



Trabajo Original

Obesidad y síndrome metabólico

Abdominal obesity and myocardial infarction risk — We demonstrate the anthropometric and mathematical reasons that justify the association bias of the waist-to-hip ratio

Obesidad abdominal y riesgo de infarto de miocardio: demostramos las razones antropométricas y matemáticas que justifican el sesgo de asociación del índice cintura-cadera

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Abstract

Background: the waist-to-hip ratio (WHR) is widely used to evaluate the association of abdominal obesity with myocardial infarction (MI).

Objective: our aim was to determine whether WHR-associated risk provides a bias.

Methods: a case-control study in 252 men. Stratification was used as an approach for removing bias effects. We created a baseline covariate ($WHR_{0.95-0.99}$) from a new matched sample in the stratum between 0.95 and 0.99. This stratum coincides with the overlap area of the distribution, where all subjects have a similar propensity score. We considered other covariate (WHR_c), conditioned on WHR < 1 and waist circumference (WC) being assigned a spurious risk. We hypothesized that subtracting hip circumference from WC (WHD) can be essential to observe the confounding effect provided by WHR.

Results: BMI: AUC: 0.694, 95 % CI (0.628-0.760); OR: 3.8. WC: AUC: 0.743, 95 % CI (0.681-0.805); OR: 5.7. WHR: AUC: 0.798, 95 % CI (0.740-0.855); OR: 8.6. Waist-height ratio (WHR_c): AUC: 0.782, 95 % CI (0.724-0.840); OR: 8.5. WHD: AUC: 0.204, 95 % CI (0.146-0.261); OR: 0.36. Prevalence in cases: WHR ≥ 0.95 (84.1 % vs. 38 %; OR: 8.6); WHR < 1 (36.3 % vs. 85.7 %; OR: 2.3); WHR ≥ 1 (63.4 % vs. 14.2 %; OR: 4.4); WC ≥ 94.4 (71.4 % vs. 30.1 %; OR: 5.7); WHD ≥ 2.2 (27.7 % vs. 75.3 %; OR: 7.9); WHRs (50 % vs. 25 %; OR: 2).

Conclusions: WHR provides an association bias in MI cases. This can be extrapolated to other study populations. The bias is explained by a mathematical misconception where the protective effect of HC is overestimated concerning WC and height. The risk associated with WHR is higher than that associated with WC and WHR entails anthropometric inconsistency and bias, to the extent of becoming epidemiologically false.

Keywords:

Abdominal obesity.
Myocardial infarction.
Body composition.
Anthropometric
indicator. Bias.

Resumen

Antecedentes: el índice cintura-cadera (ICC) se utiliza ampliamente para evaluar la asociación de la obesidad abdominal con el infarto de miocardio (IM).

Objetivo: nuestro propósito era determinar si el riesgo asociado a la ICC produce sesgo.

Métodos: estudio de casos y controles en 252 varones. Usamos la estratificación como criterio para eliminar los efectos del sesgo. Creamos una covariable basal ($ICC_{0.95-0.99}$) para una nueva muestra emparejada en el estrato de valores entre 0,95 y 0,99. Este estrato coincide con el área común de solapamiento de la distribución de puntos, donde todos los sujetos tienen un índice de propensión similar. Consideramos otra covariable (ICC_c) condicionada en $ICC < 1$ y una circunferencia de cintura (CC) donde la asignación de riesgo fuera espúrea. Hipotetizamos que restando CC del valor de la cadera se calculaba otra variable aritmética (DCC) que podría ser esencial para evidenciar el efecto de confusión que genera el ICC.

Resultados: IMC: ABC: 0,694, IC 95 % (0,628-0,760); OR: 3,8. CC: ABC: 0,743, IC 95 % (0,681-0,805); OR: 5,7. ICC: ABC: 0,798, IC 95 % (0,740-0,855); OR: 8,6. Índice cintura-talla (ICT): ABC: 0,782, IC 95 % (0,724-0,840); OR: 8,5. DCC: ABC: 0,204, IC 95 % (0,146-0,261); OR: 0,36. Prevalencia en los casos: $ICC \geq 0,95$ (84,1 % vs. 38 %; OR: 8,6); $ICC < 1$ (36,3 % vs. 85,7 %; OR: 2,3); $ICC \geq 1$ (63,4 % vs. 14,2 %; OR: 4,4); $CC \geq 94,4$ (71,4 % vs. 30,1 %; OR: 5,7); $DCC \geq 2,2$ (27,7 % vs. 75,3 %; OR: 7,9); ICCs (50 % vs. 25 %; OR: 2).

Conclusiones: el ICC produce un sesgo de asociación en los casos de IM. Ello puede extrapolarse a otras poblaciones de estudio. El sesgo se explica por un error de concepto matemático que sobreestima el efecto protector de la cadera con respecto a la CC y la altura. El riesgo asociado al ICC por encima del de la CC o el ICT presenta inconsistencia antropométrica y sesgo, llegando a ser epidemiológicamente falso.

Palabras clave:

Infarto de miocardio.
Enfermedad
cardiovascular.
Obesidad
abdominal. Indicador
antropométrico.
Composición
corporal. Sesgo.

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INTRODUCTION

Cardiovascular diseases (CVDs), mainly heart disease and stroke, remain a worldwide leading cause of morbidity and mortality (1). Anthropometrically, important differences have been found in the assessment of the effects of obesity on the risk for coronary disease (2-4). Interestingly, an accurate estimation of body composition (BC) is highly relevant from a public health perspective (5). Hence, metrics associated with abdominal obesity and a nutrition status with excess body fat are essential for establishing the impact of adiposity on the metabolic processes that result in increased myocardial infarction (MI) risk. However, association does not equate to causation on incident MI, and in non-randomized study designs baseline differences in BC between the groups to be compared may introduce a systematic bias in the results.

The INTERHEART study proved waist-to-hip ratio (WHR) was a better indicator for predicting MI risk than body mass index (BMI) and waist circumference (WC) (3). Other more recent studies have also deemed WHR to be an excellent MI risk predictor (6-9). Besides, results from the UK Biobank have conferred to WHR a greater excess risk of MI in women than in men (7). However, evidence is accumulating in support of WC for reflecting MI and cardiometabolic risk (10-17). Additionally, the use of composite metrics such as the waist-height ratio (WHtR) or whole-body fat percentage (%BF) for predicting cardiovascular events and mortality has demonstrated a validity close to that of technological methods (10-17). On the other hand, we have revealed a selection bias for WHR, where this metric explains neither total causation nor the true nature of the risk (13, 14). In fact, an important question lies in the discrepancy observed between WHR association and its worst correlations with measures of general and central adiposity (6,7,13,14).

Moreover, since a propensity score was defined, different methods have been used to address selection biases in balancing the distribution of covariates between exposure groups (18,19). Thus, the conditional distribution of risk between groups should be the same when the observed baseline covariates do not present standardized differences. However, a different BC between groups with similar baseline confounding variables may provide a bias in outcomes if the true-risk assignment does not account for the covariates that predict being assigned a true risk. In this sense, as a result of the above, a risk assignment for WHR of < 1 may be systematically the same with respect to different values for WC and hip circumference (HC), and therefore may not be directly comparable. Consequently, the bias for WHR can be substantial if both WC and HC are not controlled in the data analysis to preclude in the stratum of $WHR < 1$ the same risk assignment between subjects with equal WHR values, but not necessarily referring to the same BC at risk.

The aim of this study was to demonstrate whether the association of WHR and MI provides a bias in the results, and therefore false conclusions may be derived from a mere statistical analysis. We hypothesized that on a number line, each absolute value would represent the distance between the points corresponding to WC and HC as being mathematically the difference between

denominator and numerator in WHR. However, subtracting provides an arithmetic variable from a set of numbers that represent an estimate of whole risk, and each value does not depend on the estimate of risk for HC with respect to WC. In contrast, dividing WC by HC will give us a proper abstract fraction with an information bias for whole risk, at least between the lowest point and the 0.99 value. Thus, WHR would be a confounding variable with whole risk conditioned on WC and the estimate of risk for HC concerning WC and height. We review what is known about WHR results worldwide, which will allow us to explain in anthropometric models the reasons that justify our insight when handling whole risk.

METHODS

PARTICIPANTS AND MEASUREMENTS

A case-control study with a sample of 252 European men aged 30-74 years, was evaluated. The minimum sample size for calculations was of 90 cases and at least 1 control per case, with obesity exposure, level of safety, and statistical power at 22 %, 0.99, and 0.99, respectively. The odds ratio (OR) for detection was 3. Study participants were recruited from a 2019 database in a Health Area in Spain. Cases were selected from a post-myocardial infarction cardiac rehabilitation program between 2012 and 2019, and data were collected in the first fitting days after hospital diagnosis. Exclusion criteria were nonage or any chronic disease. One age-matched (± 5 years) control was recruited per case in the same Health Area among health center users and State Administration workers. Exclusion criteria were identical for controls and cases, with the additional criterion that controls had no previous diagnosis of coronary disease or history of exertional chest pain. Trained staff used standard protocols to obtain measurements (15,16). All subjects signed an informed consent form according to the Declaration of Helsinki, and the study was approved by the ethics committee at the referral hospital.

Weight (kg) and height (cm) were measured. WC and HC were determined at the umbilicus and at the maximum circumference around the buttocks, respectively (cm). BMI (kg/m^2), WHR, and WHtR were calculated. Waist-hip difference (WHD), obtained by subtracting HC from WC, was calculated to provide an "x" value for each subject, including positive, zero, and negative results ($x = \text{HC} - \text{WC}$).

STUDY DESIGN

A receiver operating characteristic (ROC) analysis was carried out. The cutoff points were defined where sensitivity plus specificity was highest. Other standardized cutoffs were also analyzed. We used stratification as an approach for removing bias effects for WHR, as well as to control the effects of confounding factors derived from the density and distribution of their points between groups (18). We created a baseline covariate ($WHR_{0.95-0.99}$) from a new matched sample in the stratum between 0.95 and 0.99. This stratum coincides with the common area of overlap of the distribution for WHR in both groups, where all subjects had a similar

propensity score. Thus, pairs of cases and controls were formed such that one-to-one matched subjects had the nearest equivalent fraction (caliper distance of ± 0.01 within the same stratum). If, after conditioning, no systematic differences remain between both groups, this will be an indication that the model was correctly specified, balancing the distribution of the measured covariate. Thus, in both homogeneous groups, each subject would have the same probability (nonzero) to be assigned the whole risk, and risk assignment should be strongly ignorable (18). Consequently, in the matched sample we considered other baseline covariate with binary outcomes for spurious risk assignment (WHRs). It was conditioned on a risk assignment that defined spurious risk for $WHR_{0.95-0.99}$ where WC took a lower value than both its own cut-off and HC. A standard difference that higher than 10 % will be taken to indicate a considerable difference in the prevalence of WHRs between both groups. If, after comparing prevalences, no systematic differences remain, this will be an indication that a true risk in that stratum has been correctly assigned.

STATISTICAL ANALYSIS

Data were computed using IBM's SPSS package, version 22.0. Descriptive statistics including mean, standard deviation,

and frequency are provided. Normal distributions were assessed using the Kolmogorov-Smirnov test. Student's t-test and the Chi-squared test were used to establish differences between parametric and non-parametric variables, respectively. The total area under the curve (AUC) was tested with no parametric differences, and values were used for identifying the strength of association for each indicator. ORs according to the defined cut-offs were calculated by using a binary logistic regression analysis. Contingency tables were used in the calculation of OR in other cases. The prevalence between different cut-offs or conditionings for the selected covariate was compared. OR was used to identify the strength of association for each indicator. The confidence interval was set at 95 % in all cases. A p-value < 0.01 was considered significant.

RESULTS

The baseline characteristics of participants and the established cutoffs are summarized in table I. Obesity indicators and WHD showed strongly significant differences ($p < 0.01$). Among single indicators, HC showed no differences ($p = 0.24$). WC and height showed significant differences ($p < 0.01$) in direct and inverse association with MI, respectively. There was no significant difference for $WHR_{0.95-0.99}$ ($p = 0.11$). A WHR cutoff ≥ 0.95 and

Table I. Baseline characteristics of study participants. Indicators with cut-off points defined by ROC analysis, and standardized for WHR and WHD. Values are means \pm standard deviation for continuous variables, and percentages (%) for categorical variables

Variables	MI (n = 126)	95 % CI	Control (n = 126)	95 % CI	P/OR
Age (y)	53.9 \pm 9.7	52.2-55.6	51.7 \pm 9.3	50.1-53.4	p = 0.07
Height (cm)	169.4 \pm 7.2	168.1 \pm 170.7	173.5 \pm 6.7	172.3-174.7	*p < 0.001
BMI (kg/m ²)	28.6 \pm 4.02	27.9-29.3	26.2 \pm 3.4	25.6-26.8	*p < 0.001
WC (cm)	101.7 \pm 20.3	98.1-105.3	91.4 \pm 10.1	89.6-93.2	*p < 0.001
HC (cm)	99.0 \pm 12.9	96.8-101.3	97.5 \pm 6.4	96.4-98.6	p = 0.24
WHR	1.01 \pm 0.06	1-1.02	0.93 \pm 0.06	0.92-0.94	*p < 0.001
WHD (cm)	(-1.3) \pm 6.8	(-2.5)-(-0.1)	6.1 \pm 6.6	4.9-7.3	*p < 0.001
$WHR_{0.95-0.99}$	0.97 \pm 0.1 (n: 24)	0.96-0.98	0.968 \pm 0.1 (n: 24)	0.96-0.97	p = 0.11
WHtR	0.60 \pm 0.11	0.57-0.62	0.52 \pm 0.05	0.50-0.53	*p < 0.001
WHR ≥ 0.95	84.1		38		8.6 (4.7-15.6)
WHRs	50 (n: 24)		25 (n: 24)		2
WHR < 1	36.5		85.7		2.3
WHR ≥ 1	63.4		14.2		4.4
WHD > 0	33.3		84.1		2.5
WHD ≤ 0	66.6		15.8		4.2
WHD ≥ 2.2	27.7		75.3		7.9 (4.5-13.9)
WHtR ≥ 0.54	79.3		30.9		8.5 (4.8-15.2)
WC ≥ 94.4	71.4		30.1		5.7 (3.3-9.9)
BMI ≥ 26.6	65.8		33.3		3.8 (2.2-6.9)

ROC: receiver operating characteristic; WHR: waist-to-hip ratio; WHD: waist-hip difference; MI: myocardial infarction; CI: confidence interval; OR: odds ratio; BMI: body mass index; WC: waist circumference; HC: hip circumference; WHtR: waist-to-height ratio; WHRs: spurious risk for WHR. *Level of significance.

WHR ≥ 0.54 exhibited a higher prevalence in cases (OR: 8.6 and 8.5, respectively). A WC cutoff ≥ 94.4 had a notable prevalence in cases (OR: 5.7). A WHD cutoff ≥ 2.2 presented a notable prevalence in the control group (OR: 7.9). WHR ≥ 1 (OR: 4.4) and WHD ≤ 0 (OR: 4.2) showed a notable prevalence in cases. WHR < 1 and WHD > 0 showed a notable prevalence among controls (OR: 2.3 and 2.5, respectively). The prevalence of WHRs was twice as much in cases than in controls.

Boxplots for the distribution of WHR and WHD are shown in figure 1.

In ROC curves (not shown) WHR ≥ 0.95 presented the strongest association (AUC: 0.798 (0.740; 0.855)). WHtR and WC exhibited a strong association (AUC: 0.782 (0.724; 0.840) and 0.743 (0.681; 0.805), respectively). WHD showed no association (AUC: 204 (0.146; 0.261), it being actually a protective factor associated with controls with a reciprocal AUC of 0.796 (0.739; 0.854) and a cutoff ≥ 2.2 . Graphs representing the anthropometric models used for understanding biases, and explanations about the results are plotted in figures 2-4.

DISCUSSION

In the present study the association for the metrics of abdominal obesity was comparable to that of larger samples worldwide (3,7-10,16). On the other hand, to date, WHD, WHR_{0.95-0.99} and WHRs were never referenced, whereas they are key indicators in our study. In spite of using the same two measurements, the results for WHR and WHD indicate differences in association. The selected risk cutoffs are mathematically key for understanding bias in WHR results. In previous studies (3,6-9,16) WHR showed a high magnitude of association, even consistently in studies where

WHR-associated risk presented an information bias (13,14). In our current analysis, WHR also showed a high discriminatory power, even above that of WC and WHtR; however, our purpose was to demonstrate a selection bias.

It is noteworthy, firstly, that neither at-risk BC or raised %BF is affected by HC (14). Secondly, WC and HC represent absolute values without expressing equality for whole risk as a mathematical object. In addition, WC is the strongest simple indicator linked to visceral adiposity and unhealthy BC (14,16). Besides, numbers for WHR < 1 are abstract fractions with an equivalence relation = 1 / > 1 representing a whole or unit that provides an information bias per se. In mathematics, WHR < 1 indicates the equal parts of WC that we have in HC without demonstrating anthropometric consistency or risk plausibility beyond that of WC.

Discrepancy between strong association for WHR and a lower anthropometric coherence for biological risk gave birth to our idea that something was wrong on the true-risk association (13,14). Geometrically, WC and HC represent parallel lengths from different bodily components accounting for cardiometabolic risk, while WHR is simply a way of representing size (part/whole) that is not a whole number of whole risk but a decimal value. However, WHD is a concrete number in the measuring of baseline anthropometric characteristics, but not BC *per se*.

From an anthropometric perspective, the standard human body has a HC larger than WC (WHR < 1) without posing any putative risk or protective effect. By deduction, HC $>$ WC is a natural inequality satisfying a true premise, which responds to a linear equation: HC = WC + x, where x = HC - WC, the standard value being higher in women than in men. We have deliberately drawn horizontal rays where values for WC and WHD may lie (Figs. 2 and 3). Thus, only when "x" is mathematically zero there is equality (WC = HC; WHR = 1; WHD = 0) for a risk conclusion to be certain.

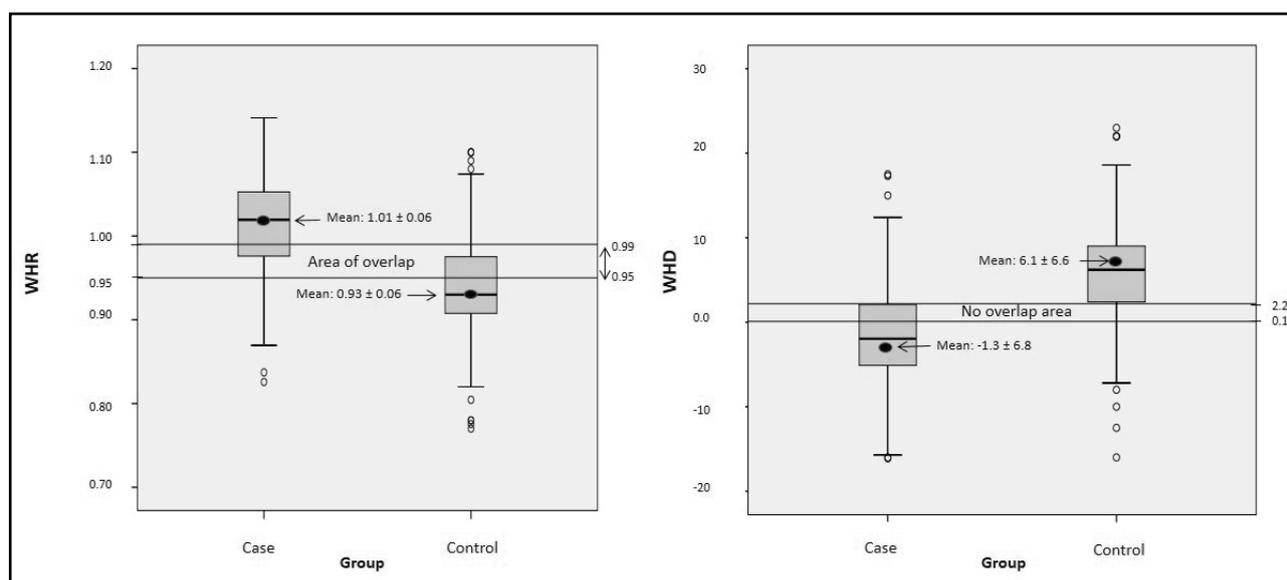


Figure 1.

Boxplots for the distribution of WHR and WHD between both groups (WHR: waist-to-hip ratio; WHD: waist-hip difference).

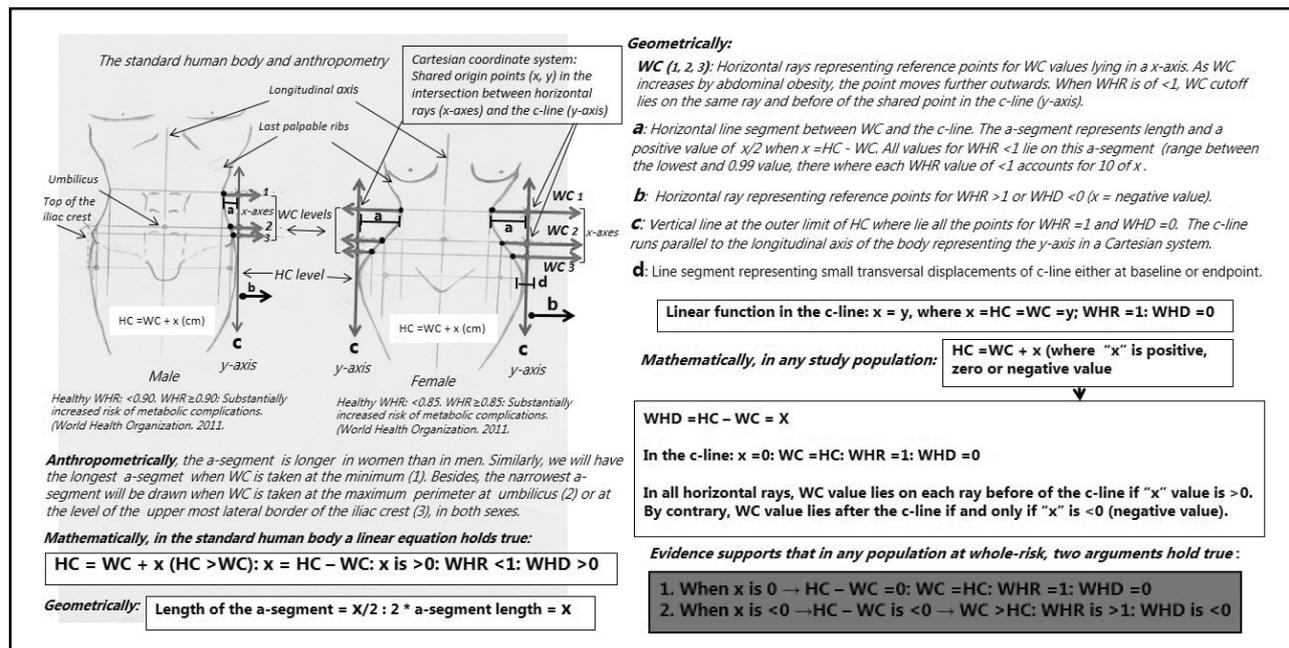


Figure 2.

Original creative assembly taken from anthropometric models and geometric lines on the standard human body. Geometrical and mathematical demonstrations for a correct anthropometric assessment of abdominal obesity and CVD risk. Drawings represent the human body (both sexes) where metrics are sample mean values per standard deviation for WC, HC, WHR, and WHD, these being actually valid for any anthropometrically healthy population and ethnicity. Within the respective lines would lie points of increased abdominal obesity representing mean values for thousands of cases of CVD, as well as biological changes pointing towards greater excess risk of CVD as WC increases. Similarly, the corresponding cut-off points associated per standard deviation, or quintiles, quartiles/tertiles, or receiver operating characteristic (ROC) analysis for WC, WHR, and WHD will always lie ahead of the c-line. These anthropometric models and schemes are valid for both case-control and cohort studies, and any type of cardiovascular event (CVD: cardiovascular disease; HC: hip circumference; WC: waist circumference; WHD: waist-hip difference; WHR: waist-to-hip ratio).

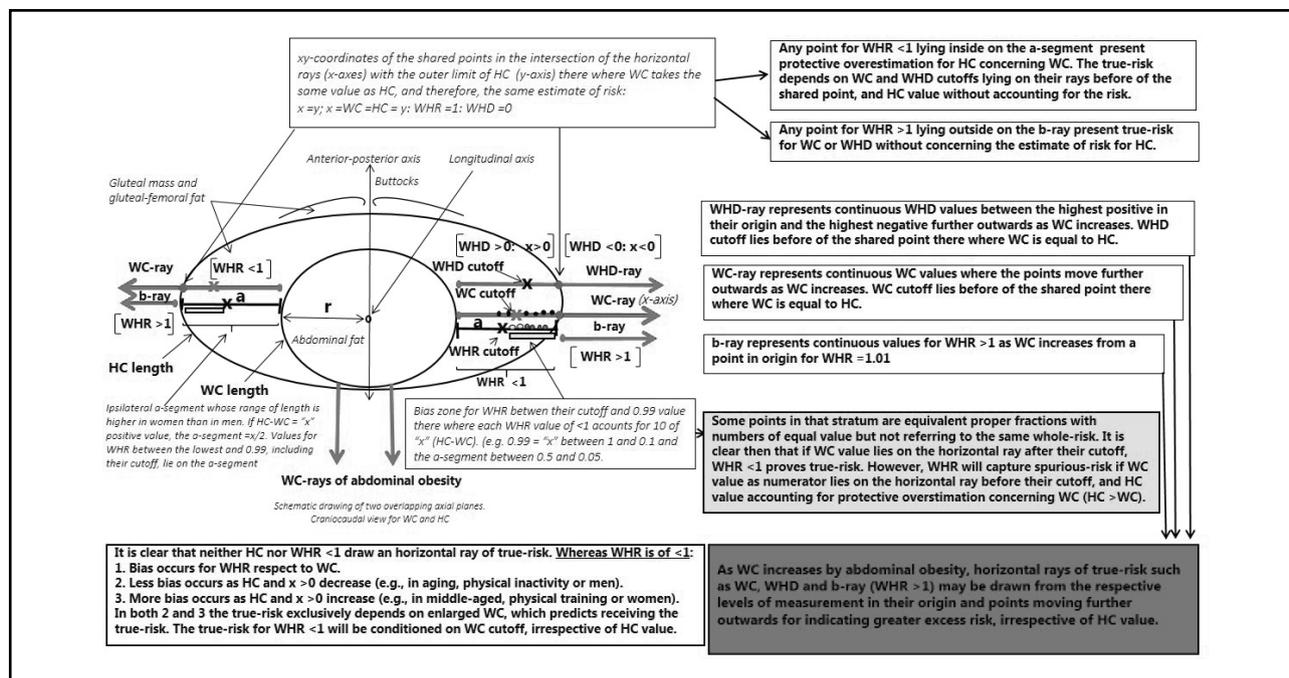


Figure 3.

Craniocaudal view for WC and HC from a schematic neutral model of the human body. Overlapping axial planes. Explanations for understanding are given in the main text. Names of lines and rays, where appropriate. The origin of the horizontal rays represent the same level of measurement for WC (HC: hip circumference; r: radius; WC: waist circumference; WHD: waist-hip difference; WHR: waist-to-hip ratio).

In fact, a narrow hip lower than or equal to WC appears unlikely in any anthropometrically healthy person. Obviously, only when WHR is ≥ 1 or WHD ≤ 0 ($x =$ zero or a negative value) may true-risk indicators be used in order to draw a valid conclusion. In our results, these arguments are taxatives because within these limits there was no overlap in the distribution of points for cases and controls (Fig. 1), and whole risk was associated to cases. On this basis, accepting a WHR cutoff < 1 as a marker of whole risk would be wrong because $HC > WC$ and $WHD > 0$ were associated with the control group. Besides, WC and HC may only coincide in one estimate of risk when WC takes the same value as HC (shared origin point (x, y) in a Cartesian coordinates system where the horizontal x -axis intersect with the vertical y -axis, and $x = y$ ($WHR = 1$; $WHD = 0$) (Fig. 2 and 3).

Mathematically, equal numbers for $WHR < 1$ would mark different individuals and an infinite number of proper fractions where $HC = WC + x$ is fulfilled for receiving the same WHR value, but not referring to the same whole risk (e.g., $93/98$ vs. $94/99$ vs. $95/100$, etc., = 0.95 : $x = 5$; $93/95.9$ vs. $94/96.9$ vs. $98/100.9$, etc., = 0.97 : $x = 2.9$; $93.8/93.9$ vs. $94.2/94.3$ vs. $96/96.1$, etc., = 0.99 : $x = 0.1$; $HC > WC$ in all). However, from a biological standpoint there would be true risk when $WC (\geq 94.4)$ predicts a whole-risk assignment, and a spurious risk when $WC (< 94.4)$ predicts a spurious-risk assignment, and therefore a bias would occur for WHR by selecting spurious-risk points as true-risk ones when they merely represent a protective overestimation for HC concerning WC. In fact, we have checked that $WHR_{0.95-0.99}$ presented no significant inter-group difference for indicating a similar baseline covariate (18). However, after conditioning, WHRs presented a higher prevalence in cases, which indicated that risk assignment was incorrect and inconsistent. Accordingly, the selected points for $WHR < 1$ at the top will yield a misclassification with respect to WC because HC values do not account for the same estimate of risk as WC. In contrast, WHD showed no overlap area between their positive cutoff (2.2) and 0.1 (equivalent to $WHR = 0.99$). Similarly, WC and WHD cutoffs also lied on their rays ahead of their shared point with HC as anthropometrically expected, but never presenting a selection bias (Fig. 2 and 3). Hence, accepting a risk-code for $WHR < 1$ without proving whole risk for WC alone would not be a valid selection. In our results, $WHR < 1$ was associated with controls whereas $WHR \geq 1$ showed a higher prevalence in cases, with a scientifically incongruous WHR-associated risk above WC. These findings and the rays of risk preclude a direct risk comparison between WC and WHR given that any WHR cutoff < 1 will always involve a protective overestimation for HC, and therefore, a systematic bias.

Surprisingly, most studies in predicting CVD risk always showed a WHR risk cutoff < 1 while selection biases were never discussed (3,7-11,16,17,20-27). Additionally, evidence supports that WHR is lower in women than in men (3,7-11,16,17,20-29) by involving a relatively larger HC and the longest a-segment, which ranges between the lowest (e.g., 0.76) and 0.99 value (Fig. 2). However, a HC larger than WC when the second predicts a risk code does not involve cardiovascular protection either. This observation may help explain a higher bias for WHR in the prediction of CVD in women

due to a higher selection of fractions there where HC does not account for the same estimate of risk as WC. Similarly, a higher bias for WHR would occur when WC is taken at the minimum level due to a longer range between the lowest value and 0.99. In both approaches, the higher the range, the higher the bias that occurs due to the selection of a higher number of spurious-risk points where the protective effect for HC would always be overestimated.

Some previous studies reported a trend towards a higher risk for CVD as HC decreased (3,8,21,22), but there is currently no supporting evidence that HC carries any cardiometabolic risk (15-17), especially because most studies showed high mean values for HC (always $HC > WC$) (3,7,9,13,14,17,29). Obviously, from any value of $HC > WC$, WHR moves towards 0.99 as HC decreases, but not necessarily affecting true risk. It is clear then that something does not add up between a high association for WHR and its relationship with whole risk (13,14). Additionally, HC-adjusted WC has shown the strongest association with coronary disease and cardiovascular mortality (21-23); but this association also appears to be wrong due to a selection bias whole risk. By combining WC and HC at the same level of equality (21-23) ($HC = WC$ instead of $HC = WC + x$), the paired equivalence of two different values would adulterate the WHR-associated risk, and we will find spurious-risk points in the strongest association even when $HC = WC + 0.1$. On the contrary, with the same baseline characteristics, when $WHD = 0.1$ there will always be true risk without selection bias or conditioning the covariate. Thus, in all direct quantitative comparisons between tertiles/quantiles, quintiles, ROC analysis and other statistical models, either WHR- or HC-adjusted WC will falsely yield stronger results for predicting risk than WC, since the model cannot distinguish between equal numbers with a different true risk each one of them, as was said above.

In another consideration, we have revealed that WHR and WHtR predict different risks if HC and height do not have a relationship such as $height / HC = 2$. This ratio would occur if, and only if, $WHR / WHtR = 2$ (e.g., $0.90/0.45$, $0.95/0.475$, $0.98/0.49$, $1/0.5$, etc.) (13), which also seems anthropologically unlikely (HC is always higher than $height / 2$). In fact, when we have compared ROC curves and ORs to identify association strength, the risk cutoff selected for $WHR (\geq 0.95)$ was always lower than that for $WHtR (0.54) \times 2$ ($WHR / WHtR < 2$), which indicated a different sensitivity and no risk equivalence between both indices. Along this line, the UK Biobank study showed an association of incident MI with WHR and WHtR, and a 1-SD higher WHR was more strongly associated than WC and WHtR in both sexes (7). However, WHR at the top was always < 1 when WHtR at the bottom showed a value of $> 0.45-0.5$ ($WHR / WHtR < 2$); so risk comparisons between both indices turned out to be biased (7,13,14). Hence, when a WHR cutoff is lower than $WHtR \times 2$, a selection bias will occur for WHR due to a protective overestimation of HC with regard to height (13).

In our research line, we have warned that risk assessment is a matter of volume in relation to mass and density of bodily components (13,14). Thus, if we consider the human body as a three-dimensional solid, shaped somewhere between a cylinder and two truncated cones, both the areas of the bases and height can be used to calculate its total volume, although without

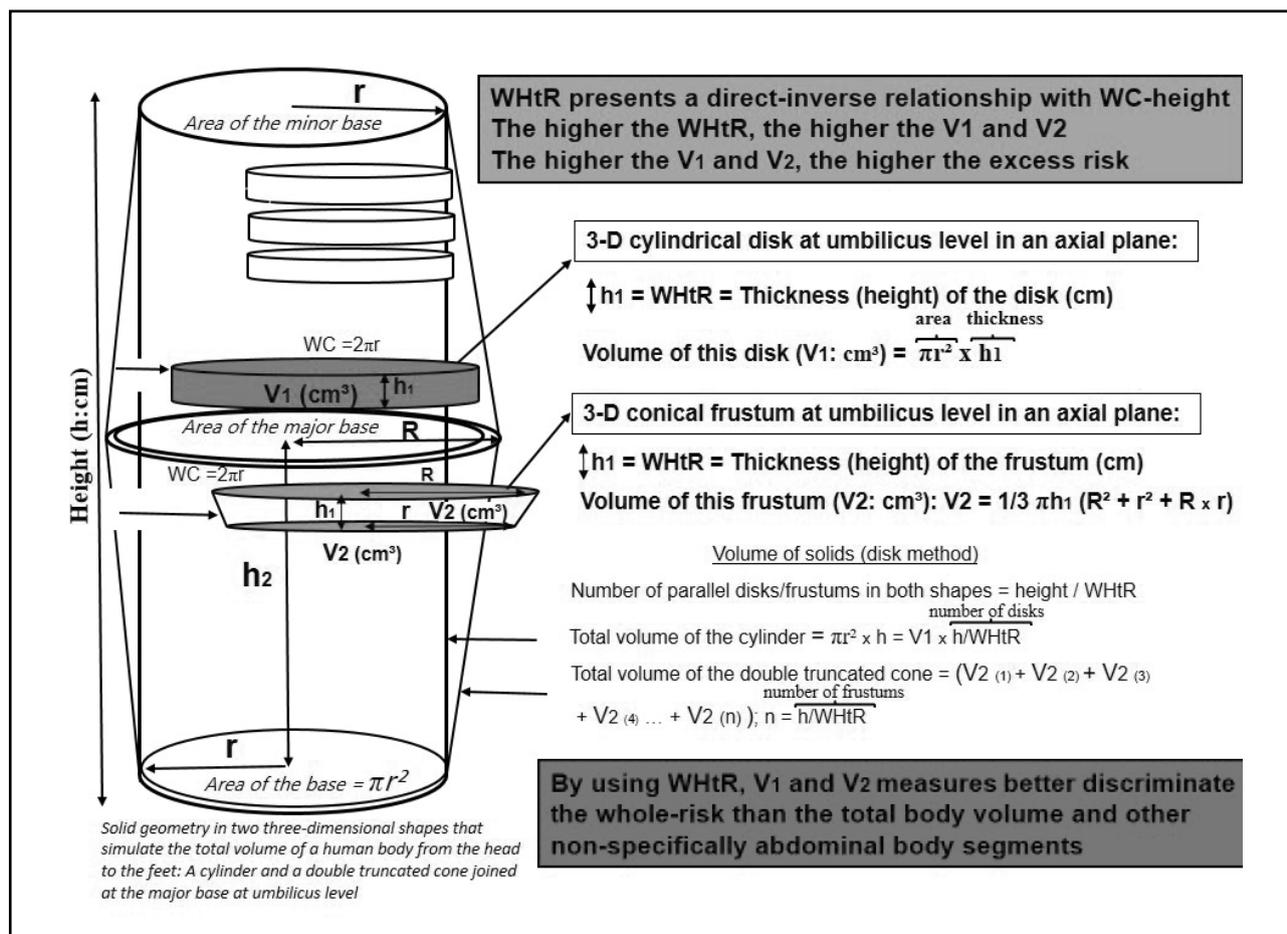


Figure 4.

Geometric model representing the human body as a solid cylinder or two truncated cones joined together at their major bases. "Volume" refers to the amount of three-dimensional space that bodily components occupy in relation to their mass and density (h : height for both shapes; h_1 : thickness of the disk and frustum; h_2 : height of a single truncated cone ($h/2$); WC: waist circumference; WHtR: waist-to-height ratio; R: radius of the major base; r: radius of the minor base; V_1 : volume of the cylindrical disk; V_2 : volume of the conical frustum. The base of the cylinder and the major base of the truncated cone have a length equal to WC as appropriate).

differentiating between biological components. However, the volume of a three-dimensional disk or frustum at the umbilicus level depends on WC and WHtR in a segment whose intra-abdominal components occupy all the space available except for a small peripheral-subcutaneous volume, which is less deleterious than intra-abdominal fat depots. Thereby, WHtR gives us the relative risk volume that we have by unit of height in direct-inverse relationship with WC-height, and the higher the WHtR, the higher the risk (Fig. 4).

Conceptually and anthropometrically, from an abdominal obesity volume, relative adiposity and at-risk BC, WC and height, and skinfolds to a lesser extent, are the basic measurements for predicting cardiometabolic and CVD risk (10,11,13,14,16,17,24-40), and technological methods should find the highest risk correlations here. It is clear that by using HC we will never capture an abdominal risk volume, nor a BC at greater risk of MI as compared to those of WC alone. Epidemiologically, this conceptual premise should be the key issue to guide anthropometric research, and to

enable us to understand the differences between association and causality for biological risk when handling physical characteristics linked to different bodily components.

The most important strength of our findings is that WHR presents a high association, but partially capturing a dimension of spurious risk (13,14). Most studies have taken WHR from where HC values were comparatively higher than WC and height / 2 ($\text{WHR} < 1$; $\text{WHR} / \text{WHtR} < 2$). That way, researchers accepted a risk assignment for true negative values of WHR, making them as mathematically incorrect by the assumption of HC as protective factor. Thus, WHR has been used in thousands of people to evaluate the association of abdominal obesity and cardiovascular event risk without taking into account our mathematical observation (3,6-9,16,17,20-23,25-29,33,34,37). Accordingly, all WHR-associated risk above WC and WHtR is misleading evidence that has fooled scientists because of the research process itself, which slanted arithmetic data in an artificial direction. While this happened in important studies our disclosures were unknown;

so recommendations made on the issue related to WHR use for determining abdominal obesity and a substantially increased risk of metabolic complications and MI turned out to be false or at least to entail an information bias when pointing to central obesity (3,6-9,16,17,29).

In our graphs (Fig. 2-4) any whole population may be represented, including cases and controls and longitudinal follow-up for abdominal obesity and CVD risk. From any WC level, the horizontal rays keep a direct and inverse-negative relationship with WC and WHD, respectively. As WC increases by abdominal obesity, the points with greater excess risk move further outward. Similarly, as WHtR increases, the higher the relative volume, the higher the whole risk. In contrast, WHR draws neither rays nor greater excess risk, at least up to a 0.99 value, where in any range a higher-lesser bias occurs as HC increases-decreases and WC does not move in their ray. Therefore, in classifying a directly progressive true risk between the WHR risk cutoff and 0.99, it appears that no valid scores may be found. The answer is mathematical: in that stratum of points for WHR we could always find equal numbers, which precludes that true risk and spurious risk may be separated without accounting for WC being assigned the true risk. In summary, in assessing abdominal obesity and MI risk prediction WHR exhibits a systematic bias because of its being a confounding variable. Since the whole risk assigned to $WHR < 1$ is a false premise (mathematically not correct), the conclusions drawn from the statistical association will be epidemiologically in error. Any WHR cutoff < 1 precludes the same estimate of risk for WC and HC, making anthropometrically impossible the validity of WHR for predicting MI risk beyond that of WC alone. Consequently, WHR neither offers any advantages above WC, nor provides an accurate estimation of volume and at-risk BC. WHR remains attractive at first sight but will never perform better than WC or WHtR, at least regarding the true nature of risk. Our detailed research anthropometrically has no limitations, quite the opposite is the case. Evidence supports that our findings exhibit external validity and may be extrapolated to other ethnically-based or sex-specific study populations. With a WHR cutoff < 1 , the association of abdominal obesity and MI is mathematically incorrect and anthropometrically unjustified, and will introduce biases in the results and provide false conclusions. It will easily be checked by transferring metrics and the corresponding risk cutoffs to the equations/formulas and our anthropometric models. Imaging-derived measurements of the real at-risk BC, especially %BF and visceral adiposity volume, should confirm it.

CONCLUSION

This study demonstrates an association bias for WHR in predicting MI risk. WHR-associated risk becomes a misleading evidence derived from a generalized mathematical misconception, which overestimates the protective effect of HC concerning WC and height. True risk exclusively derives from abdominal obesity volume and enlarged WC, which renders HC irrelevant. Any association of MI/CVD risk with WHR above WC and WHtR is mathematically biased and anthropometrically inconsistent; it becomes

epidemiologically false and clinically useless. WHtR as pointing to a relative abdominal volume will not entail any bias, and may capture a dimension of risk above WC. This only happens when height shows an inverse association for increasing the discriminative ability of WHtR beyond that of WC, as proven. We offer new insights and anthropometric demonstrations that should be incorporated into clinical understanding when rigorously handling CVD risk as associated with metrics from abdominal obesity and unhealthy nutrition status by excess %BF.

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