

A Critical Thinking: Why When Using Anthropometrics in Predicting Myocardial Infarction Risk Medical Research and Cardiology were Always in Error? Arguments Evidencing Biases

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ABSTRACT

Cardiovascular diseases (CVDs) mainly heart disease and stroke are the leading causes of death globally. Obesity is a major risk factor for myocardial infarction (MI). However, how to measure whole-risk with simple baseline anthropometric characteristics? Anthropometrically, association for metrics does not equate causation on incident MI/CVD. Besides, a different body composition between groups with similar baseline confounding variables may provide false-positives in outcomes. Thus, in predicting whole-risk all metrics are not entirely valid, and the lack of balance between the simple body measurements will be particularly prone to the generation of false-positive results. Baseline characteristics of thousands of MI cases are well known, but anthropometry and mathematics have taught us novel something. Thus, our findings reveal that anthropometrically-associated risk would appear biased if metrics to compare had no balance and equivalence relation for the whole-risk. WHR and waist circumference, present association biases when whole-risk is not conditioned on the covariate that receives true-risk. It occurs for unbalancing body measurements when healthy and cases were compared worldwide. It is clear, in any risk cutoff for $WHR < 1$ and $WHtR > 0.5$ is always fulfilled: $HC > WC > height/2$, and therefore occurring protective overestimation of hip circumference respect to waist circumference and height as well as risk overestimation for waist concerning height. Only waist-to-height ratio as being directly associated to a relative volume of risk yields no biases and should be the metric correctly used to predict the anthropometrically-measured whole-risk in both sexes. Our arguments are mathematically demonstrable.

Keywords: Myocardial infarction, cardiovascular disease, risk prediction, obesity, anthropometric, bias.

INTRODUCTION

Cardiovascular diseases (CVDs) mainly heart disease and stroke are the leading causes of death globally [1, 2]. Besides, obesity is a major risk factor for CVD included coronary artery disease. However, overweight/obesity are defined as abnormal or excessive fat accumulation measured by the body mass index (BMI) [3], but it may not correspond to the same degree of fatness and metabolic health in different individuals [4]. Thus, from the INTERHEART, largest studies in predicting myocardial infarction (MI) risk have used different anthropometrics, and waist-to-

hip ratio (WHR) appeared to have the best predictive value [5, 6, 7, 8]. In addition, in the UK Biobank study WHR has showed a greater excess risk of MI in women than in men [8]. However, bias errors when comparing healthy and cases were never discussed, neither in case-control nor in prospective studies. Interestingly, anthropometrics-associated risk may present effects of bias rather than the true putative risk may be responsible for all or much of the epidemiological causality. Besides, baseline differences on the body composition (BC) between-groups to be compared may introduce systematic bias in results. Similarly, a different BC between groups with similar baseline confounding variables may provide bias if the true-risk assignment does not account for the covariates that predict receiving true-risk. In this sense, the notion of mathematical equality in the estimate of whole-risk for the different simple body measurements should be respected when comparing healthy with MI/CVD cases. If not, the lack of balanced distribution will be particularly prone to the generation of biases. On this issue, balance between measurements and mathematical equivalence relation between anthropometrics are a key concept for specifying whether two indices/ratios are the same with respect to a given whole-risk. Thus, among measurements, body weight, waist circumference (WC), hip circumference (HC) and height represent different value and concept when assessing MI/CVD risk. Indeed, evidence supports that BMI has never demonstrated optimal MI/CVD risk prediction [5-12]. Moreover, it is well known BMI underestimates abdominal obesity. Really, BMI has not the importance of being optimal anthropometric in predicting MI risk. This is because to a large extent it depends on musculoskeletal component, which may be artificially associated to MI cases. In this line, WHR also depends on gluteal-femoral component and it has always presented the highest association for MI risk in both sexes [5-9]. On the other hand, WC is the strongest simple metric linked to abdominal obesity and cardiometabolic risk. Thereby, what would be the role of both HC and height when using WHR and waist-to height ratio (WHtR), respectively? Mathematical understanding of this concept turns out to be key to detecting the whole-risk and true unhealthy BC [13].

ANTHROPOMETRIC AND MATHEMATICAL CONSIDERATIONS

On this perspective, simple anthropometric measurements represent absolute values without expressing equality for the whole-risk as mathematical object. Consequently, in assessing anthropometrics-associated risk, some key questions should be taken in mind by the researchers. Thus, in the standard human anatomy four arguments hold true: 1. Body weight differentiates neither BC of risk nor abdominal obesity volume. 2. HC is higher than WC ($WHR < 1$: $HC = WC + X$, where subtracting HC by WC we calculate a "X" positive value higher than zero, and being their standard value higher in women than in men. 3. Height is higher than HC ($height/HC > 1$: $HC > height/2$: $WHR < WHtR \times 2$: $WHR/WHtR < 2$), and 4. WC is lower than $height/2$: $WHtR < 0.5$ (Figure 1). Mathematically, these natural inequalities should be respected when predicting MI/CVD risk. Otherwise, bias error will occur if some measurements being overestimated or underestimated over others.

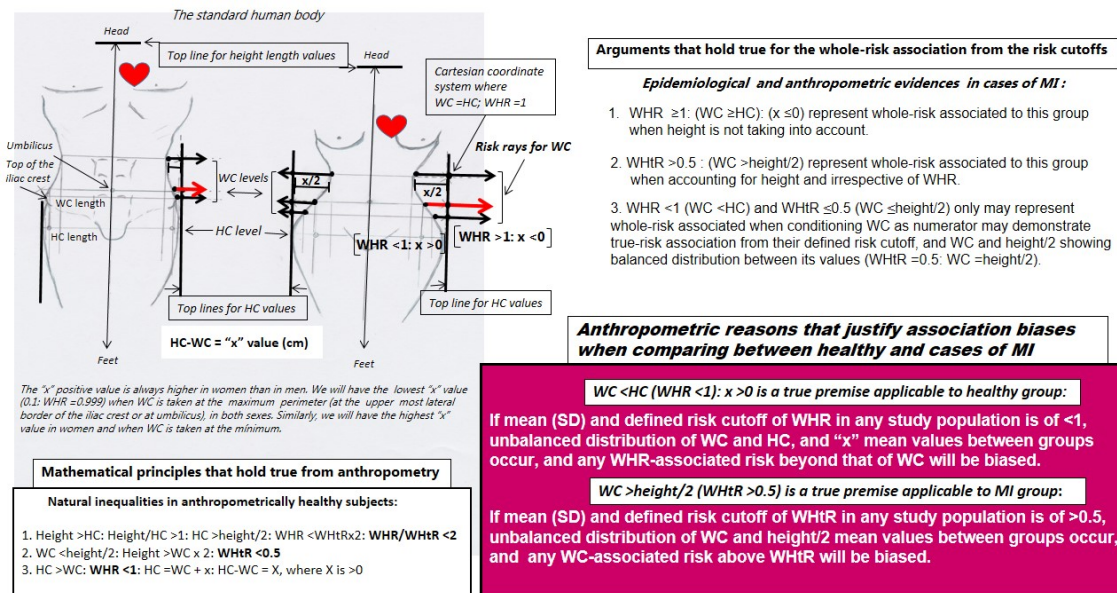


Figure 1. The standard human body and anthropometric measurements. Geometrical lines drawn for understanding metrics and rays of risk for WC. Mathematical principles as well as epidemiological and anthropometric arguments that hold true in both healthy and MI subjects

Measurements at baseline would represent mean values per standard deviation for height, WC, HC, WHR, WHtR and "x" distance being actually valid for any anthropometrically healthy population and ethnicity. On the respective rays for WC would lie points of increased abdominal obesity representing mean values (SD) for thousands of cases of MI as well as biological changes pointing towards greater excess risk as WC increases and while height condition not the whole-risk measured by WC alone. HC denotes hip circumference; MI, myocardial infarction; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; X, subtracting HC by WC. Original built by the author. Dimensions are not to scale.

To our knowledge, WHR and WHtR should have a critically correct reading. Mathematically, while being $HC > WC$ ($WHR < 1$) we have an abstract fraction and a way of representing size (part/whole) that is not whole number for the whole-risk (information bias), unlike of WC. Obviously, between any WHR risk cutoff of <1 and 0.99 value (overlapping zone between healthy and cases) we could find infinite number of fractions receiving risk-code for WHR, but not necessarily referring to the same whole-risk as WC measured (as an example, 93.1/98 vs. 93.9/98 vs. 95/100, etc., =0.95: $HC > WC$ in all, but different WC in each one) [9, 13]. Thus, WC and WHR would mathematically be equivalent for the same estimate of whole-risk if and only if mean $HC = WC$, and therefore, WHR risk cutoff =1 being the entity of whole-risk. In addition, only there would be a true-risk from any WHR cutoff (including values of <1) when WC as numerator effectively predicts receiving whole-risk and being above their own risk cutoff. If not, in the stratum of $WHR < 1$ false-positive values may be selected as whole-risk for WHR when they merely represent protective overestimation for HC concerning WC [9, 13]. In another order, the mean HC as being higher than height/2 precludes a equivalent whole-risk between WHR and WHtR if the first is lower than double of the second. Moreover, since the balanced distribution between mean WC and HC on the one hand, and between WC and height/2 on the other hand only may be found on values of $WHR = 1$ and $WHtR = 0.5$ (WC

=height/2), respectively, both indices will never capture the same whole-risk. This is because risk cutoffs for both could never anthropometrically coincide (Figure 2). Mathematically, only when the mean WC takes the same value as both HC and height/2 will occur a balanced distribution, and either WC or WHR=1 and WHtR=0.5 capturing the same whole-risk. However, distribution curves and risk cutoffs there where the mean values for WC, HC and height (or height/2) might coincide were never presented because it is anthropometrically impossible, and besides, epidemiologically a false one (Figure 2, Table 1) [13].

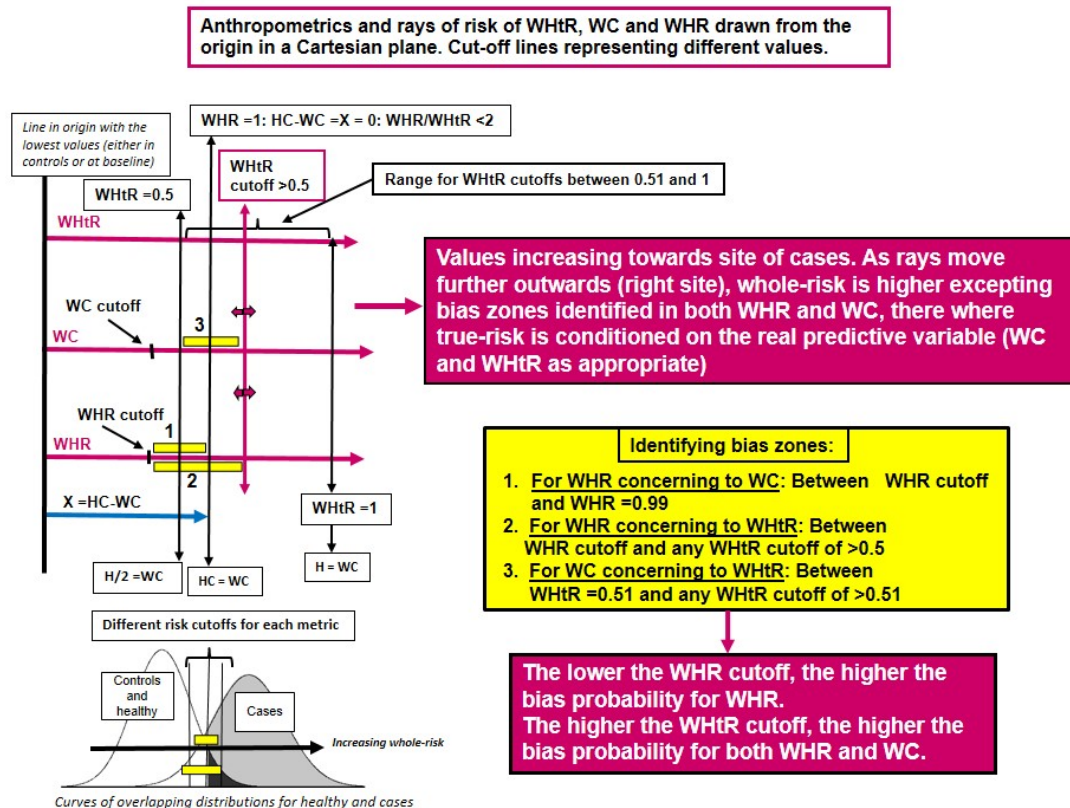


Figure 2. Geometric and number lines in a Cartesian plane for representing values in healthy and cases of MI. Subtitled curves of distribution as appropriate. This is transferable to any study population

Table 1. Defined and undefined risk cut-off points for the association of anthropometrics and MI. Unbalance between the mean values of the simple body measurements where appropriate. The risk cutoff values and mathematical inequality between measurements are extracted from thousands of MI cases worldwide [5-12]

Anthropometrics	Men	Women	Association findings**
Weight (kg)	Variable/undefined values	Variable/undefined values	(-) or weak positive
Height (cm)	Undefined (height >HC >WC)*	Undefined (height >HC >WC)*	(-) or weak inverse
HC (cm)	Undefined (HC >WC >height/2)*	Undefined (HC >WC >height/2)*	(-) or weak positive/inverse
Height/2 (cm)	Undefined (WC >height/2)*	Undefined (WC >height/2)*	(-) or weak inverse
HtHR: (height/HC)	Undefined (WC >height/2)*	Undefined (WC >height/2)*	(-) or weak positive/inverse
HC/height/2	Undefined (WC >1 (height >HC)*	Undefined (WC >1 (height >HC)*	Strong-moderate positive
WC (cm)	>1 (HC >height/2)*	>1 (HC >height/2)*	Moderate positive
BMI (kg/m ²)	>94 (102): (WC >height/2)*	>80 (88): (WC >height/2)*	Strong positive
WHR	>26.5	>25.5	Strong-moderate positive
WHtR	$\geq 0.90 < 1$ (HC >WC)*	$\geq 0.80 < 1$ (HC >WC)*	Strong-moderate positive
WHt/2R:	≥ 0.5 (height >WC >height/2)*	≥ 0.5 (height >WC >height/2)*	Strong-moderate positive
WC/(height/2)	>1 (WC >height/2)*	>1 (WC >height/2)*	Strong positive
WHR/WHtR	<2 (WHR <WHtR x 2)*	<2 (WHR <WHtR x 2)*	Strong positive

BMI indicates body mass index; HC hip circumference; 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 inequality between the mean values of the simple measurements and a non-equivalent relation in the ratios is always found.

** In all studies, measures of association such as odds ratios, hazard ratios, Receiver Operating Characteristic curves or other statistical models were used as appropriate
(-): Null or not association

^a Ethnically-specific risk cutoffs (either numerical or 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 Inequality between simple measurements and non-equivalence relations are collated from the significant differences between their mean (standard deviation) or median values already described in most studies

All reference values may be represented lying on the respective lines drawn. We may find the points with the lowest baseline values (healthy or controls) lying on a respective line in the origin. Similarly, risk cutoffs and cutting lines lying where appropriate. The highest baseline values (unhealthy or cases) would lie on the arrowhead of the rays of risk moving further outwards (site of cases). Other points would represent mean values per standard deviation for WC, HC, height, height/2, WHR and WHtR being actually valid for any study population and ethnicity. In the respective lines and risk rays drawn 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 captured whole-risk. We have 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) on datasets when pooling healthy and cases. Curves of distribution between healthy and cases are represented for a better understanding of biases. The model plotted may be applied for both case-control and cohort studies. H denotes 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.

Original built by the author

In another conceptual consideration, the higher the abdominal obesity, the higher the excess risk of MI/CVD. However, when comparing between-groups abdominal obesity may be expressed either in cm^2 (two-dimensional area determined from WC length) or cm^3 (volume of an abdominal disk determined from WC and height of the disk= WHtR cm) (Figure 3). On this insight, WC and WHtR express not the same whole-risk when comparing healthy and cases. This is because $\text{WC} < \text{height}/2$ ($\text{WHtR} < 0.5$) is a natural inequality. In that way, only if $\text{mean WC} = \text{height}/2$ ($\text{WHtR risk cutoff} = 0.5$), WC and WHtR refer to the same whole-risk. However, when mean WC increases above height/2 ($\text{WHtR risk cutoff} > 0.5$), the distribution of WC and height/2 appears unbalanced between healthy and cases, and only WHtR as entity of concrete volume may capture the whole-risk conditioned on both WC and height. Otherwise, if we accept WC alone as anthropometrically-measured whole-risk will occur a overestimation of risk for WC concerning height or protective underestimation of height respect to WC [9, 13].

EVIDENCING ASSOCIATION BIASES

On this issue, we have warned of biases in large previous studies from the INTERHEART until the CONOR [5-7]. Similarly, in largely white population from the U K Biobank [8] we have demonstrated bias of WHR and WC when simple body measurements, ratios, ratio of ratios and risk cutoffs showed non-equivalent risk, and therefore, the whole-risk comparison between healthy and cases being not the same, neither by metrics nor by sexes [13]. In this sense, data of the main studies in MI are coincident with those of the table 1 there where we have added new anthropometrics as mere mathematical expressions derived from original data and for demonstrating inequality and non-equivalence relations.

In spite of epidemiological association in most studies, anthropometric and mathematical evidence supports that in overlapping zones (identified bias zones) (Figure 2), WC and WHR may capture false-risk above WHtR. This situation occur when risk assignment for both is not conditioned on the covariate receiving the true-risk (WHtR). On the Cartesian plane, it is clear that WHtR as being > 0.5 always presents higher sensitivity for capturing the highest whole-risk. Obviously, when WHtR cutoff is of > 0.5 there is not equality between mean WC and height/2 ($\text{WC} > \text{height}/2$, Table 1), and only WHtR may be used in order to draw a valid conclusion for the whole-risk because WC by separated will always present risk overestimation in tallest and underestimation in shortest. Thereby, curves of data and overlapping distributions would explain us that in capturing whole-risk WHtR present much more real sensitivity (true positive fraction) than it is WC and WHR. This is because true negative values for WHtR are never selected as false-positive ones, unlike WC and WHR [9, 13]. On this approach, after reviewing thousands of cases of MI (Table 1) our demonstrations may mathematically be proved. Therefore, while WHR risk cutoff being of < 1 , $\text{WHR}/\text{WHtR} < 2$ and $\text{WHtR} > 0.5$, we will always mathematically find protective overestimation for HC respect to WC and height as well as risk overestimation for WC concerning height. It is clear, any WHR-

associated risk above WC will be a false conclusion drawn from a mathematical misconception. Similarly, if WHtR >0.5 is associated to cases and occurring unbalance between mean WC and height/2 ($WC > \text{height}/2$), any WC-associated risk beyond that of WHtR will not be a valid conclusion. Likewise, as being mean WHR/WHtR <2, any WHR-associated risk beyond that of WHtR will always draw a wrong conclusion [13]. In short, in any population, captured whole-risk depends on each indicator per se and its sensitivity rather than on its magnitude of association respect to others.

For the first time in cardiovascular-anthropometric research by using propensity score model and matching, association bias of WHR has been demonstrated [9]. Then, we have explained the reasons that justify bias errors from thousands of MI/CVD cases when the unhealthy BC was not well compared [13]. Additionally, it has been explained that height turns out to be a body volume factor, and raised WHtR would determine a higher volume by unit of height, there where the higher the WHtR, the higher the whole-risk, and the higher the excess risk of MI (Figure 3) [9, 13].

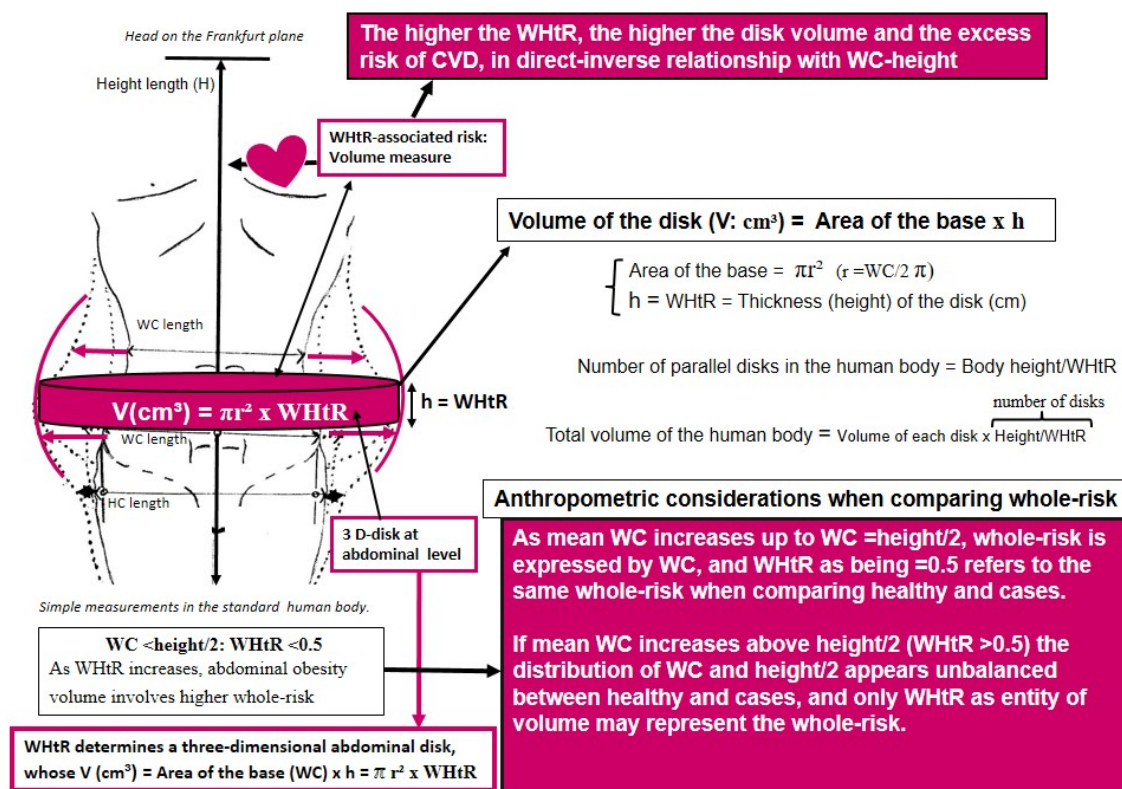


Figure 3. Anthropometric length measurements in the standard body human and mathematical considerations for determining measure of volume on a three-dimensional abdominal disk

Measurements at baseline would represent mean values per standard deviation for WC, HC, H, height of the disk and WHtR being actually valid for any study population and ethnicity. The model of disk for representing volume at all times may be applied for both case-control and cohort studies from the respective mean values (SD) and risk cutoffs for WHtR. Anthropometric considerations are explained for understanding volume of whole-risk as WHtR increases. CVD

denotes cardiovascular disease; H, body height; h, height of the disk; HC, hip circumference; r, radius of the base of the disk; V, volume of the disk; WC, waist circumference; WHtR, waist-to-height ratio.

Original built by the author. Dimensions are not to scale

In a similar conceptual line, the true unhealthy BC derives from whole-body fat percentage (%BF), fundamentally the part linked to intra-abdominal fat depots. Thus, WHtR and %BF have showed the highest discriminative abilities in relationship with a unhealthy BC, and WHtR has been more strongly correlated with %BF and adiposity variables in men than it is with WC [10, 14, 15]. Hence, WHtR and %BF as being anthropometrically valid for biological risk assessment in both sexes appear to be strengthened for the estimate of whole-risk [13]. Thereby, WC and height in keeping a relationship with both abdominal obesity volume and %BF would be the basic simple measurements for faithfully evaluating MI/CVD and cardiometabolic risk [13]. As mathematical object, inequality between values of the body measurements in healthy gave birth to our idea that something did not add up on the true-risk association for compound metrics. In that way, the whole-risk comparison between healthy and cases appeared to be unbalanced. Once the biases have been identified, findings may be endorsed (Figure 1, 2 and 3) [13].

As a proposal, if in any study population both WHR and WHtR risk cutoffs present unbalance between mean values of numerator and denominator ($HC > WC > \text{height}/2$), the stratum between respective risk cutoffs and their balanced points ($WHR = 1$ and $WHtR = 0.5$, respectively) should be matched in a new sample there where confounding variables in overlapping zones ($WHR < 1$ and $WHtR$ between 0.51 and their risk cutoff, respectively) present similar baseline characteristics in all subjects. Then, after conditioning true-risk on both inequality between measurements and real predictive variable (WC and WHtR as appropriate) we would check if the true-risk assignment for similar points of $WHR < 1$ and $WHtR > 0.5$ was correctly specified in the statistical model without stratifying for matching [9, 13]. Obviously, as a result if WHR-associated risk is higher than it is WC and WHtR, or WC-associated risk higher than that of WHtR the model would have been incorrectly specified due to false-risk assignment to points true negatives from WHR and WC, respectively, and which artificially were slanted to the site of cases [9, 13]. It is clear, risk points from WHR and WC lying in bias zones before the WHtR risk cutoff will never capture whole-risk while being not true positives lying after the same risk cutoff for WHtR (Figure 2) [13].

Until our findings by using matching in the overlapping zones, no other research had demonstrated biases. Thus “statistics had confused medical research and cardiology, but mathematics fooled not the heart”. Hence, researchers have the responsibility to conduct studies in a way that make then capable of demonstrating balance between anthropometrics, ratios and risk cutoffs when predicting MI/CVD risk. Unfortunately, anthropometrically healthy subjects present natural inequality between body measurements, and therefore, all statistical models that reflect compound indicators and respective risk cutoffs with unbalanced distributions for body measurements will present biased results in confounding variables, which capture not whole-risk but a false one. Thus, as being anthropometrically and mathematically demonstrable, we could say that when being WHR risk cutoff < 1 and mean WC higher than $\text{height}/2$ ($WHtR$ risk cutoff > 0.5) neither WHR nor WC by separated may capture a correctly-measured whole-risk.

Our discoveries refer to pure mathematics and biases in research when assessing anthropometrically-measured risk. In this line, our findings have several strengths by involving cross-sectional and prospective studies, smalls and larges sample sizes, any type of ethnicity, sex and CVD, and besides, anthropometrics collated on thousands of participants. Our cartesian demonstrations are strong in any clinical endpoint, and besides, being supported by data and mathematical inequalities not discovered in the largest previous studies (see Table 1). Future studies for understanding and evidencing association biases already described are not needed. Our findings determine the generalizability to any study population if mathematically satisfy the same observations by unbalancing body measurements when comparing healthy with cases.

CONCLUSION

In predicting anthropometrically-measured MI risk, bias errors were made worldwide because inequality between body measurements and non-equivalence of risk in the ratios, ratio of ratios and risk cutoffs were ignored. Thus, when being WHtR risk cutoff >0.5 in both sexes this index turns out to be the entity of whole-risk instead of that of WC, and WHtR would be the gold standard for the whole-risk assessment. This is because WHtR as volume measure would always capture the highest biological-risk dimension above WC as two-dimensional area, and becoming the optimal unbiased metric with an anthropometrically and mathematically correct prediction. On the issue related to body measurements and association of abdominal obesity and MI risk, HC renders irrelevant while height turns out to be a modulator factor for whole-risk, which derives from enlarged WC as abdominal volume increases.

Our relevant findings should be extended to scientific community, and a critical thinking should be carried out. It is necessary for avoiding biases in research as well as in clinical practice. Hence, public health goals with non-optimal metrics such as BMI and WHR should be shifted, especially when tackling prevention and control programmes and gauging MI true-risk.

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