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Review Article

Why Predicting Health Risks from Either Body Mass Index or Waist-to-Hip Ratio Presents Causal Association Biases Worldwide: A Mathematical Demonstration

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Abstract

Elevated body mass index (BMI) and waist-to-hip ratio (WHR) are associated with increased health risks. However, both of these obesity metrics may present causal association biases when assessing different individuals with identical risk values for each anthropometric. Thus, an accurate interpretation of the body composition as well as body fat excess or musculoskeletal mass deficit is important before inferring any causal risk. Hence, although higher BMI and WHR may be associated with health outcomes, they might not be appropriate for causal inference due to different origins in the bodily components contributing to them (i.e., fat mass [FM] and fat-free mass [FFM] within BMI, and waist and hip circumferences within WHR).

Biologically, each body measurement and ratio between two measurements present a different relationship with the risk. Thus, two conflicting factors as being the numerator and denominator of an abstract fraction (e.g., FM vs. FFM and waist vs. hip) may generate over- or under-estimates of the overall risk if the mentioned factors are differentially distributed between groups being compared. That way, if the absolute differences between mean FM and FFM, or between mean waist circumference and hip, are not balanced when comparing healthy with unhealthy cases, false outcomes may be generated. This approach considers the absolute difference between two means (e.g., mean FFM minus FM) as a new variable or modulus |x|. Thus, any difference in means of non-zero (i.e., mean |x|>0) means that you are comparing for diferent "x" values between groups, and therefore, assessing for a different body composition.

After investigating, in most population studies, an unbalanced distribution for the corresponding mean differences of the |x| values may be demonstrated, irrespective of any anthropometrically or technologically-measured body composition. Thus, causal association biases occurred worldwide when using BMI-or WHR- cut-offs without taking into account the modulus |x| as potential confounding factor, and therefore, accepting a protective overestimate of FFM and hip with respect to FM and waist, respectively. It may be demonstrated mathematically and in the Cartesian space that any mean FM-to-FFM ratio <1 and WHR <1 may never represent the overall risk.

We recommend that the historical paradigm in predicting health risks from BMI and WHR should be shifted.

Keywords: Body Mass Index; Waist-to-Hip Ratio; Cardiovascular Disease; Anthropometrics; Health Risk; Bias

Abbreviations

BMI: Body Mass Index; CVD: Cardiovascular Disease; HC: Hip Circumference; FM: Fat Mass; FFM: Fat Free Mass; FMFFMR: Fat Mass-to-Fat Free Mass Ratio; WC: Waist Circumference; WHR: Waist-to-Hip Ratio

Cardiovascular diseases (CVD) are the leading cause of death globally [1]. In addition, elevated body mass index (BMI) and waist-to-hip ratio WHR) are associated with increased risk of CVD and all-cause mortality [2-14]. However, both of these obesity metrics may present causal association biases when assessing different individuals with identical risk values for each anthropometric (e.g., BMI >27.6 kg/m^2, and WHR >0.90) [15-18]. Thus, an accurate interpretation of the healthy and unhealthy body composition (BC) as well as body fat excess is important before inferring any causal risk and apply it to the clinical practice. Hence, a correctly estimated BC could predict better the actual risk of CVD and mortality.

It is well known that mere association does not equate to causation of disease incidence. Besides, weight excess (e.g., BMI >24.9 kg/m^2) and elevated WHR (e.g., >0.85 or >0.90) are not the same as body fat excess [19,20]. Thus, although higher BMI and WHR may be associated with health outcomes, they might not be appropriate for causal inference due to different origins in the main bodily components contributing to them (i.e., fat mass [FM] and fat-free mass [FFM] within BMI, and waist circumference [WC] and hip circumference [HC] within WHR). Biologically, each factor or component presents a different relationship with the risk, but they would be intrinsically linked in each ratio or mathematical fraction (i.e., in the FM-to-FFM ratio [FMFFMR] and in WHR). Therefore, a high-risk BC is hardly measurable from either BMI or WHR in isolation because of two conflicting factors (i.e., FM vs. FFM and WC vs. HC) that may generate over- or under-estimates of the overall risk if the mentioned factors are differentially distributed between groups being compared, either by sex, age, and race or ethnicity [16-18,20]. This is because, although BMI and WHR are strongly correlated with unhealthy body fat across populations, there are limitations in its predictive ability if the absolute differences between FM and FFM, or between WC and HC, are not balanced when comparing healthy with unhealthy cases, or when evaluating survival in any whole-population study [16,20]. This approach considers the absolute difference between two means of simple body measurements (e.g., mean FFM minus FM and mean HC minus WC) as a new anthropometric variable or modulus |x|. Thus, we may have the difference in means between two mean values in a parallel group analysis (e.g., mean FFM minus FM = "x" = |x| as the mean absolute value of the total group), or the mean of individual differences in a pairwise comparison (i.e., [mean FFM minus FM in one group (x_1) + mean FFM minus FM in another group (x_2)] divided by two = "x" = mean |x| in the total group). Similarly, a cut-off for |x| when comparing risk between healthy and unhealthy groups may be established, as appropriate. However, mathematically, a non-zero difference in means (i.e., a |x| cut-off of >0) would indicate a unbalanced distribution between groups being compared [20]. By deduction, if, and only if the mean of differences in two groups (i.e., mean x_1 and x_2) take the same value and different sign, the mean |x| of the total group is equal to zero (|x| = 0), and therefore, a balanced distribution between the mean measurements mathematically would be accepted. Obviously, a mean |x| value consideres no direction or sign, but the distance from zero that a number is on the number line. Nevertheless, in the mean of individual differences for each group, the sign matters, and any mean "±x" value is crucial for demonstrating balance or imbalance of the concerned measurements between groups being compared [20]. That way, any difference in means of non-zero (i.e., mean |x| >0) means that you are comparing for diferent "x" values between groups, and therefore, a different-equal risk assignment between subjects who have equal-different high-risk BC may occur [16,18,20].

Since difference in means has been only described, but not actually applied worldwide [16,20], either BMI or WHR might present a biased clinical information due to hiding some confounding factor that distorts their true relationship with CVD and mortality outcomes [20].

In spite of the many large and prominent studies that make use of BMI and WHR, causal association biases for BMI and WHR have not been well addressed [3-14,20], even though arguments are, in fact, accumulating in support of association biases when predicting CVD risk from both indices [15-18,20-22]. In many published studies, selection biases were introduced due to a protective overestimate of HC with respect to WC, so that in any WHR risk cut-off <1, the difference in means between WC and HC was always unbalanced (i.e., the mean difference was non-zero), leading to distorted health outcome predictions [16-18,20-22]. Such bias may occur in any population study where the WHR risk cut-off always occur before establishing a balanced distribution between mean WC and HC or HC and height/2 (i.e., mean differences being zero), and besides, for demonstrating bias zones for WHR with respect to WC and the waist-to-height ratio (WHtR) [14-18,20-22], (Figure 1).

Figure 1: Number lines and horizontal anthropometric risk rays in the Cartesian space for representing values of WHtR, WC, WHR (in magenta), and the absolute difference between HC and WC (termed as modulus |X| = HC-WC; in blue), either in healthy population or in cases of CVD or mortality. Metrics-associated risk increases as each risk ray is followed towards the right in the sense pointed by the arrowhead (the region of cases). Cut-off lines representing a balanced distribution for the difference in means between (WC−height)/2 (mean WHtR = 0.5) and WC−HC (mean WHR = 1: mean |X| = 0) are drawn where appropriate. Identified bias zones for WHR are located where appropriate.

Data from any ethnically-based and sex-specific population study may be translated to the model. Any reference value for metrics may be represented from the origin and on its proper axis. We may find the points with the lowest baseline values for WHtR, WC and WHR (healthy/controls or unhealthy cases) on the respective axis at the origin. Similarly, different risk cut-offs are drawn where appropriate. The highest baseline values (generally in unhealthy cases) would lie on each ray of risk moving further outwards (right site). Remaining values of WHtR, WC and WHR would lie on each risk ray before or after each risk cut-off (in either the healthy or unhealthy zone, respectively), as appropriate. On the respective risk rays drawn, there would be points of increased abdominal obesity representing values for thousands of CVD or mortality cases as well as biological changes pointing towards greater excess risk as each risk ray moves into the right site. Values in the |X|-risk ray, from a maximum positive value in their origin up to zero, as well as the |X| risk cut-off would be represented on the corresponding ray of risk, where appropriate, and in all, the |X| value is non-zero and equal to +X (X>0). Values lying on the |X|-risk ray, after the corresponding cut-off line for WHR = 1, would have a |X| value higher than zero, but equal to -X (X<0). This is in consonance with a high-risk body composition, where mean WC is higher than HC.

* This model may be applied to both case-control and cohort studies.

HC denotes hip circumference; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio; |X|, modulus as result of subtracting WC from HC.

|HC−WC|; =, balanced distribution between the simple measurements concerned.

Source: original model was partially published. It was designed and built by the author, who has the copyright.

BMI also may present the same mathematical issue, which has already been explained [20]. BMI-defined health risk may lead to confounding conclusions in a wide variety of investigated situations such as CVD, obesity paradox, metabolically healthy obesity or the BMI nadir in a U- or J-shaped mortality curve [8-10,12,13,20-24]. Surprisingly, in the BMI risk association concluded in the UK

Biobank study, FM and skeletal muscle mass were not superior to BMI in predicting CVD events and all-cause mortality [13]. The question, however, is not the magnitude of association for these metrics, but the risk compared between groups or tertiles due to differences in the underlying FM and FFM being two associated conflicting factors, but with different pathophysiological properties [20]. In fact, any BMI-associated risk may correspond to different FM percentages if the mean FFM is higher than FM (non-zero difference in means, and mean FMFFMR <1, i.e., an unbalanced distribution), which is prone to generate a protective overestimate of FFM with respect to FM, and therefore, the BMI assigning false outcomes [20,22]. The problem is that any particular FM percentage and different non-zero differences between FM and FFM may correspond to different BMI values, thus misclassifying the risk measured from BMI when allowances of risk are not made for FM and FFM [20]. Similarly, a same mean BMI may correspond to different FM percentages and different |x| values. In addition, if FM and FFM increase or decrease about a same concrete value in kg, the mean final weight and percentages for both will be different even though the variation of the difference in means may be null. On these bases, FM and FFM may be factors associated to a risk status [17,18,20]. However, any non-zero difference associated with the risk status (mean |x|>0) will always lie in a bias zone for BMI due to unbalacing for their two conflicting factors. Moreover, BMI might be compromised as a measure of total risk if FFM is always more than 50% of body weight whether in healthy subjects or in any BMI-based epidemiological risk threshold [13,20,22], (Figure 2).

Figure 2. Graphical abstract. Relationships between FMFFMR and BMI displaying a U-shaped curve from theoretical values in any total population study. Dashed lines to the right and to the left on the two branches would display a J-shaped curve, where real values of FMFFMR are higher on the right than on the left. Health-related risk rays for a new anthropometric variable or modulus |X| as result of subtracting FM from FFM have been drawn. Cut-off lines for weight changes to up 150% and 50% of mean initial weight to the right and to the left, respectively, were drawn, where appropriate. Similarly, FM and FFM percentages may be represented from a nadir (0% vs. 100%, respectively) to up a top point, where FMFFMR =1 (50% for each component) on the corresponding Y-axis. The hypothetical nadir for FMFFMR =0 in the Y-axis of both branches, only would occur when FM is of zero and FFM being 100% of mean final weight. Healthy or unhealthy status as well as BMI ranges are established in agreement with WHO BMI categories. Different cut-offs for BMI, FM and FFM percentages, cut-offs for modulus |x|, and FMFFMR may be applied from any ethnically-based and sex-specific population study.

* Values for FM, FFM, modulus |x|, and FMFFMR in the normal-weight range may be universally known by using either anthropometry or technological methods.

** Modulus |X| and (±X) values mathematically operating in a different way. Mathematically, modulus |X| may be equal to +X or it may be equal to –X. A |X| modulus equal to –X (X<0) only may be found in underweight range (on the left) or in high-obesity range (on the extreme right, and where the FM percentage at the maximum may represent more than 50% of mean final weight: FMFFMR >1: |X|>0: |X|= –X (X<0). Between the normal-weight and obesity range, where FMFFMR =1 and |X|=0, always occurs that modulus |X| is non-zero and equal to +X (|X|>0: |X|= +X (X>0).

BMI denotes body mass index; CVD, cardiovascular disease; FM, fat mass; FFM, fat free mass; FMFFMR, fat mass-to-fat-free mass ratio; MHO, metabolically healthy obesity; MUO, metabolically unhealthy obesity; OP, obesity paradox; |X|, modulus as result of subtracting FM from FFM.

Source: original design was built by the author, who has the copyright.

It is noteworthy that FM and FFM percentages in the normal weight range (<25-30% and >75-70% [men-women], respectively) are unbalanced and may be universally known and, therefore, we might collate any unbalanced distribution for their difference in means in any BMI risk cut-off, when assigning CVD risk [20]. Hence, in any BMI cut-off in the normal or overweight/obesity range, where mean FM is lower than FFM (mean FMFFMR <1, mean difference is non-zero), body weight may always involve a protective overestimate of FFM with respect to FM, and leading to an association bias when assigning causal risk to BMI (see Figure 2).

From the normal-weight range (e.g., a mean weight of 80 kg: FM = 25% [20 kg], FFM = 75% [60 kg], and |x| = 60-20 = 40 kg), two negative transitions may develop over time: weight gain (essentially by increasing FM) or loss (essentially by musculo-skeletal mass deficit). In this approach, a relationship between FMFFMR and BMI may be established by examining the two branches of a theoretical U-curve from its nadir in the normal-weight range (0< FMFFMR <0.3-0.4 value, FM <25-30%, and FFM >75-70%) up to those points where FMFFMR = 1 and the difference in means is zero (|x| = 0), (see Figure 2). In addition, a cut-off line on the right site may indicate that, only when a mean final weight is about 150% (e.g., 120 kg) of mean initial weight (e.g., 80 kg), do FM and FFM coincide (at 50%), at the same point where FMFFMR = 1 and |x| = 0 (e.g., 60 kg of FM [50%] vs. 60 kg of FFM [50%]). Thus, both measures estimate the same overall risk in mathematical terms. Similarly, a cut-off line on the left site may indicate that, when a mean final weight is about half (e.g., 40 kg) of mean initial weight (e.g., 80 kg), do FM and FFM theoretically coincide (at 50%), at the same point where FMFFMR = 1 and |x| = 0 (i.e., 20 kg of FM vs. 20 kg of FFM). Obviously, only if FM does not move from the nadir of FMFFMR = 0 (FM = 0% vs. FFM = 100%), can one find two opposite points to the right and to the left, where in the nadir of the y-axes FMFFMR is zero and mean |x| = FFM (FFM = 100% of final weight). Nevertheless, this biological transition is epidemiologically impossible on the right, while being more plausible on the left in situation of sarcopenia [25], (see Figure2).

In our opinion, one thing is clear: FM usually increases with weight gain, while FFM usually decreases with weight loss. Thus, regarding FMFFMR the right branch will always rise higher than the left branch and, therefore, resemble a J-shape curve similar to that describing BMI-associated mortality in large epidemiological studies [8-10,12,13]. Moreover, values for the mean difference of |x| in the right branch would always be positives (|x| = +x) while being negatives (|x| = -x) in the left. It means that the high-risk BC measured in both branches is well different and, therefore, any difference in means showing unbalanced distribution for FM and FFM (|x|>0: FMFFM<1 and |x| = +x) may involve association biases for any BMI cut-off lying in the right branch.

On the other hand, from the normal-weight range, in the same horizontal direction, three further difference-related risk rays may be drawn regarding sense and origin in the Cartesian space (see Figure 2).

To the best of our knowledge, each X-risk ray has their own Cartesian origin and sense, and besides, representing different magnitude (in kg) and sign, which mathematically operate for calculating each mean |x| value. Obviously, in underweight and overweight-obesity range can one find two X-risk rays with opposed senses and different magnitudes, but both being inversely associated with an unhealthy status (i.e., the lower the "x" positive value to the right [close to zero], the higher the risk, and, the lower the FFM to the left, the higher the risk). In contrast, the third X-ray is drawn in the anthropometric space of metabolically unhealthy obesity, for having their coordinates origin in a high obesity degree (FMFFMR = 1: FM = FFM: |x| = 0), and showing a direct association with the risk as FM increases (i.e., the higher the "x" negative value to the extreme right [far from zero], the higher the risk). Thus, when comparing healthy and unhealthy obesity in a population subset, any unbalanced distribution for the difference in means will demonstrate a selection bias, and overall, after knowing that in metabolically unhealthy obesity the mean of differences is negative (x<0: FM>FFM), (see Figure 2).

Our arguments are key when comparing individuals with different anthropometric risk and taking into account the mean of individual differences for "x" in each group of comparison. It is clear, when having different "x" values and signs in each group, the mathematical sum for calculating whether the mean of differences or difference in means should respect the negative signs. Thus, an "x" negative value (x<0) should be assigned in underweight (FMFFMR <1) and metabolically unhealthy obesity (FMFFMR >1) situations, while when having between normal-weight range

and overweight-moderate obesity (FMFFMR being always of <1), the "x" value is always positive (x>0) (see Figure 2). Hence, after considering sign and magnitude for all values of "x" in agreement with each BMI stratum, in any epidemiologic BMI cut-off can one find a difference in means of non-zero (cut-offs for |x| of >0: unbalanced distributions) [18,20,22]. This is because belonging to the same or different BMI stratum there are individuals, who may measure for different ±x values, and therefore, estimating for different unhealthy BC. Thus, when in the UK Biobank study, FM, skeletal muscle mass and BMI were associated with health risks by using bioimpedance, an unbalanced distribution for the difference in means between FM and FFM may be proved too [13]. As verified, a mean weight of 85.8 ± 14.3 kg and mean BMI of 27.6 ± 4 kg/m^2 in men may involve myocardial infarction and mortality risk. However, after knowing that mean FM was of 25.4% (mean of 21.8 ± 7.8 kg), a mean FFM of 74.6% (64 kg) may be mathematically calculated. Based on this values, a mean FMFFMR of 0.34 (<1) and a mean |x| of 42.2 kg may be established. Similarly, when analyzing values in women can one find a mean FMFFMR of 0.58 and a mean |x| of 18.8 kg. Thus, in both sexes, the mean FMFFMR was far from one and mean |x| far from zero (unbalanced distribution between quintiles: |x|>0: 42.2 in men and 18.8 in women) [12], (apply in Figure 2). For more information, the previous UK Biobank and Rotterdam studies also presented association bias for BMI when anthropometrically measuring FM and FFM percentages [5,7,20]. Thus, when the mean FFM and FM in both studies was recalculated, the mean FMFFMR becomes of <1 (0.38 in men [|x|≈37 kg] and ≥0.60 in women [mean |x| between 15 and 18 kg]), and, therefore, bringing about a protective overestimate of FFM with respect to FM. As published, differences between FM and FFM for men and women justify a different |x| value in each sex. In this line, when associating BMI and CVD risk, a higher bias in men than in women may be found [20]. However, an inversely associated mean |x| value of >0 has the importance of comparing different amount of FFM and FM (i.e., a significant difference in kg), and therefore, supporting the idea of an unbalanced distribution between both components in most epidemiologic studies. Moreover, when you compare said factors you are comparing for different risk volume because of density (g/cm^3) in each factor is well different, and it makes BMI an inappropriate risk indicator [18,20,22].

By using a syllogistic approach, whether FMFFMR <1 is associated to anthropometrically healthy individuals (first true major premise), and being the mean FFM percentage higher than FM percentage on a population dataset (second true minor premise), any BMI-associated risk above FM percentage will be a false conclusion drawn from a mathematical misconception. Similarly, since a difference in means between FFM and FM may be inversely associated with any unhealthy status (i.e., mean |x|>0), if FM is directly associated with the unhealthy group, any BMI cut-off lying between normal-weight range and moderate obesity (i.e., FMFFMR <1) may show association bias for a causal inference (see Figure 2). In addition, if you anthropometrically compare healthy (FMFFMR <1) and unhealthy (FMFFMR >1) obese people, a balanced distribution between FM and FFM should be respected (i.e., difference in mean should be zero). If not, selection bias may occur due to comparing for different ±x values or having between groups a non-homogeneously distributed sample size, what is epidemiologically likely.

Unfortunately, each anthropometric as construct has its own meaning in mathematical terms. Thus, the difference in means between WC and HC in any whole-population study may justify an unbalanced distribution between the groups being compared, and, therefore, comparing for different values may occasion selection bias [14-18,20,22]. Similarly, if among FM and FFM as mathematical parts of body weight there are different mean values (i.e., mean FMFFMR of <1: mean |x|>0), a protective overestimate of FFM with respect to FM may occur, and therefore, causality for BMI cannot be assumed [20].

It is well known that anthropometrics exhibiting some degree of association do not necessarily imply a direct causal pathway for the risk, at least not without removing biases or assessing distributions of the simple measurements between groups being compared [20]. When thinking this way in epidemiology, BMI and WHR have always been associated with CVD and mortality, yet always showing a protective overestimation of FFM and HC with respect to FM and WC, respectively. In this undisputable clinical and anthropometric context, the corresponding raw differences were always omitted, hiding them as unmeasured confounding factors that led to distorted and false causal outcomes. This was an artifact of selecting the study samples and assigning false positive values in place of true negative ones [15-18,20,22]. As a result, risk assignment for BMI and WHR were systematically biased because comparisons of FM vs. FFM and WC vs. HC never presented risk

equivalence, and they always showed an unbalanced distribution of the mean differences between groups of comparison [15-18,20,22]. In such cases, thresholds defining risk associations should be informed by the scientific and anthropometric context, and all causality criteria should be taken into account in any BMI- or WHR-associated risk. That way, the true risk assignment to BMI and WHR - in light of potential confounding factors - should be conditioned on the covariates receiving the realistic risk, such as FM percentage or WHtR as expressing a risk volume concept [16,18,20,22]. Thus, a causal inference from BMI and WHR beyond what can be explained without confounding factors would be unacceptable because the associations observed worldwide may be attributable to differences in metrics other than that being investigated, and, thus, causality cannot be assumed.

In most large-sample studies worldwide, any anthropometrically or technologically-measured BC will always showed an unbalanced distribution for the corresponding mean differences of the |x| values, irrespective of other non-anthropometric risk factors (e.g., cardiovascular risk factors, cardiorespiratory fitness, specific physical training, education level etc.,), [3-14,20,22]. In this approach, any WHR-associated risk beyond of that of WC will always occur by overestimating HC with respect to WC [15-18,20,22]. Similarly, any BMI-associated risk without balancing between FM and FFM will always appear to be biased because of FM percentage or FFM by unit of height may be differentially distributed between the groups being compared [20]. In this line, if FM percentage and a difference in some particular metric may show significant differences between groups of comparison, any nadir of BMI-associated mortality in normal or overweight range may also show association biases. The same premises might be applied in any BMI risk cut-off for CVD, obesity paradox or metabolically healthy obesity, where mean FMFFMR <1, and, therefore, FFM showing a protective overestimate with respect to FM [20], (see Figure 2). Hence, since any BMI cut-off biologically may involve an abstract fraction (FMFFMR <1), BMI mathematically may never express the whole-risk. This is because always can one find BMI-assigned false risk (selection bias), while FM percentage and |x| value involving not a true risk.

On the other hand, when intrinsically using abstract fractions (i.e., FMFFMR and WHR), health outcome predictions become a misleading evidence and a historical error. Thus, in both ratios (i.e., a risk factor divided by a protective factor), the numerator and denominator are conflicting factors showing different relationship with the risk. In this approach, opposite biological factors are parts of the same fraction, where the numerator and denominator showed never mathematical equality in most studies (mean FMFFMR and WHR <1: mean |x|>0), [17,18,20,22]. Moreover, the biological and mathematical sense of each factor at play was always overlooked. This is because the impact on the risk from FM and WC is quite different to that of FFM and HC. On this basis, biologically and mathematically, the different risk rays drawn should be well interpreted (see Figures 1 and 2). Thus, the arrowhead of FFM deficit represents an opposed sense ($x<0$) to that of FM increasing ($x>0$). Similarly, increasing WC up to WHR = 1 ("x" range of ≥0) is not the same as WHR >1 ("x"<0: negative value). Therefore, biological risk derived from increased FM (e.g., CVD or cardiovascular mortality risk in overweight-obesity range) is not the same as decreased FFM (e.g., mortality in situations of sarcopenia, malnutrition, cancers etc.). That way, neither mean BMI nor WHR may be optimal metrics representing the true risk, at least without controlling for realistic changes experienced in FM and FFM, and in WC and HC.

For the first time in medical sciences and epidemiology, general obesity and abdominal obesity measured by BMI and WHR, respectively, meet mathematical demonstrations justifying causal association biases. Effectively, considering both of these obesity metrics as continuous numerical variables derived from abstract fractions, the causal risk directly associated with their cut-offs was a mathematical misconception because of the difference in means between their respective conflicting factors was omitted. Consequently, quantitative changes experienced by the conflicting factors at play as well as percentages of the variations in each one of them were ignored. In this sense, the differences in means between the concerned factors were hidden in the epidemiological data [20]. That way, the biological meaning of the variations in each component had no a mathematical translation. In fact, the "x" value in each stratum of BMI or WHR is key when mathematically operating and calculating mean of differences in each group of comparison (see Figures 1 and 2). Indisputably, when pointing underweight range due to weight loosing, FFM has experienced a decreasing from an initial origin and the "x" value is equal to -x ($x<0$). As said above, the same mathematical fact occurs in

metabolically unhealthy obesity when having high obesity degree and a FM percentage higher than that of FFM (x<0). Similarly, when having high abdominal obesity, if the mean WC is higher than HC (mean WHR >1), the "x" value is equal to -x (x<0). Therefore, when anthropometrically pooling a sample of healthy and unhealthy participants, the "x" value and its sign involving for different anthropometric risk should be a controlled factor. If not, the mean or cut-off point of any anthropometric associated with health risk outcomes may be biased. In any case, it will always occur if between groups you are comparing for different sign and magnitude of the "x" values (unbalanced distribution), and the mean |x| remaining slanted towards one of the groups. This happened in most population studies when using BMI and WHR cut-offs without taking into account the modulus |x| as potential confounding factor, and therefore, overestimating the protective factors with respect to those others receiving true risk [17,18,20].

Our mathematical findings are not limitations. In any observational study, risk assignment is not random, and a balanced mean of differences between the aforementioned measurements is anthropometrically impossible (the difference in means was always non-zero). Thus, both BMI and WHR always presented selection biases [20]. It may be demonstrated mathematically that any mean FMFFMR <1 and WHR <1, expressed abstractly as proper fractions, may never represent the whole risk in mathematical terms, at least without conditioning on other covariates that inform the true risk. After understanding mathematical inequalities between WC and HC as well as differences for FM and FFM in healthy people, the components linked causally with the total risk (i.e., total body fat and unhealthy abdominal fat) should show a balanced distribution with the protective factors (i.e., those derived from musculoskeletal component). This issue is essential before assuming causality for any anthropometric-associated risk, at least if the intention is to compare for a uniform BC and true health risk. Likewise, inferring causality from BMI and WHR is difficult due to differences in the unhealthy BC (different FM percentage or non-equivalent relative abdominal volume or different FFM by unit of height) between groups being compared. In this approach, to avoid over- or under-estimate of some measurements with respect to others, propensity score methods have also been recommended [16-18,20,22].

Finally, if by omitting some anthropometric or mathematical factor in epidemiological data the medical sciences were confused for a long time, these novel discoveries are keys for the advancement of knowledge in scientific community. Anthropometrically, associations between BMI and mortality outcomes as well as risk cut-off points for BMI in overweight-moderate obesity range and WHR <1 always provided a biased epidemiological association instead of biological causality. Likewise, when anthropometrics are used in public health to address the treatment and prevention of diseases, the conflicting bodily components that mathematically define each metric should be distinguished and quantified, what is anthropometrically possible.

We strongly recommend that in clinical practice and in public health politic the anthropometric insight and historical paradigm when truly assessing health risks from BMI and WHR should be shifted, especially to avoid biases in current risk values, whether by sex, age and race or ethnicity.

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