation for WC concerning height in the tallest subjects or an underestimation in the shortest, including sex differences[38,39,46]. Hence, while collating imbalances between the said measurements and statistically associating MI risk, any WHR-associated risk beyond that of WC and WHtR should be checked for bias and causal association. Similarly, the same issue occurs when WC-associated risk reflects a higher strength than that of WHtR, irrespective of sex[39].

On the other hand, in order to identify MI risk by measuring WC alone, another important issues lies in the volume that represents WHtR[32,38,39,46]. Only when WC and height/2 are mathematically equivalent (mean WC =height/2: WHtR risk cut-off =0.5), is there a notion of equality and balance for the same estimate of risk from WC and WHtR. When the WHtR risk cut-off is >0.5, there is an inequality between WC and height/2, and only WHtR as a concrete volume measure may be used to draw a valid conclusion for estimating the highest true risk. Thus, in any study population, if the mean WC >height/2 risk overestimation occurs for WC respect to height, WC alone will present a risk overestimation in the tallest people and an underestimation in the shortest. As said above, a WHtR cut-off >0.5 and <1 is a proper fraction and expresses a relative volume measure, but WC as a numerator never refers to the entity of whole-risk as a mathematical object. Quite the opposite is the case; the higher the WHtR, the higher the risk overestimation for WC as compared to WHtR. Similarly, the higher the WHtR, the higher the probability of bias for WC, and if WHtR does not indicate true risk, WC might capture a false risk beyond that of WHtR[39]. Hence, while collating differences between area and volume as WC and WHtR, respectively, any WC-associated risk above WHtR should also be checked for bias and causal association. While

WHtR <0.5 holds true in healthy subjects, any risk cut-off for WC and WHtR ≤0.5 will express the same risk in any study population. On the contrary, when a WHtR risk cut-off >0.5 is an epidemiologically true premise, WC as the area and WHtR as a relative volume measure will never express the same whole-risk as a mathematical object. In this situation, in the assignment of true risk, only WHtR from its own risk cut-off fulfils causality criteria without yielding bias[39].

Epidemiologically, while shorter stature may be significantly associated with cases of MI (WHtR risk cut-off >0.5) and the mean values of HC are higher than both WC and height/2 (WHR <1: WHR/WHtR <2: HC >WC >height/2), WHtR will always capture the highest dimension of risk above WC and WHR. This is because WHtR in any risk cut-off >0.5 and <1 represents a concrete volume measure of one abdominal disk of WHtR cm of thickness, which is a whole number (volume in cm^3) that indicates a higher biological risk dimension than that of WC alone[39]. Similarly, a determined abdominal volume of risk may be quantified from the sum of the volume of several disks together and each one with the same thickness (WHtR cm) and similar area of the base ($\pi r2$, where WC $=2\pi r$: r $=WC/2\pi$)[38,39,46]. Therefore, when the unbalanced distribution between the simple measurements may be checked and the true risk may be conditional on the real predictive variables (WC or WHtR >0.5 as appropriate), WHtR becomes the gold standard for a correct risk assessment. It is mathematically clear; the same values of risk for WC between different individuals with the same ethnicity and sex refer to a similar risk from WHtR, if, and only if, the mean WC is ≤height/2 (WHtR cut-off ≤0.5) with no important differences existing in height. Nevertheless, this epidemiological situation is not realistic, and most studies show the mean WC >height/2 (WHtR cut-off >0.5) and, therefore, there are significant differences when comparing WC and height (see Table 1). Therefore, in different studies, a spurious risk might be artificially slanted towards the group of cases in metrics such as BMI, WHR or WC, if our observations were not confirmed[8,13–15,17,19,21,50–52].

Our demonstrations are a touchstone on the risk associated to WHR and WC from many studies in cardiovascular research, so universal recommendations made regarding WHR and WC alone for determining abdominal obesity and substantially increased risk of metabolic complications may turn out to be fallacious or at least presenting information bias[22–24]. It is clear that, when a WHR risk cut-off <1 or WC alone are used as measures of higher association in a large study population, it will be impossible to distinguish the highest BC of risk and relative volume, at least without accounting for the height factor and a defined WHtR risk cut-off. Since a part of the assigned risk for WHR and WC may be spurious, the conclusion for the true risk prediction will be spurious due to the fallacious argument. Similarly, the assumption of true risk for categorised risk cut-offs of overweight/obesity without measuring the true BC of risk or abdominal obesity volume will be a misleading proposition, which will provide a false conclusion for the associated causal risk, or at least with paradoxical information and bias[39].

It is worthy to note that the universally categorised risk cut-offs for metrics – such as BMI ≥25 (overweight/obesity)[3], WHR ≥0.90 in men and ≥0.85 in women (<1 in both sexes)[23], WC >94 (102) in men and >80 (88) in women[22–24], and WHtR ≥0.5 in both sexes – may provide confounding and association biases for the causal risk. This occurs when a spurious risk assignment is artificially slanted in the direction of the group of cases in the overlapping areas of the confounding metrics or from their established risk cut-offs. At the same time, in the overlapping areas, subjects with similar baseline values for these metrics must present different risk assignments conditional on the imbalances between the simple measurements and accounting for the covariates that predict the receiving true risk[39].

The risk captured by each metric depends on its sensitivity, specificity, consistency, coherence, biological plausibility and anthropometric validity, rather than on its strength of association with respect to other metrics. Therefore, when ignoring bias in research, false inferences could be drawn to predict MI risk in both sexes. Mathematically and anthropometrically, only WHtR-associated risk above BMI, WC and WHR will hold true while considering it as a relative abdominal volume linked to a pathophysiological causal pathway of higher cardiometabolic risk, and therefore, biologically more plausible[38,39,42–46]. Broadly speaking, it would occur while the degree of accumulated adiposity still determines a homogenously distributed body fat volume. A continuous and dynamic process of body fat accumulation over time provides anthropometric changes that are measurable in body shape before BMI reaches the degree of obesity[3]. Otherwise, a very high degree of adiposity would involve a higher risk and non-homogeneously distributed volume excess, which, therefore, is not faithfully measurable from WC and height. In any case, a high degree of fatness will always highly correlate with perivisceral adiposity, WHtR, %BF and somatotype risk components[21,31–33,40–46]. From our research work,

abdominal obesity and BMI-defined obesity will never be equivalent to assess the high-risk BC. Besides, WHtR as proxy of adiposity that has higher biological plausibility will always predict MI risk before other anthropometrics showing biases and lower sensitivity[31,32,38,39,46].

Our findings have both internal and external validity, and mathematically and epidemiologically satisfy the scientific criteria for justifying that WHtR better meets causality criteria than other metrics. In addition, a classification of WHtR categories from normality to a severe degree or even morbidity (0.4<0.5/≥0.5≤0.55/>0.55≤0.6/0.6+<1/(>1) may be important because it refers to a different abdominal volume of risk as WHtR directly increases, unlike BMI, WHR and WC alone. Consequently, all simple body measurements should always be checked in data analyses to preclude a different–equal risk assignment between subjects who have equal–different high-risk BC. Thus, in assessing a true risk association, discussion should end once the imbalance between the simple measurements is verified, checked for confounding factors and biases, conditional on each metric regarding the truer predictive variable.

6. CONCLUSION

In our research work, association biases in predicting MI risk in both sexes mathematically and anthropometrically have been demonstrated. BMI is a mathematical fraction, which demonstrates a sub-optimal MI risk prediction due to a confounding factor such body weight. Without accounting for a covariate that predicts receiving the high-risk BC, BMI may present paradoxical and biased information. Mathematically, WHR always appears to be a confounding variable with respect to WC and WHtR due to differences in the mean WC and HC values, and HC and height/2, respectively, either between groups or by sex. This is because epidemiologically there is always a WHR risk cut-off <1 and WHR/WHtR <2. 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 in the mean WC and height/2, comparing either by group or by sex. Mathematically, it occurs if, and only if, the WHtR risk cut-off is >0.5, therefore creating an overestimation of risk for WC with respect to height in the tallest people and underestimation in the shortest, and besides, epidemiologically without accounting for a relative volume of risk by unit of height.

Anthropometrically, any association of MI risk for WHR beyond that of WC and WHtR becomes mathematically biased, anthropometrically inconsistent, and biologically less plausible and epidemiologically a false one. In brief, WHtR as relative volume measure yields no bias and is biologically more plausible and consistent; it may capture a dimension of risk above WC. This only happens when height shows an inverse association with MI status and significant differences between the mean WC and height/2, and besides, the WHtR risk cut-off is >0.5.

7. RECOMMENDATION

Following the past decades of medical research on anthropometrics, our findings should be extended to the broader scientific community for the advances regarding adiposity and MI risk prediction. These findings will help avoid bias in research as well as in clinical practice.

By using non-optimal metrics, public health goals may be impacted by inaccuracies and biased information. Thus, monitoring ideal cardiovascular health by measuring BMI or WHR or WC in isolation will always be less accurate than using relative abdominal volume measure indirectly obtained from WHtR. Clinical and research protocols in cardiovascular sciences should be changed because using misleading metrics will lead us remaining anchored in the past.

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