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RESEARCH ARTICLE

Association of Body Mass Index and Abdominal Obesity with Myocardial Infarction: We Reveal Confounding Factors that Historically Distorted Causal Inferences

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ABSTRACT

Cardiovascular diseases, mainly myocardial infarction and stroke, are the leading cause of death globally. Therefore, epidemiological research seems necessary to prevent cardiovascular events and mortality. However, real-world data from obesity metrics has intrinsic limitations for the assessment of causality. Despite of historical studies showing that the body mass index (BMI), the waist-to-hip ratio (WHR) and the waist circumference (WC) have been associated with increased risk of myocardial infarction, they might not be accurate from a causal inference.

Our aim was to summarize historical and novel findings about obesity metrics and myocardial infarction to evidence causal association biases. Method: an epidemiological review study was conducted while being original research when adding new anthropometrics in study design. Mathematical inequalities between the simple body measurements in anthropometrically healthy adults were described. Mean values and cut-offs for classic and several newer anthropometric variables were established. Classic metrics, ratios between the means of the simple measurements, a modulus |x| as a result of subtracting some measurement means from others (e.g., mean fat free mass minus fat mass) and somatotype ratings were collated. Mathematically, a non-zero difference for each modulus |x| in any population study would indicate an unbalanced distribution of the measurements between groups being compared, and therefore, the risk exposure levels differing. Thus, when between-groups the high-risk body compositions and somatotype ratings differ, any metric-associated risk is biased from a causal inference. After investigating large epidemiological studies, the historical omission of key anthropometric variables is stated, and as being uncontrolled confounding factors distorted causal inferences. Therefore, a protective overestimate of fat free mass and hip circumference over fat mass and WC, respectively, always occurred. Similarly, when the waist-to-height ratio values of >0.5 are associated; a protective underestimate of height over WC occurs. Any metric-associated risk is biased if prediction is made from WC or technologically measured body compositions without accounting for relative risk volume measures. In conclusion, summarizing the historical and novel findings regarding risk prediction, BMI, WHR and WC alone show evidence of causal association biases because of high-risk body compositions and risk exposure levels always differ between the groups being compared.

Keywords: Myocardial infarction, body mass index, general obesity, abdominal obesity, kinanthropometry, bias, somatotype.

1. Introduction

Cardiovascular diseases (CVDs), mainly myocardial infarction (MI) and stroke, are the leading cause of death globally and are a common cause of morbidity[1]. Epidemiological research is necessary to prevent cardiovascular events and mortality. However, real-world data from different countries and ethnicities has led to different conclusions regarding the superiority of different obesity metrics, such as the body mass index (BMI), the waist circumference (WC), or the waist-to-hip ratio (WHR), in predicting CVD and MI risk[2-9]. Epidemiological anthropometric data has intrinsic limitations regarding the assessment of causality that are not completely mitigated even following the application of statistical methods designed for nonexperimental data. For instance, in several studies[2,3,5,7-9], association biases when handling anthropometric data have been demonstrated[4,10-14]. Novel research has proven that some obesity metrics may present causal association biases between groups when comparing the risk associations of different body compositions (BCs)[4,6,10-14]. In cardiovascular prevention, an accurate assessment of BC and body fat distribution is important before assuming any causal risk assigned to each metric[10-15]. Doing so ensures that the true anthropometric risk is derived from a high-risk BC rather than any obesity metric statistically indicating an association. Therefore, a high BMI (>24.9 kg/m²), WHR in women and men (>0.85 and >0.90, respectively), or WC in women and men (>80-88 cm and >94-102 cm, respectively) does not indicate an unhealthy BC, particularly if you overlook other key variables that also are associated with high-risk BCs[10-14]. Therefore, although high BMI, WHR and WC values have been associated with an increased risk of MI and mortality, they might not be optimal indicators of a causal inference due to different origins and densities of the main body components contributing to them[4,6,10-14,16]. These components include fat mass (FM) and fat-free mass (FFM) constituting total body weight, and abdominal fat and musculoskeletal structures of hip circumference (HC) determining for WHR. Similarly, from WC and height we may determine the waist-to-height ratio (WHtR), which modulates a relative risk volume or anthropometrically measured relative fat mass from different mathematical formulas[4,6,10-14,16].

Anthropometrically, simple body measurements depend on structural components that do not account for pathophysiological mechanisms or cardiovascular risk factors[12-14]. Therefore, anthropometric risk and cardiovascular risk are not interchangeable concepts. While all simple measurements may be related to each other and participate in BC, not all measurements are independent cardiovascular risk factors. Some anthropometric measurements may indicate associations; however, they do not necessarily indicate a high-risk BC. Therefore, while anthropometric data may be statistically associated with CVD and mortality, it does not equate to the biological plausibility of risk. Similarly, BMI-defined obesity and abdominal obesity metrics might not reach the same conclusions regarding high-risk BC due to the different simple measurements participating in each metric[10,12,14]. General obesity by increasing weight may never be the same as abdominal obesity by increasing unhealthy adiposity. In fact, using other metrics without weight measures might detect MI risk before an individual's BMI reaches the obesity range (>30 kg/m²)[10-14,17,18]. Regarding the World Health Organization (WHO) BMI categories, a BMI >30 kg/m² is defined as general obesity and is recognized as a major cardiovascular risk factor[17,18]. Thus, high BMIs in the overweight (>24.9–≤30 kg/m²) and obese ranges may never express the same risk exposure level. In this approach, the FM to FFM ratio (FMFFMR) is important because FM and FFM only may be the same value in instances of high or severe obesity, with each component being about 50% of 100% of total final weight (i.e., FM [50%] + FFM [50%]=100% as a final weight). It means the weight measure estimates for 100% as one whole in mathematical terms, and only then, FM and BMI may estimate for the same overall risk[13,14,17,18].

Previous important studies, such as the INTERHEART, UK Biobank, and SWEDEHEART registries, have published important findings focusing on WHR and WC as metrics significantly associated with an increased risk of a first or recurrent MI[2,3,5,7,19]. Many epidemiological studies have reported BMI to be a worse predictor of MI incidence than WHR and WC[2-7,19]. In addition, while BMIs in the overweight range appear to be epidemiologically associated with MI and cardiovascular mortality, the lowest rates of all-cause mortality have been found in the normal weight or slightly overweight ranges[2-14,20,21]. Thus, the fact that an overweight BMI may be associated with MI and cardiovascular mortality and at the same time showing a lower all-cause mortality risk might actually indicate bias errors due to comparing different high-risk BCs and risk exposure levels within the same metric.

2. Method and study design

This study has been conducted revising epidemiological data of the body of the literature, while being original research when adding new anthropometric factors. Classic and several newer anthropometric variables were established and calculated from the anatomic knowledge in anthropometrically healthy adults[10-14,21]. FMFFMR, WHR and WHtR

were considered mathematical fractions of a numerator over denominator, and mean values ± standard deviation (SD) of the simple measurements in epidemiological studies were used for establishing ratio values and risk cut-offs. A significant difference between two concerned simple measurements will be taken to indicate a considerable difference for the ratios ($p<0.05$). Mean values (SD) for WHR and WHtR and respective risk cut-offs from multiple studies were used as appropriate. Similarly, any mean or median BMI in normal-overweight range will be taken to indicate a significant difference between FFM and FM (mean FMFFMR <1)[14,21]. The difference in means between each two simple concerned measurements (the numerator vs. denominator) becomes a modulus |x|, and measures the absolute difference as a result of subtracting one simple measurement or their mean from one another. Absolute value describes the distance from zero that a number is on the number line, without considering direction or sign. A standard difference that higher than 0.5 will be taken to indicate a considerable difference for each modulus |x| (|x|>0.5). Additionally, modulus |x| for FFM minus FM and mean FM or FFM were divided by unit of height (i.e., by height in m^2 or height in cm–100) for mathematically establishing the corresponding absolute values.

Somatotype ratings and respective risk cut-off ranges were extracted from historical and new studies where comparing shape and BCs[22-25]. A significant difference between values of each rating will be taken to indicate a considerable difference for somatotype components ($p<0.05$).

After investigating variables, an update on epidemiological risk cut-offs worldwide was carried out. The cut-offs were established through different measures of association. If, after checking risk cut-offs for associations systematic differences between the simple measurements (i.e., being the corresponding ratios and modulus |x| of <1 and higher than zero, respectively) and somatotype ratings remain, this will be an indication that an over- or under-estimate of some simple measurements may occur, and also, different BCs and risk exposure levels being compared.

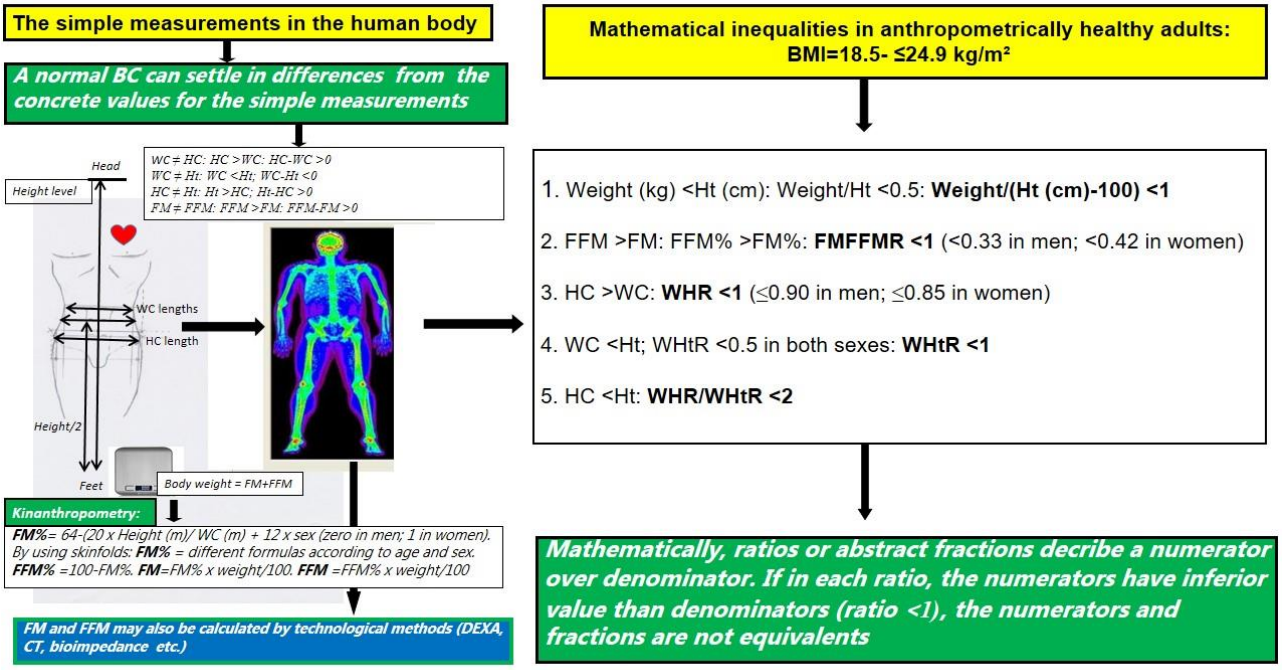
3. Historical and novel findings in predicting myocardial infarction risk from anthropometric measures

As advanced in recent research, a normal BC in anthropometrically healthy adults is in consonance with mathematical inequalities between the simple body measurements[10-14]. Historical and new data are shown in Table 1 and Figure 1. Therefore, if inequalities between measurements are not considered when assigning risks for the concerned metrics, an over- or under-estimate of some simple measurements may occur, biasing outcomes and causal inferences[4, 13,14,21]. In each ratio or mathematical fraction, both the numerator and denominator are intrinsically linked when estimating the risk as one whole or 100%. When the numerator and denominator take the same value (ratio =1), the numerator and fraction may refer to the same 100% as one whole risk in mathematical terms[10-14]. Therefore, a high-risk BC cannot be determined from BMI, WHR, or WC measurements in isolation because of the two different simple measurements (i.e., FM vs. FFM, WC vs. HC, and WC vs. height) that may be differentially distributed between groups being compared, either by sex, age, or race and ethnicity[4,6,10-14].

After knowing classic metrics and somatotype components, other newer key anthropometric variables, such as the FMFFMR and modulus |x| have been added to the body of the literature[10-14]. This enables a novel perspective regarding the association between anthropometric risk and CVD and MI[10-14,21-25]. While other real anthropometric measures as mathematical constructs may be associated with MI, they may not be causative factors (Table 2). However, these variables may demonstrate different baseline anthropometric characteristics between groups, allowing differences in BC of risk to be identified between healthy and unhealthy cases. As an example, dividing the numerators by the denominators many epidemiological risk cut-offs for BMI, WHR and WHtR are proper abstract fractions, and it is possible to observe a protective overestimate of FFM and HC over FM and WC and a protective underestimate of height with respect to WC[10-14,21]. In many epidemiological studies, when the corresponding modulus |x| is accounted for, an unbalanced distribution between the concerned simple measurements has been mathematically demonstrated, with all respective differences in means being higher than zero[4,10-14,21]. This ensures that the "±x" value, as the mean of the individual differences for two simple measurements, is always different between the groups being compared. This means that between-groups can be compared for different "±x" values between the concerned simple measurements and, therefore, different high-risk BCs can be assessed between individuals, who having the same risk ratio value[10-14,21]. Although BMI, WHR and WC are strongly associated with MI and mortality, an over- or under-estimate of some simple measurements could result in causal association biases due to a BC and new mathematical factors that do not incorporate causality [4,10-14,21]. Con-

sequently, evidence generated from nonrandomized real-world data may increasingly contribute to false conclusions and causal inferences.

Figure 1. Determination of the simple body measurements in the human body. Mathematical relationships between simple measurements in anthropometrically healthy adults with normal body compositions. Fat mass and fat free mass may be determined either anthropometrically or technologically.



BC indicates body composition; BMI, body mass index in kg/m²; FFM, fat free mass in kg or %; FM, fat mass in kg or %; FMFFMR, fat mass-to-fat free mass ratio; HC, hip circumference in cm; Ht, height in cm; WC, waist circumference in cm;
WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.
§ Mathematical signs as appropriate. Differences between absolute values of the simple measurements may either be positives (>0) or negatives (<0) as a result of subtracting one measurement from one another or vice versa.

Previous studies have failed to measure these abstract fractions and their corresponding modulus |x|; therefore, the true risk relationship between classic obesity metrics was distorted[2-7,10-14,21]. This is because hidden confounding factors were associated with healthy or unhealthy statuses, despite not being causative risk factors (see Table 2). On this basis, if the relative musculoskeletal component and the mean |x| within BMI were historically associated with MI status, it remains a question as to whether how BMI measures body mass could capture the true causative risk related to an unhealthy FM, as this weight in kg would always be lower than FFM value (mean FMFFMR <1). Similarly, if a mean |x| within WHR historically showed a direct–inverse association with the healthy–unhealthy status, it remains to be seen whether a WHR-associated MI risk cut-off of <1 could capture the overall risk without a protective overestimate of HC over WC occurring. Moreover, if a mean |x| within WHtR historically showed a direct–inverse association with healthy–unhealthy status, and the mean WHtR lies between 0.5 and <1 (see Tables 1 and 2), it is impossible that a WC risk cut-off could separately capture the overall risk without overestimating in the tallest or underestimating in the shortest values[4,6,10-14,21]. In these approaches, each obesity metric captures a different risk derived from their own mathematical relationships in terms of the ratios between the numerators and denominators[10-14,21]. Mathematically, only in theoretical risk cut-offs with ratios indicating ≥1 would the whole-risk exclusively depend on the numerators (e.g., in high obesity range where FMFFMR≥1 or high abdominal obesity where WHR≥1 or WC ≥height), with the numerators and ratios being risk equivalents[10-14,21].

Table 1. Classic and several key anthropometric variables described in anthropometrically healthy adults. Values and mathematical inequalities do not mean causative or protective effect while body compositions being normal either anthropometrically or technologically measured

Anthropometric variables	Men	Women
FM% vs. FFM% within BMI	<25% vs. >75%	<30% vs >70%
FFM+FM (kg)/(Ht (cm)-100)	<1	<1
FFM+FM (kg)/(Ht (m)^2)	<24.9	<24.9
FM or FFM (kg)/unit of height	>0	>0
FMFFMR	**<0.33 (<1)**	**<0.42 (<1)**
FFM–FM (kg) = |x|	**|x|>0=+x**	**|x|>0=+x**
FFM–FM (kg)/(Ht (cm)–100)	**|x|>0=+x**	**|x|>0=+x**
FFM–FM (kg)/(Ht (m)^2	**|x|>0=+x**	**|x|>0=+x**
HC–WC (cm)= |x|	**|x|>0=+x**	**|x|>0=+x**
WHR	<1	<1
WC–Ht (cm) = |x|	**|x|>0: |x|= –x**	**|x|>0: |x|= –x**
WHtR	**<0.5 and <1**	**<0.5 and <1**
HC–Ht, (cm) = **|x|**	**|x|>0= –x**	**|x|>0= –x**
WHR/WHtR	**<2**	**<2**
Endomorphy rating	Mid-high range (>2)	Mid-high range (>2.5)
Mesomorphy rating	Mid-high range (>2.5)	Low-mid range (>1.5-2)
Ectomorphy rating	Mid-high range (>2)	Mid-high range (>2)

BMI indicates body mass index in kg/m^2; FFM, fat free mass in kg or % as appropriate; FM, fat mass in kg or % as appropriate; FMFFMR, fat mass-to-fat free mass ratio; HC, hip circumference in cm; Ht, height in cm; WC, waist circumference in cm; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; unit of height refers to Ht (m)^2 or Ht (cm)-100 as the divisor or denominator; |x|, modulus as the absolute difference between the corresponding simple body measurements, and it may mathematically be +x or –x (±x).
* Values and mathematical inequalities derive from the anthropometric and scientific knowledge, where the mean values (standard deviation) were measured in the anatomy and body compositions of anthropometrically healthy adults, and in a normal weight (18.5 - ≤24.9 kg/m^2) range, according to WHO BMI categories.
§ Somatotype ratings can vary in agreement with genetic and acquired physical characteristics.
Source: original table built by the author who has the copyright. Data are result of an own investigation. Real-world data has partially been published by the author, and other newer variables are now added.

Regarding values and pathophysiological properties for the simple measurements, an updated interpretation of the association between the causal risk of obesity metrics and MI has been developed[4,6,10-14,21,22]. Anthropometrically, none of BMI, WHR, or WC alone can capture the best risk dimension due to imbalances between their simple measurements, which can be observed in the association findings reported worldwide (see Table 2). In addition, MI risk does not depend on any arithmetic indicator, but instead on high-risk BCs related to anthropometric profiles and increased intra-abdominal adiposity[6,10-14,21-24].

Table 2. Generalised cut-off points for the association of classic obesity metrics and other newer variables with MI worldwide. Concrete values for all risk cut-offs in large populations necessarily were not established

Anthropometric	Men	Women	Findings**
FFM+FM/(Ht (cm)-100)	>1*	>1*	Positive
FFM+FM (W)/(Ht (m)^2)	>24.9*	>24.9*	Positive
FM%	>25%*	>30%*	Positive
FMFFMR	>0.33 (<1)*	>0.42 (<1)*	Positive
FFM–FM=|x|	**|x|>0=+x***	**|x|>0=+x***	Inverse
FFM–FM/(Ht (cm)–100)	**|x|>0=+x***	**|x|>0=+x***	Positive
FFM–FM/(Ht (m)^2	**|x|>0=+x***	**|x|>0=+x***	Positive
FM or FFM/unit of height	**>0***	**>0***	Positive
HC–WC= |x|	**|x|>0= +x***	**|x|>0= +x***	Inverse
WHR	**<1***	**<1***	Positive
WC–Ht= |x|	**|x|>0= –x***	**|x|>0= –x***	Inverse
WHtR	≥0.5 (<1)*	≥0.5 (<1)*	Positive
WHR/WHtR	<2*	<2*	Positive
Endomorphy rating	Mid-high range (>4)*	Mid-high range (>4-5)*	Positive
Mesomorphy rating	Mid-high range (>4-5)*	Midrange (>4)*	Positive
Ectomorphy rating	Low-minimal range (≤1)*	Low-minimal range (≤1)*	Inverse

BMI indicates body mass index; FFM, fat free mass in kg; FM, fat mass in kg or %; FMFFMR, fat mass-to-fat free mass ratio; HC, hip circumference; Ht, height; W, total body weight; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; |x|, modulus as the absolute difference between the corresponding simple body measurements, it may mathematically be ±x.

* Statistically significant: $p<0.05$; $X>0.5$

** Measures of association such as odds ratios, hazard ratios, receiver operating characteristic curves or other statistical models were used for indicating which type of association was found as appropriate.

§ Ethnically-specific risk cut-offs are taken into account when reflecting the inequality between the simple body measurements and their subsequent unbalanced distribution between groups being compared (|x| risk cut-offs being different to zero).

§§ Mathematical inequalities and absolute differences between the simple body measurements were extracted from the differences between the mean values (standard deviation) described or inferred in most epidemiological studies.

Based on the existing literature and after summarizing the current findings, we developed an original graphic design (graphical abstract) on the Cartesian space. From an anthropometric perspective of a normal-weight range (18.5 - ≤24.9 kg/m^2)[17,18], two main and antagonistic forms of high-risk BCs through different biological risk rays over time can be identified. First, weight gain and increased FM percentage may be measured by different metrics as each identified risk moves to the right for predicting MI and cardiovascular mortality risk[4,6,10-14,21]. Second, weight loss and decreased FFM may also be measured by both BMI and an |x|-risk ray moving to the left, indicating a higher risk of cause-specific mortality due to a deficit in energy reserves (e.g., in cases of some cancers, malnutrition, sarcopenia, etc.,). However, in the left side never lies a risk cut-off for cases of MI or cardiovascular mortality, because of anthropometrically and technologically measured FFM is always higher on the right side[10-14,21]. Both types of high-risk BCs present different and opposite biological senses over time. Subsequently, if FM and FFM are not respected in their biological sense regarding risk, acquired anthropometric changes and variations within the same BMI may

result in causal association biases due to different risks being estimated[14]. In the risk cut-offs for FMFFMR (always being of <1) and |x| (always being different to zero), FFM and FM always appear to be differentially distributed between healthy and MI cases, with BMI cut-off and FM percentage cut-off not necessarily indicating the same overall risk level[13,14,21]. Interestingly, in any cut-off line indicating severe obesity, where mean FMFFMR=1, mean |x|=0 and mean FM percentage =FFM percentage, each ray may be risk equivalent. Conversely, no risk cut-off point lying before this point is equivalent, (see Graphical Abstract). Hence, any BMI cut-off may correspond to different ratio values quantified in hundredths, |x| in tenths, and FM in percentages, and therefore, the risk exposure level between each is inequivalent. Similarly, when a FMFFMR risk cut-off of <1 appears to be associated with all-cause mortality, cardiovascular mortality, CVD, the obesity paradox, and metabolically healthy obesity, then, BMI-associated risk can distort the true risk relationship[14,21]. Thus, selection biases for BMI values preceding the severe obesity range may occur under different clinical conditions[13,14,21]. It is clear, when using mathematical functions of different sign and sense (e. g., different ±x values within BMI), if differences in means or the mean of the individual differences are ignored, a bias error may occur in any association determined from the mean or median of any ratio between two simple measurements[10-14,21].

To identify at-risk subjects, the risk historically associated with MI may depend on metabolically unhealthy BC rather than metrics that might be responsible for all or much of the statistical association[10-14,21-24]. In healthy adults, FFM is usually higher than FM; however, FM percentage, FFM by unit of height, and somatotype components are also associated with MI status (see Tables 1 and 2)[10-14,21-25]. Consequently, based on historical Framingham studies and novel findings it is possible to say that either FFM by unit of height or high mesomorphy and low ectomorphy ratings are anthropometric variables associated with MI, but not causative factors[13,14,21-25]. Thus, the existing evidence indicates that somatotype components and other baseline anthropometric characteristics differ between healthy and MI cases[4,6,10-14,21-25]. Therefore, when ratios differentiate no fundamental aspects of a high-risk BC, there might be errors associated with predicting the overall risk using those ratios. As already reported, the historical anthropometric profile in MI cases is endomorphic mesomorph, which is associated with excess FM, high mesomorphy and FFM by unit of height, and a high relative volume by unit of height (i.e., low ponderal index, low ectomorphy and linearity, and high WHtR)[10-14,21-25]. Based on these findings, simple indicators of mass (i.e., BMI >24.9 and <35 kg/m²) and areas (i.e., WC and HC) may never indicate the same risk exposure levels between healthy and MI cases, particularly if risk volume measures, mesomorphy and ectomorphy ratings and FFM by unit of height may demonstrate discriminatory associations[10-14,21-25]. Consequently, only metrics indicating relative volume measures and higher biological risk dimensions could be anthropometrically valid for capturing the overall risk, with cardiometabolic risk being to unhealthy fat volume as measured by WHtR[4,6,10-14,21,22].

4. Summarizing kinanthropometric lessons for understanding myocardial infarction-associated risk

It is known that anthropometric measurements can be defined using units of length and anatomical points as landmarks in the human body (e.g., WC, HC, height, muscle perimeters, bone diameters, and skinfolds), and as units of mass (e.g., body weight, FM, and FFM). Thus, each simple measurement is derived from the body structures physically marked by a researcher. However, a high-risk BC may not be easily determined from any simple body measurement or by the calculation of the obesity metrics widely used in epidemiological research, although this may be improved by balancing the other simple measurements. There are several points that shape the rationale behind this consideration:

1. Anthropometrically healthy adults (i.e., with a BMI between 18.5-24.9 kg/m²) and with theoretically minimum risk exposure levels present with a normal BC; however; they also demonstrate mathematical inequalities between the main simple body measurements (see Table 1 and Figure 1)[8,10-14,17,18].
2. When measuring BMI variations in an individual with an anthropometrically healthy status, changes over time in weight measures do not equate to a higher captured biological risk. BMI alone is not able to distinguish between FM and FFM, and may assign the same risk to people with different BCs. This is because FM and FFM are conflicting factors showing metabolically different properties within the same BMI measure. As a novel approach, two different biological senses and several horizontal risk rays for high-risk BCs may be drawn on the Cartesian space (see Graphical Abstract)[6,13,14,17,18,21,22].
3. Measuring a mean BMI in any disease condition and population may hide the true risk

relationship between FM and FFM due to different biological risks associated with excess FM and FFM deficits, therefore, the difference in these means is an unmeasured confounding factor[13,14,21].

4. Measuring WHR determines the relationship between two-dimensional areas with different associations with cardiometabolic risk; however, it does not capture the overall risk. This is because determining true risk depends on a high-risk BC derived from intra-abdominal fat volume, but not from HC as a musculoskeletal structure[4,6,10-14,21,22].
5. Measuring mean WHR in any disease condition and population may hide the true biological risk relationship associated with WC and HC due to estimating different risks in each. If mean WC divided by HC gives a mean value <1 and mean |x| is >0, then, the difference between the means will be an unmeasured confounding factor that distorts the risk determined using WHR[4,10-14,21].
6. Measuring WC alone involves an abdominal area linked with the cardiometabolic risk, however, it does not consider relative abdominal volume, which is modulated by height and captures a higher risk dimension[10-14,21]. In addition, enlarged WC values will always depend on accumulated abdominal fat rather than significant variations in muscle mass area at the same abdominal level.
7. Measuring mean WC in isolation for any disease condition and population may hide the true biological risk relationship between WC and height due to estimating different risks for each. If mean WC divided by height gives a mean value of <1 and mean |x| is >0 (mean WC<height), then, the difference in means will be an unmeasured confounding factor that distorts the risk determined from WC measurements[10-14,21].
8. Based on WHtR at an abdominal level, a relative volume in cm^3 may geometrically be quantified. This has a direct and inverse relationship with WC and height, respectively, and is closely linked with intra-abdominal fat deposits and is the highest cardiometabolic risk dimension[10-14,21].
9. Fat mass and fat free mass are two mathematical factors, which constitute the total body weight. These complementary masses may anthropometrically or technologically be measured as percentages and absolute values in kg[14,16,21].
10. Measuring relative FM and WHtR may determine an individual's whole-body fat percentage and relative abdominal volume, respectively, using a body component linked with biological risk and unhealthy BC[6,10-14,16,21].
11. Fat free mass and fat mass as body components are opposing mediators regarding cardiometabolic risk. Their values were never balanced (weight by weight) when most of studies associating BMI and CVD or MI and mortality[6,10-14,21].
12. By measuring somatotype ratings and unhealthy BCs, differences between healthy and MI cases have been well-established, with somatotype components consistently showing clear degree of association with MI[10-14,21,22-25]. In this approach, mid-high mesomorphy, mid-high endomorphy, and low ectomorphy ranges are seen in MI patients, who are in the overweight/obesity range. Thus, somatotype ratings in MI cases differ from the mean somatotypes found in subjects who are categorised as normal weight or underweight. Low mesomorphy, low endomorphy, and high ectomorphy can be detected in individuals in the underweight BMI range and in those with FFM deficits, indicating a low relative volume by unit of height and lower perimeters, diameters, and skinfolds than individuals classed as overweight or obese[13,14,21,22-25].

Using kinanthropometry, the risk of MI and all-cause mortality may be significantly associated with BMI, WHR and WC. However, a lack of balanced distribution between the corresponding simple measurements leads to the generation of false outcomes[4,10-14,21,22]. In this approach, if the simple measurements present an unbalanced distribution between the groups being compared, a selection bias when assigning risk to BMI, WHR and WC may occur, and causality cannot be assumed[4,10-14,21,22]. This is because, in these anthropometric situations, the numerators and respective fractions are never risk equivalents. That way, the BCs, risk exposure levels, and somatotype characteristics between healthy and unhealthy cases will always differ. Therefore, between-group comparisons never compare the same overall risk.

5. Discussion

After summarizing the historical and novel findings regarding predicting MI risk, there is evidence that causal association biases exist for BMI values or abdominal obesity measured by WHR and WC alone[4,10-14,21,22]. As stated, statistical methods that incorporate anthropometric measures may involve association biases in their causal inferences if the risk equivalences between the simple body measurements are overlooked[6,10-14,21]. False conclusions of causality have been drawn in several large epidemiological studies where BCs and

several key anthropometric variables were omitted despite being differentially distributed between healthy and unhealthy subjects[2,3,5-7,10-14,21]. Conceptually, anthropometric measures indicating obesity are not the same as non-anthropometric cardiovascular risk factors predicting MI risk. Obesity metrics are mathematical constructs that assess relationships between simple structural measurements; however, they do not measure pathophysiological functions, such as those derived from blood pressure, lipids, glycemia, tobacco, and cardiorespiratory fitness. Therefore, if obesity metrics are not conditioned on independent anthropometric covariates that represent the true risk (e.g., with propensity score methods), different high-risk BCs can be compared between individuals who have the same values of risk in each concerned metric[4,10-14,21,22].

5.1. DISCUSSING ABOUT GENERAL OBESITY AND BODY MASS INDEX-ASSOCIATED RISK

To our knowledge, gaining weight might increase MI risk if anthropometrically or technologically measured FM leads to this increased risk. Conversely, losing weight might not actually improve health statuses if the FFM deficit involves a biological risk due to worsening the nutritional status. In this line, no BMI cut-off was found in underweight range (e.g., from <20–<18.5 kg/m²) when CVD and all-cause mortality were analyzed[1-14,17,21,26-34]. Under this observation, it is only when mean FM and FFM have the same value within the BMI cut-off that weight measures can be used to estimates the overall risk as one whole in mathematical terms. In this anthropometric situation, FM and FFM present a balanced distribution between the groups of comparison (mean FMFFMR=1: mean |x|=0). In this instance, the WHO BMI categories for severe obesity and FM may reach risk equivalence and estimate the same overall risk (see Graphical Abstract)[13,14,17,18]. However, this situation over time is only possible when the mean final weight is approximately 140 and 150% (in women and men, respectively) of the mean initial weight, as then the FM and FFM percentages are equal (50% of the final total weight each)[13,14,21], (see Graphical Abstract). Unfortunately, while this acquired change is anthropometrically or clinically possible, it does not epidemiologically exist in the overall population. Therefore, all BMI risk cut-offs for MI association, where the mean FFM is higher than the FM (mean FMFFMR <1: |x|>0) could result in causal association bias and distort the true risk relationship associated with BMI[13,14,21]. This is because FM and FFM are conflicting yet complementary parts that make up different proportions of an individual's total weight. In addition, with a FMFFMR risk cut-off of <1, a protective overestimate of FFM with respect to FM may always occur, biasing the respective causal inference. In other words, as FM percentage increases, a higher overall risk may be reported (see Graphical Abstract). However, this does not mean that FM values are responsible for the majority of the overall risk. While FM and FFM comprise different percentages of an individual's BMI, it is only when the mean FFM percentage decreases that the FM percentage and overall risk may increase. Conversely, if the mean FFM increases, FM may also increase without resulting in a higher FM percentage. This dynamic is key to understanding biases associated with using BMI values, as it explains how individuals with identical BMIs may have different FM percentages and risks, and vice versa[14].

Acquired anthropometric changes in which FFM is gained (e.g., via physical activity and training) may result in healthy FM percentage changes, even if the FM and BMI values increase. Even if an individual's BMI is high, if this is only due to an increasing FFM percentage, anthropometrically or technologically measured FM may indicate no increased risk. In fact, of the mean final weight, the higher the FFM percentage, the lower the FM percentage, and vice versa. Therefore, biological risk over time only increases if the mean FM percentage increases, never due to increasing weight alone. In contrast, losing weight does not lead to greater health status and cardiovascular protection, particularly if the weight loss involves a lower FFM due to inadequate nutrition status, medical treatment, or other clinical conditions. Therefore, using FM and FFM values within WHO BMI categories without accounting for FM percentages and risk cut-offs could confuse epidemiological conclusions, irrespective of other non-anthropometric cardiovascular risk factors[13,14,17,21].

The measuring or recalculating of FM and FFM percentages in epidemiological studies has demonstrated a relationship between FMFFMR, |x| values, and BMI, highlighting causal association biases stemming from using BMIs[14,21]. For example, using bioimpedance analysis, the UK Biobank study concluded that the risk association between FM and MI and all-cause mortality was not superior to that of BMI[7]. However, after checking the FMFFMR and |x| values, an association bias for BMI was proven[14]. This is because an unbalanced distribution of FM and FFM was demonstrated in both sexes when the BMI cut-off was in the overweight range. In this situation, the FMFFMRs were 0.34 and 0.58 in men and women, respectively. Similarly, the |x| values were 42.2 kg and 18.8 kg in men and women, respectively (all >0)[7,14]. Therefore, any

BMI-associated risk equal or above that of the FM percentage is anthropometrically inconsistent and causally unacceptable, at least when the mean FM is lower than the FFM and the BMI risk cut-off is in the overweight range (<30 kg/m²)[14,17,18,21]. Similarly, in most epidemiological studies[2-14,17,18,21,22,26-34], regardless of the country, a protective overestimate of FFM with respect to FM is often evidenced when the risk cut-offs for BMI, FMFFMR, and |x| are always <30 kg/m², <1, and >0, respectively (see Graphical Abstract)[13,14,21]. Therefore, although BMI-associated risk has historically been collated, epidemiologically it will never be possible to ensure a risk equivalence between FM percentages and BMI values[6,13,14,21]. Individuals who have high BMI may not have a high-risk BCs based on excess FM (e.g., athletes and physically trained subjects). Similarly, not all subjects who have high BMI are at risk of MI. Therefore, a high BMI does not indicate a high-risk BC or the same risk exposure level between subjects, particularly if the BMI does not indicate severe obesity (see Graphical Abstract)[14,17,18,21]

Conceptually, as unhealthy body fat increases from a normal or slightly overweight level, risk increases. However, gaining weight due to increasing FFM does not necessarily lead to higher overall risk. Therefore, weight gain may or may not involve higher biological risk over time. In contrast, losing weight when at an anthropometrically healthy status usually results in FFM deficits, resulting in a worsened health status due to having a high-risk BC different to those associated with MI or cardiovascular mortality (i.e., anthropometric situations with excess FM and higher mesomorphy and FFM per unit of height; see Table 2)[6,13,14,21-24]. Moreover, two different clinical conditions each demonstrating a FFM deficit and increased FM are not comparable due to potentially opposite biological risks and different BCs and somatotype ratings[14,21-25]. When omitting the FMFFMRs and ±x values in each group of comparison, the mathematical and biological senses of two different BCs may be hidden, consequently leading to bias errors. Therefore, associating BMI with MI or all-cause mortality cannot determine causality if differences in high-risk BCs between the groups being compared are not considered. From our observations, the anthropometric risk in subjects who experience cardiovascular events and other specific causes of mortality and have a high BMI, high mesomorphy, and low ectomorphy ratings differs from that associated with other causes of mortality, which may be associated with an underweight BMI, low mesomorphy and FFM by unit of height, and high ectomorphy[9,14,21-32,34]. Clearly, the mean |x| value for BMIs will always differ for cardiovascular and all-cause mortality. This is due to the fact that at the cardiovascular events level, BMI remains strongly correlated with elevated mesomorphy and endomorphy, low ectomorphy, high FFM by unit of height, high FM percentage, and higher volume by unit of height[6,10-14,21-25].

Historically, a nadir of mortality has been demonstrated in individuals within normal weight (>20–<25 kg/m²) and overweight (≥25 kg/m²) ranges, with such associations being derived from mean or median BMI values below the obesity range[9,14,17,18,23,26-32,34]. However, this could be mitigated by adjusting for other covariates, such as FMFFMR, ±x values, and WHtR between the groups being compared[13,14,21]. Evidence supports the idea that in any nadir of all-cause mortality or regarding CVD- or MI-associated risk, BMI cut-offs produce different mean |x| values, resulting in an unbalanced distribution between the groups of comparison[13,14,21], (see Graphical Abstract). In previous studies, the ±x values and high-risk BCs of healthy and unhealthy cases differed and could not be well compared for the same risk exposure levels[2-7,9,10-14,21,26-32,34]. If cardiovascular epidemiology accepts any nadir of mortality using BMI as a causal risk without between groups comparisons for the same risk exposure level, it is impossible to ensure the same causal effect in the overall population. As previously stated, underweight BMIs have been associated with adverse mortality outcomes, visualised in the left branch of a U- or J-shaped mortality curve[9,29-34] (i.e., in subjects showing low mesomorphy, high ectomorphy, and a mean |x| value equal to −x)[14,21-25]. In contrast, in the right sides of the same curves, being overweight (up to 24–27 kg/m²) has been associated with increased mortality risk; although, reduced risk has also been seen in overweight individuals compared with individuals at a healthy weight[9,14,29-34]. Nevertheless, the anthropometric profiles and "x" values seen in the right branches differ from those of individuals with underweight BMIs (i.e., being overweight is associated with higher mesomorphy and endomorphy, lower ectomorphy, and a mean |x| value equal to +x)[14,21-25]. Biologically and mathematically, cases of mortality in the right branches have different BCs than in the left branch with an underweight range; however, any cut-off point for |x| is always higher than zero, and |x| =+x demonstrates a protective overestimate of FFM with respect to FM in all cases[14,17,18,21,25-32]. In this approach, while BMI is a continuous variable that does not differentiate the BCs and ±x values of subjects, any association with different types of cause-defined mortality is anthropometrically incoherent, with any ±x value being different

between groups and the |x| cut-off being different to zero[14,17,18,21]. Similarly, if when predicting MI risk groups are being compared regarding different baseline anthropometric characteristics and somatotypes of risk (i.e., different ±x values between the simple measurements of focus), it is impossible to ensure the same risk exposure levels; therefore, the concerned metrics never capture the same overall risk.

Due to the number of studies investigating it, it remains important to understand that when associating BMI with CVD, MI, and all-cause mortality, causal association bias should be discussed. This is because BMI is not an independent cardiovascular risk factor comparable to those such as hypertension, hyperlipidaemia, and hyperglycaemia, particularly for BMI cut-offs not in the obese range and when the corresponding |x| cut-offs remain uncontrolled for as confounding factors[14,21]. While BMI remains a widely used measure of adiposity in cardiovascular epidemiology, it has several limitations, including its inability to differentiate between FM and FFM and the mean |x| value always being unbalanced[10-14,21]. In addition, in any ethnically-based population study, the higher the mean |x| value of the BMI (i.e., too far from zero), the higher the probability of bias (e.g., nadirs in all-cause mortality)[9,14,29-32]. Similarly, cardiovascular mortality studies have allowed to check lower |x| risk cut-off values (i.e., closer to zero) than for all-cause mortality, with BMI always appearing to be biased (mean |x|>0)[14,21]. Moreover, the mean |x| value for women will always be lower than in men due to women having higher mean FM and lower FFM, (see Tables 1 and 2, and Figure 1). Consequently, any epidemiological study measuring BMI alone, in men or in women, will be unable to ensure that the overall risk is captured. If the causal risk from BC within BMI is not defined, and the FM and FFM values are unbalanced, BMI will never be an accurate metric, as excess FM and FFM deficits represent health risks with opposite mathematical and biological senses[14,21], (see Graphical Abstract). Therefore, any BMI risk cut-off preceding to obesity/severe obesity WHO category, could always demonstrate causal association biases due to imbalances between these two opposing factors.

5.2. DISCUSSING ABOUT ABDOMINAL OBESITY AND METRICS-ASSOCIATED RISK

Regarding abdominal obesity metrics in patients with MI, evidence regarding its association with WHR has been found worldwide[2-7,34]. WHR has been shown to be a better anthropometric predictor of MI incidence than BMI and WC and detects a higher risk excess of MI in women than in men[3,5,7,34]. Using mathematical concepts and propensity score matching, a causal association bias of WHR has been sufficiently explained in recent publications[4,10-14,21]. WHR-associated bias in large studies, such as the INTERHEART, European Prospective Investigation into Cancer, UK Biobank, Norwegian cohort and a review[2,3,5,34,35], may be identified after collating different WC and HC means between the groups of comparison[10-14,21]. For example, in the UK Biobank study, the mean WHR per 1 SD was 0.82 and 0.93 in women and men, respectively[5]. However, the corresponding mean |x| value for HC minus WC was 18 cm in women and 7 cm in men, indicating an unbalanced distribution (|x|>0)[12-14]. Selection biases involving WHR have occurred when comparisons have been made between groups with different ±x values, resulting in a protective overestimate of HC with respect to WC[4,10-14,21]. Similarly, any WC-associated risk beyond that of WHtR may always present biases, particularly if the mean WHtR is >0.5 and there is an imbalance corresponding mean |x| value within WHtR between the groups being compared[10-14,21]. Using this approach, finding different association magnitudes for WC and WHtR, such as in the UK Biobank study, indicates some selection bias has occurred[5,12-14]. In the UK Biobank study, the mean WHtR was 0.52±0.1 and 0.55±0.1 for women and men, respectively; therefore, WC and WHtR never compared the same whole-risk due to imbalances in mean WC and height among the study population[5,12-14]. While WC-associated risk could biologically be the same as that of WHR, this only occurs when there is an existing risk equivalence between WC and HC (mean WHR =1; mean |x|=0). Therefore, when the mean WHR or the risk cut-off is an improper abstract fraction (WHR ≥1), WC and WHR may be risk equivalents and able to estimate the same whole risk. However, this anthropometric situation is epidemiologically unlikely in any population-based study because of mean HC appears to be higher than WC[10-14]. Conversely, any WHR-associated risk above WC is epidemiologically possible when the WHR risk cut-off is <1; however, it would be anthropometrically inconsistent and biologically unacceptable due to an association bias caused by imbalanced WC and HC means between the groups being compared[4,10-14,21].

It is noteworthy, the biological risk related to epidemiologically measured WC can only be anthropometrically accepted if the mean heights of the groups being compared present no significant differences[10-14,21]. This is because height may be inversely associated with any unhealthy group (mean WHtR>0.5 and <1), and this index as a relative volume measure is the only one which is anthropometrically valid and epidemiologically possible[10-

[14,21]. In this regard, MI-associated findings and recommendations for determining a substantially increased risk of metabolic complications using WHR or WC alone[2,3,5,34-41] are misleading if the mean |x| value within WHtR and abdominal fat volume are ignored[13-14,21]. In contrast, biological risk related to FFM deficits in underweight individuals may be better assessed from a measure of mass (i.e., BMI), without accounting for volume measure. Additionally, FFM and FM are associated with higher and lower density (mass divided by volume: g/cm^3), respectively. Therefore, unhealthy variations in FFM will be better measured using units of mass, while unhealthy abdominal adiposity is better measured using units of volume[10-14,21]. Quantifying WHtR in cm^3 provides a relative abdominal volume that may indicate the highest biological risk dimension, irrespective of the somatotype rating and mean |x| value within WHtR[10-14,21]. Therefore, abdominal obesity metrics that involve a two-dimensional area might not actually capture the highest BC of risk related to unhealthy adiposity, at least with transversal and longitudinal body measurements of groups being compared being unbalanced in real-world data.

5.3. NOVEL PERSPECTIVES IN CAUSAL RISK ASSIGNMENT WHEN BODY COMPOSITIONS AND CARDIOMETABOLIC RISK ABDOMINAL VOLUMES ARE ACCOUNTED FOR

When statistically assigning risk to BMI and WHR where the risk cut-offs for FMFFMR and WHR are <1, one may be using a false premise. This is because FFM and HC are typically higher than FM and WC, respectively, and FMFFMR <1 and WHR <1 appear to be directly associated with MI status (see Table 2)[10-14,21]. Similarly, accepting a WC-associated risk when the mean WC is significantly lower than height (mean WHtR >0.5 and <1) is another false premise. This occurs in subjects who have a WHtR >0.5 which is below the independently calculated WHtR risk cut-off[10-14,21]. Thus, while a mean WC lower than the height may anthropometrically be found, epidemiologically no true risk can be captured from any WHtR risk cut-off of >0.5. From a deductive inference, if a false premise is used when assigning a binary risk code for BMI values in the normal-overweight range, WHR<1, and WC <height while being a false positives in the distribution curves for FM percentage, WC, and WHtR, respectively, any final conclusion drawn regarding metrics-associated risk might not be causally true[10-14,21]. Any BMI-, WHR-, or WC-associated risk should only be accepted if the risk assignments are conditioned on risk cut-offs for FM percentages, WC, or WHtR values of >0.5 (±SD)[10-14,21]. However, while assigning risk codes from values of <1 in proper abstract fractions, such as FMFFMR, WHR and WHtR, an equal–different risk to individuals with different–equal high-risk BCs may be assigned, distorting the true predictive ability of BMI, WHR, and WC[10-14,21]. Conversely, when assigning risk associated with severe obesity (mean FMFFMR ≥1) or when population characteristics are grouped using a more optimal central adiposity metric (e.g., WHtR), outcomes without bias errors could be anthropometrically and cardio-metabolically accepted[10-14,18,20,21,28,42-47].

For the first time, we have integrated the historical and novel findings regarding somatotypes and anthropometric risk into the anthropometric profiles of MI subjects[4,6,10-14,21-25,48-51], allowing a new perspective to be considered. Mesomorphy ratings and unhealthy FM values have always been strongly associated with MI, while ectomorphy and WHtR appear to be associated with MI in an inverse and direct relationship, respectively[5,6,10,14,21-25,48,49,51]. Obesity metrics that capture part of the musculoskeletal component (e.g., BMI and WHR) or two-dimensionally measured unhealthy FM might not actually capture the same overall risk as those that measure the relative volume of abdominal adiposity (e.g., WHtR). In this approach, since FFM as a unit of mass and unhealthy adiposity as a unit of relative volume may be associated with unhealthy status, neither total weight nor two-dimensional area measures will be comparable with other metrics that capture volume without depending on musculoskeletal mass. Capturing a relative volume of unhealthy FM may anthropometrically be in consonance with ectomorphy ratings, which show an inverse association with coronary heart disease (see Table 2)[21-25,48,49,51]. Similarly, a two-dimensional measurement of abdominal adiposity may bias outcomes with respect to higher abdominal volumes based on units of height, which are inversely correlated with ectomorphy[4,10-14,21-25,51].

To the best of our knowledge, if MI risk depends on unhealthy adiposity, and height is not causally correlated with body fat[3-7,10-14,21], some concepts have been mathematically and historically overlooked. Notably, the mean |x| value and volume factor within WHtR have been omitted in most studies[10-14,21]. Therefore, only in a hypothetical situation where mean WC is equal to the height (WHtR=1) would the mean |x| value within WHtR equal zero (i.e., mean [WC/2]/[height/2]=1 as a theoretical equivalent fraction, and mean [WC/2] minus [height/2]=0). Only in real-world data, when the mean WHtR=0.5, can WC and height/2 estimate the same whole risk and demonstrate a balanced distribution[13,14,21]. Hence, in a real epidemiological situation, if the mean WHtR is between >0.5 and <1, WC and height will never be balanced, which

leads to the risk of overestimating WC over height[3-7,10-14,21,29,33,40,44,47,53,55]. Only when a sex-specific and ethnically-based WHtR risk cut-off of >0.5 appears to be associated can a true risk be captured despite healthy and unhealthy cases showing different baseline anthropometric characteristics and somatotype ratings[6,10-14,21-25,48,49,51]. Thus, the higher the WHtR, the higher the relative volume; therefore, capturing the whole risk depends on both WC and body height[4,10-14,21]. By contrary, if WC and WHtR do not epidemiologically demonstrate a risk equivalence when estimating the same cardiometabolic risk, any WC-associated risk beyond that of WHtR will always generate a false causal inference.

Assessing abdominal obesity, it is possible to say that all used metrics estimate a cardiometabolic risk related to unhealthy visceral adiposity; however, WHR and WC may present causal association biases if the WHR risk cut-off is <1 and mean WHtR is >0.5 (±SD)[2-7,10-14,21,22,33,35,47,52-55]. In this approach, only WHtR can capture cardiometabolic risk volumes in any abdominal segment and has been strongly correlated with technological methods measuring areas or volumes of unhealthy visceral fat[4,6,10-14,21,22,47,51-60]. Current evidence supports that higher WHtR values are associated with higher visceral fat-to-subcutaneous fat ratios and visceral fat volumes[10-14,21,56-60]. Thus, when high-risk BCs and cardiometabolic risk volumes are accounted for, the metabolically healthy obesity, obesity paradox, and BMI-associated causal risks for CVD and cardiovascular or all-cause mortality disappear or decrease[14,21]. Similarly, when risk equivalent, neither WHR nor WC can capture higher cardiometabolic risks as those measured from a mean WHtR of >0.5 (±SD)[4,6,10-14,21,22,52,54]. In addition, evidence supports that excess abdominal adiposity increases the risk of CVD due to different pathophysiological mechanisms involving inflammatory and atherogenic pathways[10,14,56,57], and technologically measured abdominal fat deposits have been strongly associated with MI, metabolic risk profiles, and mortality[56-62]. Interestingly, a high-risk BC with technologically differentiated visceral and subcutaneous adipose tissue could predict cardiovascular events independently from BMI and other cardiovascular risk factors[10-14,21,56-60]. However, technologically measuring risk abdominal areas is not the same as measuring the abdominal volume of unhealthy visceral fat. This means that at-risk individuals who have the same risk areas at the abdominal level may accumulate different unhealthy fat volumes with WC and WHtR not being risk equivalent[10-14,21]. That way, while mean WC and height may result in unbalanced distributions in any population-based study, neither WC nor technologically measured unhealthy fat areas can estimate the same cardiometabolic risk as measured by units of volume, particularly when the relative abdominal volumes between the groups of comparison are significantly differentiated[4,10-14,21,22,51,58]. Similarly, when any association may mathematically depend on musculoskeletal structures (e.g., weight, HC, height, and muscle perimeters) or relative volume measures[10-14,21-24,47,48,51], any anthropometric associations do not involve causal inferences of whole-risk. It may be argued that BMI values or ratios between two-dimensional areas capturing part of mesomorphy may account for part of spurious risk. This is because mesomorphy, FFM by unit of height and |x| values are not causative factors involving the highest risk BC, and despite being factors associated with MI status (see Table 2). In contrast, WHtR captures cardiometabolic risk volumes irrespective of musculoskeletal components, making it the best anthropometric measurement for predicting MI risk that is not inferior to technologically measured BCs, and besides, avoiding bias when real-world data cannot be compared with randomized controlled trials[4,6,10-14,21,22].

These novel discoveries and innovative advances indicate the presence of association biases in historical cardiovascular research, potentially limiting the anthropometric validity and conclusions drawn in previous studies regarding the association between obesity metrics and MI. These conclusions were drawn without using propensity score methods or taking into account risk codes depending on other independent anthropometric covariates, such as FM percentages, WHtR values, and somatotype characteristics[4,6,10-14,21-25,48,49,51]. Consequently, healthy and unhealthy real-world cases and data were never balanced, meaning the same risk exposure levels or BCs were not measured between the groups being compared.

6. Conclusions

Here we have summarised the historical and novel findings regarding predicting MI risk using BMI and abdominal obesity metrics, such as WHR and WC alone, showing evidence of association biases from causal inferences. Other key anthropometric variables, which have been historically omitted in large epidemiological studies, may demonstrate biases relating to these obesity metrics. Some somatotype components and other mathematical factors are non-causative confounding factors that appear to be associated with MI status and demonstrated unbalanced distributions in the simple body measurements taken from healthy and MI cases. Therefore, high-risk BCs and risk exposure

levels derived from baseline anthropometric characteristics and somatotype ratings always differ between the groups being compared. In most studies, a protective overestimate of FFM over FM and HC over WC or height has been demonstrated. Similarly, regarding sex and ethnicity in any population study, when WHtR values of >0.5 (±SD) are associated with MI, any WC- or abdominal area-associated risk beyond that of WHtR or relative abdominal volume is biased due to a protective underestimate of height with respect to WC measure.

As somatotype ratings, abstract fractions and their respective modulus |x| have been uncontrolled confounding factors in previous studies, combined with imbalances for simple measurements within BMI, WHR, and WC values no causal inferences can be assumed for overall populations. Only anthropometrics such as WHtR, which capture cardiometabolic risk irrespective of other baseline anthropometric characteristics and somatoype, may provide MI causal risk without generating biases.

Recommendations

When predicting causal risk, any metric is invalid if confounding factors are not strictly controlled. Propensity score methods might be used in observational studies to reduce the effects of these confounding factors. Consequently, any risk stratum in a proper abstract fraction in which systematic differences between the means or medians of the simple measurements remain would indicate that the propensity score model is incorrectly specified due to imbalances in the distribution of the simple measurements. Therefore, the risk assignment in these strata should not be accepted without removing selection biases. We recommend that in binary logistic regression analysis, the risk anthropometrically assigned should be conditioned on the independent covariates receiving the true risk. Thus, FM percentages within BMI and WHtR associated with the risk related to unhealthy abdominal fat volumes meet the criteria for establishing a true risk assignment, with WHtR better predicting early risk. When WHtR expresses a relative abdominal volume measure, WC and height are not potential confounding factors, while WC and WHtR are not risk equivalents. Thus, although mean WC and height are never equal, the higher the WHtR, the higher the MI risk. To reduce the burden of CVD, guidelines on hypertension, dyslipidaemia, diabetes and physical exercise has been developed providing new advice on patient management, which include weight control. However, to reduce the burden of MI, controlling the anthropometric profiles and abdominal fat volumes provide better advice than those of measuring BMI, WHR or WC in isolation. It is time to change the historical paradigm regarding the topic.

7. Conflict of interest

The author declares that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

8. Author contribution

AMC contributed to the conception and design of this research. AMC described several newer anthropometric variables. AMC contributed to the acquisition, calculate, analysis, and interpretation of the data. AMC drafted the manuscript and substantially revised the submitted version. The author critically revised the final manuscript.

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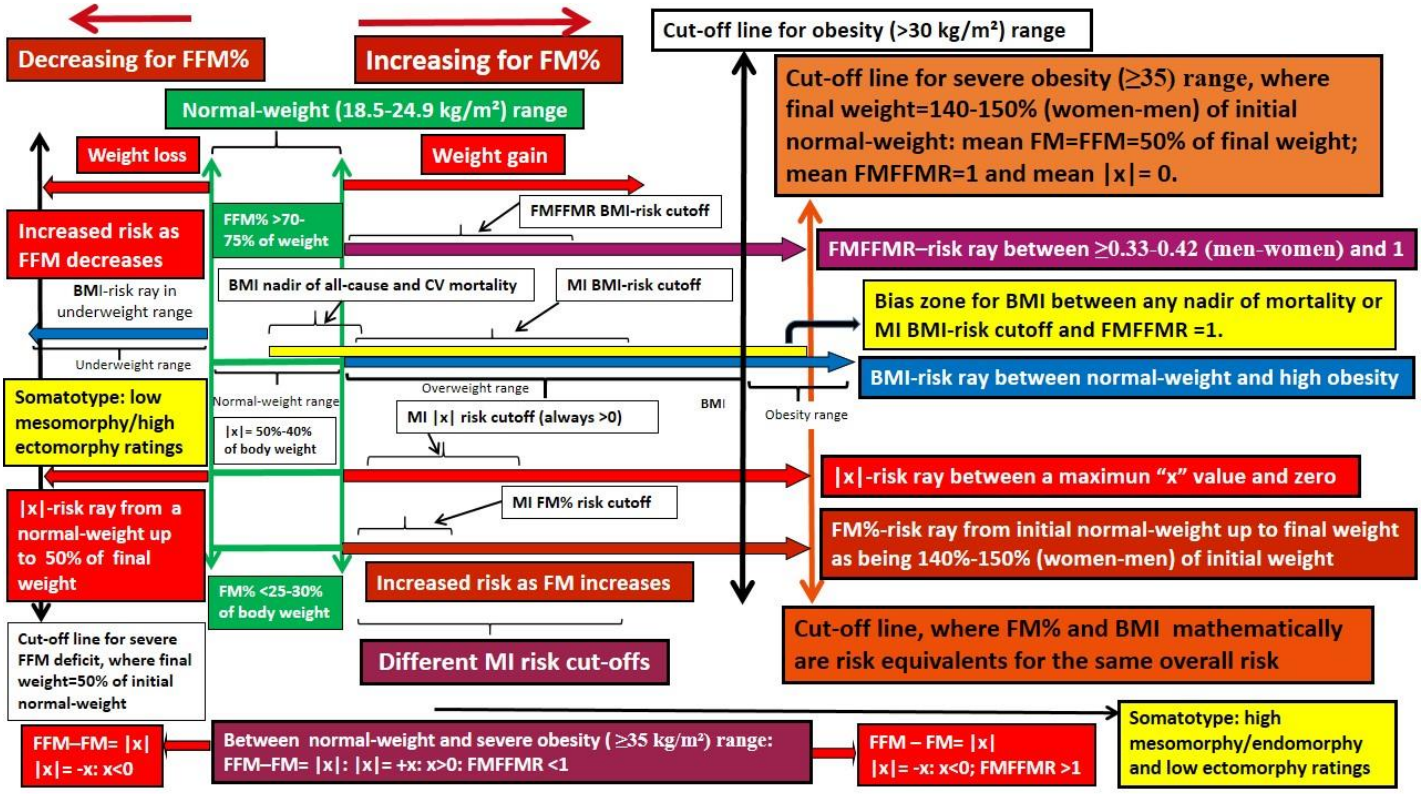

Graphical Abstract: Number lines and horizontal biological risk rays drawn on the Cartesian space for representing values of FMFFMR (in magenta color), BMI (in blue), modulus |X| (in red), FM% (in brown) and FFM% deficit (in red), either in healthy population or in cases of MI and mortality. Metrics-associated risk increases as each risk ray moves to the right or to the left in the sense pointed by the arrowheads. Cut-off lines indicating a normal-weight range (in green), obesity >30 kg/m² (in black), severe obesity ≥35 kg/m² (in orange) or severe FFM deficits are drawn where appropriate.

Data from any ethnically-based and sex-specific population study may be translated to the graphical abstract. Any reference value for metrics may be represented from an origin towards the arrowheads. We find the points with normal baseline values in the region of normal-weight range (in green color) as an origin of each risk ray. The highest risk values for MI would lie on each ray of risk moving further outwards (generally in right side). Different risk cut-offs are drawn where appropriate. On the respective risk rays drawn in right direction would lie points of increased risk representing values from acquired biological changes pointing towards greater risk excess of MI. A bias zone within BMI, from any nadir of all-cause mortality up to severe obesity, was drawn in yellow. Values in the |X|-risk ray drawn to the right, from a maximum positive value in their origin up to zero, and the corresponding |X| risk cut-off would be represented where appropriate. Mathematically, all "x" values lying on this |X| risk ray after the corresponding cut-off line indicating severe obesity would have a |X| value higher than zero, but being |X| = –X (X<0). Similarly, all "x" values lying in the |X|-risk ray drawn to the left (in underweight range) would be equal to –X (X<0). The two corresponding |X|-risk rays present different high-risk body compositions because of excess FM to the right and FFM deficits to the left indicate for different type and sense of biological risk as well as different somatotype ratings.

§ This graphical may be applied to both case-control and cohort studies.

§§ Modulus |x| as absolute value describes the distance from zero that one number is on the number line, without considering direction or sign. In this approach, an absolute value is always ≥0 and never being negative, but as mathematically explained, |x| may be = +x or = –x.

BMI indicates body mass index in kg/m²; CV, cardiovascular; FFM, fat free mass in kg or % as appropriate; FM, fat mass in kg or % as appropriate; FMFFMR, fat mass-to-fat free mass ratio; MI, myocardial infarction; |x|, modulus as the absolute difference between FFM and FM, and it may mathematically be =+x or = –x, in agreement with initial and final values from each one.

Source: original graphic design built by the autor, who has the copyright. This graphical was drawn from MI and mortality data worldwide, and as a result of original research.