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Original article

Validation of new anthropometry-based standard for metabolic syndrome and nutritional status screening: A pilot study

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SUMMARY

Background and aims: Metabolic syndrome is one of the greatest health threats in the modern world. Challenges associated with diagnostics and absence of a preventive strategy contribute to the evolution of metabolic syndrome towards central obesity and type 2 diabetes. Indicators such as body mass index (BMI) and body fat percentage (BF%) have limited clinical applications. Although anthropometrical indicators strongly correlate with risk of mortality, they have limited clinical applicability due to their inability to grade risk of cardiovascular and metabolic disease. We evaluated the ability of an anthropometry-based method, the Morphogram, that integrates body segment circumferences with validated cut-offs from the literature, to estimate body composition (BF% and lean mass percentage, LM%) and compute a score for metabolic syndrome risk (MSR). The aims of our study were (1) to assess the extent to which BF% and LM% measured by dual energy X-ray absorptiometry (DXA) can be captured by Morphogram and (2) to propose a novel method to quantify the stage of MSR.

Methods: We tested 52 study participants (26 males, 26 females; age: 39.2 ± 8.4; BMI: 28.9 ± 2.6). We compared BF% and LM% estimated by Morphogram vs. DXA and the MSR score vs. health risks associated with DXA adiposity parameters and anthropometric variables. Morphogram is based on changes in body fat that occur at the waist, abdomen and hips, which correspond to approximately 90% of changes in total body fat. Therefore, we expected Morphogam to underestimate BF% relative to DXA while correctly estimating changes in central adiposity. We also hypothesized the MSR scores to exhibit stronger correlations with anthropometric variables than DXA parameters.

Results: BF% and LM% estimated by Morphogram (mean ± S.E.: 31.37 ± 1.09 % and 68.50 ± 1.08 %, respectively) significantly under-estimated and over-estimated BF% and LM%, estimated by DXA (34.68 ± 1.30 % and 65.41 ± 1.35 %, respectively; $p < 0.001$). The largest under-estimation discrepancies (≥ -5 % of BF%) were caused primarily by excessive subcutaneous fat and relative fat-free mass deficits, in a subset of participants (35 %). Lastly, we found stronger correlations between MSR scores and risk factors that have been linked by epidemiological studies to anthropometric variables than adiposity parameters measured by DXA.

Conclusion: Morphogram has significant potential in the assessment of body composition in individuals with central adiposity and as a screening and monitoring tool of metabolic status. Therefore, Morphogram can be considered a clinically relevant approach for the prevention and monitoring of central adiposity and metabolic diseases.

1. Introduction

Metabolic syndrome can be considered one of the greatest health threats in the modern world. Although global data are lacking, the prevalence can be estimated at about a quarter of the

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world's population, as it is three times more prevalent than diabetes [1]. It follows that over a billion people in the world are affected by metabolic syndrome, but 90 % do not know it [2]. Therefore, both the challenges associated with diagnostics and the absence of a preventive strategy contribute to the evolution of metabolic syndrome, cardiovascular disease, and type 2 diabetes. Furthermore, we are witnessing with increasing concern the epidemic evolution of obesity, which currently affects over 600 million adults worldwide [3]. These data are particularly alarming for the US population, where 42 % of women and 43 % of men are affected by obesity [4].

It is now becoming increasingly clear that the use of the body-mass index (BMI, i.e., the ratio between body weight and height squared) to assess obesity is insufficient. Specifically, although BMI is a universally recognized index to quantify stages of obesity, high values do not necessarily reflect the amount of fat, as they can also be influenced by muscle mass [5]. According to a recent study, obesity occurs when the body fat percentage (BF%) is respectively >25 % in males and >35 % in females [6]. However, when individuals with normal (non-obese) BMI values were scanned using dual energy X-ray absorptiometry (DXA), it was found that 26 % of men and 38 % of women participants exhibited an excess of adiposity. In contrast, within the overweight group (as classified by BMI), 30 % of men and 10 % of women participants had a normal BF% [6]. Combined, these results confirm that BMI is an insufficient tool for identifying and assessing stages of obesity, while emphasizing the need to measure BF%.

The gold standard for measuring BF% is via DXA, which is characterized by a 3 % margin of error and very low radiation exposure [7–10]. Nevertheless, the main disadvantages of DXA lie in the fact that the analysis requires expensive equipment and the examination is not suitable for outpatient and routine patient management. Most importantly, DXA's ability to predict metabolic syndrome is lower than the simple measurement of waist circumference (WC) and waist/height ratio (WHtR) [11]. Furthermore, DXA cannot accurately estimate visceral abdominal tissue, for which computerized tomography and magnetic resonance imaging are required [12].

To address these limitations, the recent National Institute for Health and Care Excellence (NICE) guidelines have emphasized the use of the WHtR in conjunction with the BMI [13]. These guidelines also point out that, whereas WHtR is individualized and valid for all ethnic groups, the BMI identifies the health risks associated with being overweight at a lower value for individuals with South Asian, Chinese, Middle Eastern, African, and Caribbean ethnic backgrounds than White Americans and Europeans (>23 and < 27.5, respectively), as well as the risk of obesity ($\geq$27.5). Importantly, the NICE guidelines also provide instructions for self-measuring WC and WHtR with the aim of increasing awareness of the general population about central adiposity [13].

We note that the use of any surrogate method for estimating body fat (skinfold measurement, bioelectrical impedance analysis, etc.) is characterized by measurement errors with respect to DXA. Nevertheless, in clinical practice, detecting changes in central adiposity for individual monitoring of cardiometabolic health is more important than detecting minimal changes in total fat. It should also be emphasized that methods used to estimate body composition do not provide sufficient diagnostic support to the nutritionist at critically important time points [14–16]. In particular, the work by Borga and colleagues has shown that BIA cannot estimate visceral adipose tissue (VAT), whereas DXA can only provide an approximate estimate of VAT [12].

To address these gaps, the Morphogram method uses selected body segment circumferences (waist, abdomen, and hip circumferences) to estimate changes in total body fat and monitor central obesity and related individual risk factors. The rationale for the Morphogram's algorithm is that ~90 % of the entire body fat variation is concentrated between the waist and hips [17]. Additionally, the measured variations in waist, abdomen and hip circumferences are used to compute anthropometric indicators (WC, WHR, WHtR). Lastly, Morphogram grades individual risk factors for metabolic syndrome by using anthropometric indicators (WC, WHR, WHtR) and related scores attributed in the literature to cut-offs for “moderate” and “high” risks.

The present study was designed to determine the extent to which Morphogram can be used as a reliable tool for the identification of stages of central obesity, assess its diagnostic potential to identify stages of risk for cardiometabolic disorders, and assess risks for metabolic syndrome and related problems. We pursued two objectives: (1) to quantify the extent to which body composition (BF% and LM%) estimated by DXA can be captured by Morphogram; and (2) to evaluate the usefulness of a novel method to quantify the stage of metabolic syndrome risk (MSR score) relative to the risk levels identified by individual DXA parameters and anthropometric variables.

We tested two hypotheses. (1) Morphogram would underestimate BF% and over-estimate LM% relative to DXA, with these discrepancies being larger for individuals with subcutaneous fat and fat in the arms and thighs, and relative deficits in lean mass. This differences between DXA and Morphogram are expected to be caused by the Morphogram algorithm weighing anthropometric variables of central adiposity (waist, abdomen, and hip circumferences) more than upper and lower limb circumferences. (2) MSR scores would exhibit stronger linear correlations with anthropometric variables than DXA parameters.

2. Material and methods

2.1. Subjects

Fifty-four (n = 54) participants were recruited by online advertising through an Arizona State University webpage. Participants completed the study according to two eligibility criteria: (1) BMI (computed as the subject's weight in kilograms divided by the square of the subject's height in meters) between 25 and 34.9, and (2) age between 25 and 55 years old. We chose our BMI eligibility criterion because we wanted to focus on individuals that fall into the Class 1 obesity category. Our rationale for using BMI as one of our eligibility criteria was that it remains a universally-recognized metric to assess obesity even though BMI is an incomplete metric (see section *Morphogram as a screening tool for metabolic syndrome risk* in the *Discussion*). The age range of study participants was chosen because prior work has focused on the same age range for clinical intervention.

After prospective participants contacted the research team, height and weight were measured to verify the BMI eligibility criterion and ages were confirmed. Subjects gave their written informed consent according to the declaration of Helsinki. All protocols were approved by the Institutional Review Board at Arizona State University. Two participants were excluded from analysis due to not meeting the inclusion criteria upon arrival. One participant was outside the BMI range and the other was outside the age range. Neither excluded participant completed the protocol nor were randomized into the study. Therefore, we performed analysis on data from fifty-two participants (age: 39.4 $\pm$ 8.6 years [mean $\pm$ standard deviation]; 26 females).

Besides age and BMI, prior to starting data collection participants were asked for their ethnicity and to report an approximate number of steps they walked daily. Gender was self-reported by participants during the initial interest survey. The distribution of age, gender, physical characteristics, and physical activity level is shown in Supplemental Table 1. Participants were compensated for their participation ($40) and were given a free report regarding their body composition.

2.2. Apparatus

Two techniques were used, each conducted on the same day, to measure body composition of our study participants: Dual-energy X-ray Absorptiometry (DXA) scan and (Morphogram, an algorithm based on anthropometry. We chose to use DXA as the only validated benchmark for body composition analysis for our comparison with the analysis provided by Morphogram.

Height and weight were measured using a digital stadiometer and scale (Seca 286 Ultrasonic Measuring Station, Hamburg, Germany). These values were used to compute the BMI. Participants were required to refrain from food and drink 4 h prior to the test and avoid strenuous exercise, alcohol, and caffeine in the 12 h prior. Participants were instructed to wear either leggings and a sports bra or very lightweight thin clothing typical of clothing used for exercise. No participants wore anything that was thick or stiff (e.g., denim, khaki, or dress clothing).

DXA. A Lunar iDXA scanner (GE HealthCare, Illinois USA) was used to perform a whole-body composition assessment. The DXA exposes the participant to low-intensity x-rays. However, the amount of radiation from the DXA scan is very low and the dosage has been estimated to be less than that used in dental x-rays (approximately 6 mrem/scan), which is equivalent to 1/20th of a chest x-ray (e.g., the radiation exposure of a long airplane trip). This amount is well below the radiation safety guidelines issued by the National Institutes of Health (i.e., 3000 mrem to any tissue in a 13-week period and 5000 mrem in one year). A certified radiology technician conducted the DXA scans.

Morphogram. Morphogram provides two types of analysis, *Full* and *Smart*. The Full Analysis (FA) uses 10 variables whereas the Smart Analysis uses a subset of variables (5 variables) used for FA (Fig. 1). Morphogram is a proprietary algorithm that uses measurements of body segment circumferences to infer body composition, nutritional needs and risk factors for cardiovascular disease and metabolic syndrome. Both FA and SA output body composition (fat and lean mass; BF% and LM%), nutritional needs (basal metabolism, total energy expenditure and protein requirements and risk factors for cardiovascular disease and metabolic syndrome.

The equations used by Morphogram are based on anthropometry literature [18–26]. Morphogram focuses on the equations that can effectively capture variations in abdominal-visceral and gluteo-femoral fat while factoring in the effects of age (e.g., fat mass tends to increase with age). The Morphogram algorithm integrates Lean's equations that use age and WC [18], equations for estimating relative lean mass that use height and abdominal circumference [19], and the body adiposity index that uses hip circumference (HC) relative to height [20]. These equations are used by both FA and SA. FA also uses the formula by Hodgdon [23] for males and by Vogel [24,25] for females.

Body composition. The Morphogram algorithm estimates body composition (fat mass, lean mass) by considering that ~90 % of the entire body fat variation is concentrated between the waist and hips [17]. Therefore, the estimation of BF% is strongly weighted by variations in waist, abdomen, and hip circumferences relative to height, weight, and age. The estimated abdominal fat is used to estimate metabolic health risks.

2.3. Integrated assessment of BMI and BF% with anthropometric risk factors of central obesity

Morphogram uses BMI e BF% as generic health risk factors. BMI classifies individuals as under-weight (BMI <18.5), normal (BMI between 18.5 e 24.9), overweight (BMI between 25 e 29.9) and obese (BMI >30) [26,27]. Regarding BF%, there is only one cut-off value that separates non-obese individuals from obese ones (males: >25 %; females: >35 %) [28,29]. However, since there is no classification of cardiovascular disease and metabolic syndrome based on BF%, we hypothesized that a “low risk” is associated with BF% <25 % for males and <35 % for females, a “moderate risk” is associated with BF% between >25 % and <30 % for males and between >35 % and <40 % for females, and a “high risk” is associated with BF% >30 % for males and >40 % for females (Table 1).

Since BMI and BF% provide information that can vary significantly depending on individual characteristics and ethnicity, Morphogram assesses individual risk through integrated analysis of anthropometric risk factors of central obesity (Fig. 2). It is important to note that the cut-offs of these variables have been correlated in the literature with adverse health events. These

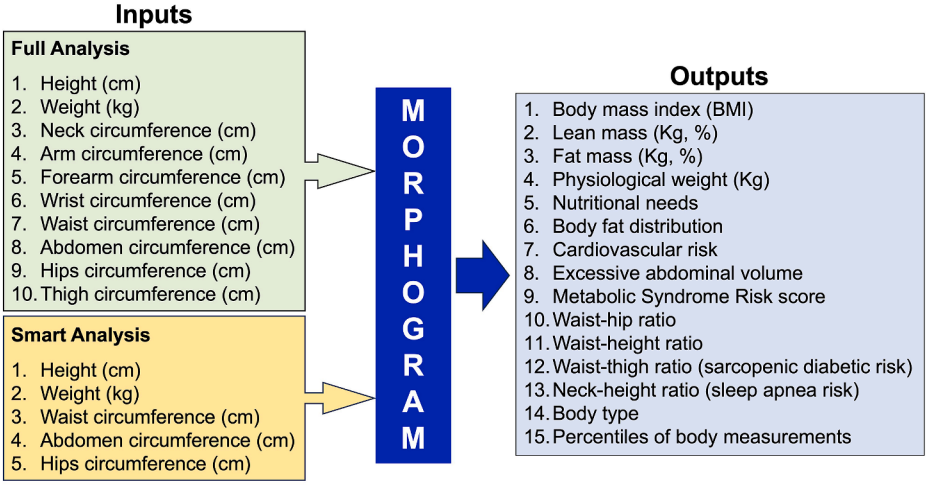

Fig. 1. *Inputs and outputs of Morphogram analysis.* Morphogram can be used to perform a Full Analysis of 10 variables or a Smart Analysis of a subset (5) of the same variables. The Full Analysis outputs metrics 1–15, whereas the Smart Analysis outputs metrics 1–11.

Table 1
Cut-off values of anthropometric indicators for calculating risk of metabolic syndrome. The top part of the table shows the risk of metabolic syndrome based on the cutoffs of waist circumference (WC), waist-to-height ratio (WHtR), and waist-to-hip ratio (WHR) for men and women (M and F, respectively). The Morphogram algorithm assigns a metabolic syndrome risk score of 0, 1 and 2 to the low, moderate and high risk, respectively, of the respective anthropometric indicators, adding them together, and classifying the risk as low (0–2), moderate (3–4) and high (5–6). The bottom part of the table shows the body fat percentage (BF%) cutoffs and ranges that Morphogram indicates as low, moderate, and high.

Anthropometric indicators	Sex	Cut-off values to quantify risk of metabolic syndrome		
		Low risk	Moderate risk	High risk
Waist circumference (WC)	M	<94 cm = 0	≥94 & < 102 cm = 1	≥102 cm = 2
	F	<80 cm = 0	≥80 & < 88 cm = 1	≥88 cm = 2
Waist-height ratio (WhTR)	M, F	<0.50 = 0	≥0.5 & > 0.6 = 1	≥0.6 = 2
Waist-hip ratio (WHR)	M	<0.9 = 0	≥0.9 & < 1 = 1	≥1 = 2
	F	<0.8 = 0	≥0.8 & < 0.9 = 1	≥0.9 = 2
		Low risk	**Moderate risk**	**High risk**
Body fat percentage (BF%)	M	<25 %	≥25 % & < 30 %	≥30 %
	F	<35 %	≥35 % & < 40 %	≥40 %

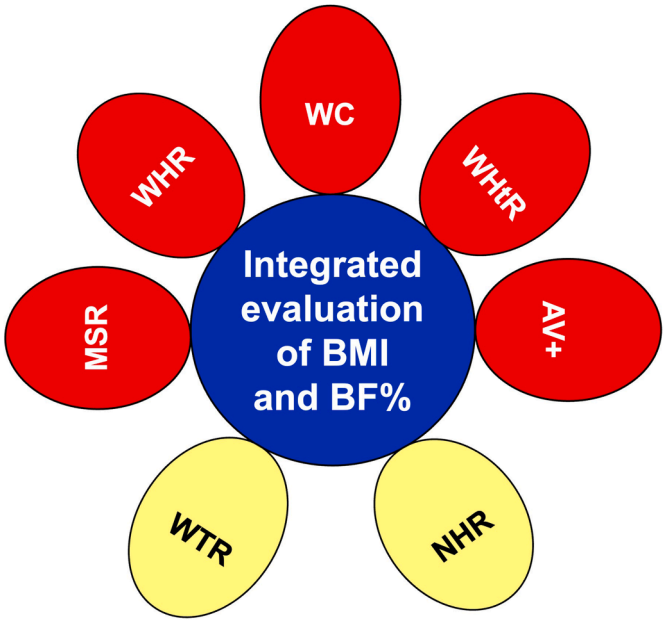

Fig. 2. *Integrated evaluation of body-mass index (BMI) and body fat percentage (BF%) with anthropometric risk factors for central obesity.* The risk factors highlighted in red are computed by both Full and Smart Morphogram analyses. WC: waist circumference. WHtR: Waist-height ratio. AV+: Excessive abdominal volume. NHR: Neck-height ratio. WTR: Waist-thigh ratio. WHR: Waist-hip ratio. MSR: Metabolic syndrome risk score.

anthropometric indicators are described in **"**Supplementary material**"**.

2.4. Metabolic syndrome risk score

The MSR score individually integrates the risk levels of the respective anthropometric indicators (WC, WHR, WHtR), based on the cut-offs present in the literature and reported in Table 1. MSR scores identify three ranges of risk: "low" (scores: 0–2), "moderate" (scores: 3–4) and "high" (scores: 5–6). The MSR gradation criterion is very useful for screening and monitoring purposes because WHtR and WHR are valid across all ethnic groups. Therefore, even a low-risk score (0–2) can be re-evaluated by considering the WC risk cut-off values in relation to a given ethnic group (for more details, see **"**Supplementary Material**"**).

2.5. Experimental protocol

DXA. All participants were asked to wear metal-free clothing and remove any jewelry while lying face up on the DXA scanner bed for approximately 7–10 min. Prior to the DXA scan, female participants were required to complete a pregnancy test to ensure safety. One measurement per participant was taken.

Morphogram. Three sets of measurements were taken by one of the experimenters who was certified to take the measurements and to input in the Morphogram algorithm. To ensure across-trial repeatability within each of the three sets of measurements, we used a self-locking, spring-loaded, no-stretch Gulick tape measure (Creative Health Products, Ann Arbor, MI), which are designed to apply a constant tension when measurements are taken on the human body.

2.6. Experimental variables

All body composition assessment techniques provided fat and lean mass estimates, as well as fat and lean mass percentages (BF% and LM%, respectively). Our statistical analyses focused on the comparison of BF% and LM% estimated by Morphogram versus DXA. The risk of metabolic syndrome score was computed from the Morphogram Full and Smart Analyses.

2.7. Statistical analysis

Statistical analyses were designed to test several hypotheses addressing the ability of Morphogram to accurately estimate body composition (fat mass, lean mass) relative to DXA, as well as its diagnostic ability to provide effective metrics to analyze anthropometric indicators connected to metabolic health status. We performed separate repeated-measures ANOVA on body fat percentage (BF%) and lean mass percentage (LM%) with *Measurement technique* (3 levels: DXA, Morphogram FA, Morphogram SA) as the within-subject factor. When the sphericity assumption was violated, the Greenhouse-Geisser correction was used for assessing statistical significance of main effects. For all ANOVA's revealing a main effect of a given factor, multiple post-hoc comparisons were corrected using Bonferroni corrections.

To further assess agreement of body composition estimation by DXA versus Morphogram, we used Bland–Altman (B&A) analysis of differences [30,31] to identify if there was a consistent bias between the two techniques and whether the measurements from both methods agree within acceptable limits. Briefly, we first performed the Kolmogorov–Smirnov with two-tailed Lilliefors significance correction to verify that differences (Morphogram

minus DXA) in BF% and LM% were normally distributed. After normal distribution of these differences was confirmed, we generated B&A plots of the Morphogram minus DXA differences versus their average estimates. We then performed linear regression analysis on the Morphogram minus DXA differences versus their average to quantify the dependence of the differences on the magnitude of BF% and LM% averaged across the two methods. We further analyzed the distribution of differences across subjects to identify the potential sources underlying the differences in body composition estimates. For the ANOVA's, the average of three trials per body segment was used for the Morphogram estimates of BF% and LM%. Data from each subject were used for the B&A analysis. Lastly, linear regression analysis was performed to quantify the relation between DXA parameters and BMI, risk factors for metabolic syndrome, and metabolic syndrome risk scores computed by Morphogram.

3. Results

3.1. Body composition assessment by DXA and Morphogram

Body composition (body fat and lean mass percentages; BF% and LM%, respectively) as measured by DXA was used as the reference for comparing body composition assessed by the Morphogram method (Full and Smart Analyses, FA and SA, respectively). As expected, Morphogram FA and SA under-estimated BF% (on average −3.31 and −2.74 BF%, respectively) and over-estimated LM% (3.09 and 2.63 LM%, respectively) relative to DXA (Fig. 3A and B, respectively).

A main effect of *Measurement technique* (BF%: $F = 27.88$, $p < 0.001$, Fig. 3A; LM%: $F = 24.23$, $p < 0.001$, Fig. 3B) was also evident. Post-hoc tests revealed that BF% and LM% estimated by Morphogram were significantly lower and higher than BF% and LM % estimated by DXA, respectively ($p < 0.001$ for both FA and SA). The comparison between Morphogram FA and SA revealed no significant difference for BF% ($p = 0.073$) and a small (0.46 %) but significant difference for LM% ($p = 0.041$).

3.2. Analysis of differences: Bland Altman method

To investigate the discrepancies between body composition estimated by DXA and Morphogram, we performed analysis of differences using the Bland Altman (B&A) method. Figure 4A and B show the B&A plots for BF% estimated by DXA and Morphogram FA and SA, respectively.

Most of the differences between BF% estimated by Morphogram and DXA (94 % and 92 % for FA and SA, respectively) lie between the upper and lower limits of agreement (±2 SD of the mean difference denoted by red dashed lines).

The differences in BF% estimates were normally distributed (Kolmogorov–Smirnov with two-tailed Lilliefors significance correction, $p > 0.05$). For both FA and SA, the difference in BF% estimated by Morphogram minus DXA, i.e., a negative bias, tends to be larger for greater average BF% values. This observation was confirmed by linear regression analysis showing a weak but statistically significant negative relation (FA: $R^2 = 0.17$, $p < 0.01$; SA: $R^2 = 0.26$, $p < 0.001$). For both FA and SA, the 95 % confidence interval (CI) of the mean difference in BF% estimated by Morphogram minus DXA is significant as it lies outside the CI of the line of equality (zero difference). Therefore, Morphogram constantly under-estimated BF% relative to DXA.

Figure 5A and B show the B&A plots for LM% estimated by DXA and Morphogram FA and SA, respectively. Most of the differences between LM% estimated by Morphogram and DXA (96 % and 92 % for FA and SA, respectively) lie between the upper and lower limits of agreement (±2 SD of the mean difference denoted by red dashed lines). The differences in LM% were normally distributed (Kolmogorov–Smirnov with two-tailed Lilliefors significance correction, $p > 0.05$). For both FA and SA, the difference in LM% estimated by Morphogram minus DXA, i.e., a positive bias, tends to be larger for greater average LM% values. As found for BF%, we found a weak but statistically significant negative relation (FA: $R^2 = 0.25$; SA: $R^2 = 0.31$; both p-values <0.001). Like the results for BF%, the 95 % confidence interval (CI) of the mean difference in LM % estimated by Morphogram FA and SA minus DXA is significant as it lies outside the CI of the line of equality. Therefore, Morphogram constantly over-estimated LM% relative to DXA.

3.3. Discrepancies in body composition between DXA and Morphogram

To investigate the source of discrepancies in body composition estimation by Morphogram, we examined the distribution of errors across subjects. As BF% and LM% are inversely correlated, to avoid redundancy we discuss below the distribution of BF% differences only. To better visualize the patterns of Morophogram − DXA BF% differences shown in Fig. 4, these differences are shown as a frequency distribution in Fig. 6.

As noted above, Morphogram tends to under-estimate BF% relative to DXA. However, most study participants exhibited small discrepancies (±5 %) (FA: 34/52 subjects, 65 %; SA: 33/52 subjects, 63 %; blue bars, Fig. 6). As the under-estimation error (negative bias) equal or greater than −5 % occurred in 35 % and 37 % of participants (18 FA and 19 SA, respectively; red bars, Fig. 6), we sought to investigate the underlying causes of error in this group of subjects to understand the full range of Morphogram applications and possible strategies to improve its predictive capability in this subgroup of subjects. The causes of discrepancies for the sample of

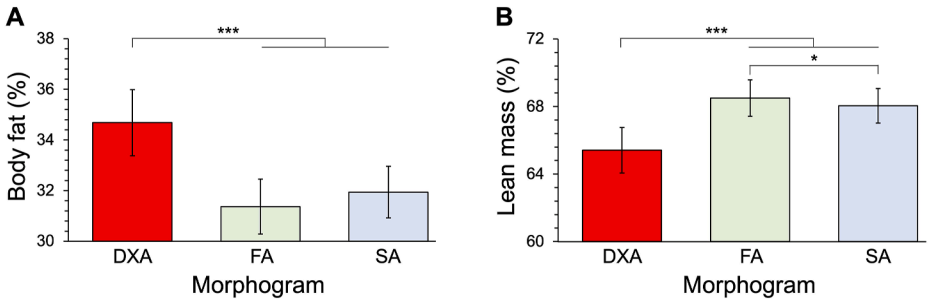

Fig. 3. *Body composition assessment by DXA* and *Morphogram.* A and B show body fat percentage and lean mass percentage, respectively, assessed using DXA, Morphogram Full Analysis (FA) and Smart Analysis (SA). Data are averages of all subjects ($n = 52$). Vertical bars denote standard errors of the mean. * and *** denote statistically significant differences ($p < 0.05$ and 0.001, respectively).

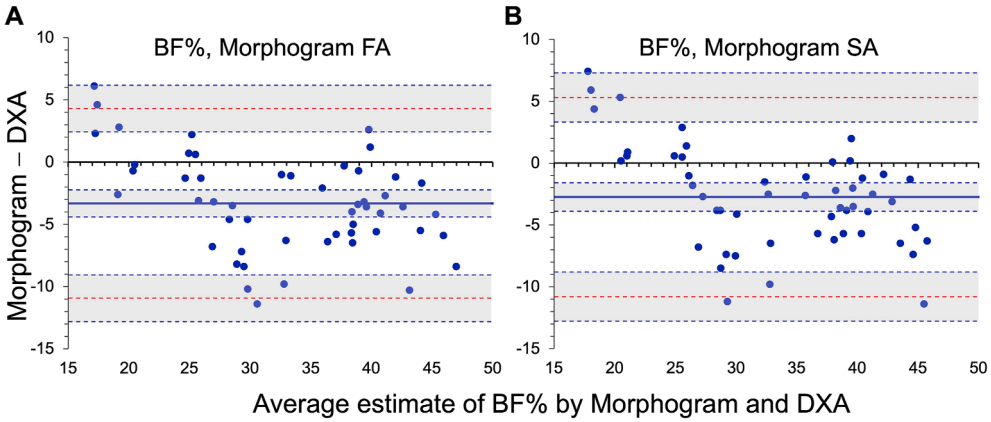

Fig. 4. *Comparison of body fat percentage estimated by Morphogram versus DXA.* Bland–Altman plots of the difference in body fat percentage (BF%) estimated by Morphogram Full Analysis (FA) and Smart Analysis (SA) minus DXA plotted against the average estimate of BF% by DXA and Morphogram FA and SA (A and B, respectively). In each plot, the horizontal solid blue line denotes the mean difference between BF% estimated by Morphogram and DXA, top and bottom horizontal dashed red lines denote the limits of agreement (mean difference ±2 SD, respectively), and grey areas within dashed blue lines denote 95 % confidence intervals.

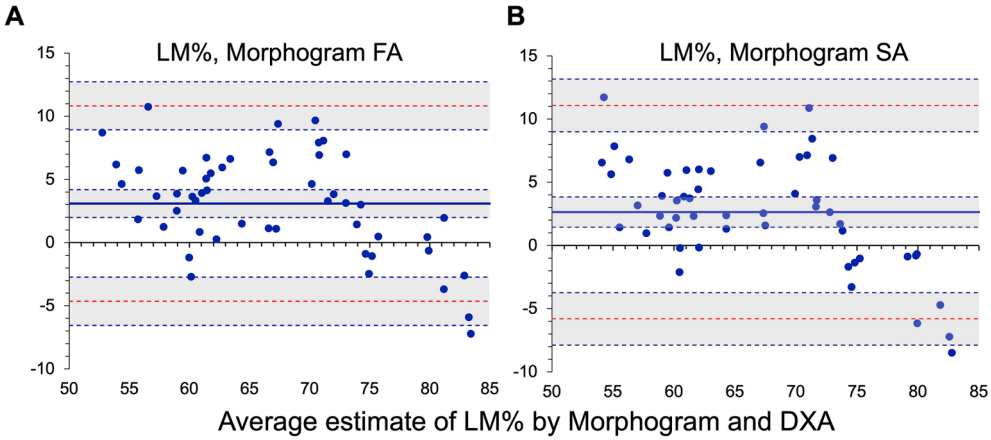

Fig. 5. *Comparison of body lean mass percentage estimated by Morphogram versus DXA.* Bland-Altman plots of the difference in body lean mass percentage (LM%) estimated by Morphogram Full Analysis (FA) and Smart Analysis (SA) minus DXA plotted against the average estimate of LM% by DXA and Morphogram FA and SA (A and B, respectively). Data are plotted in the same format as Fig. 5.

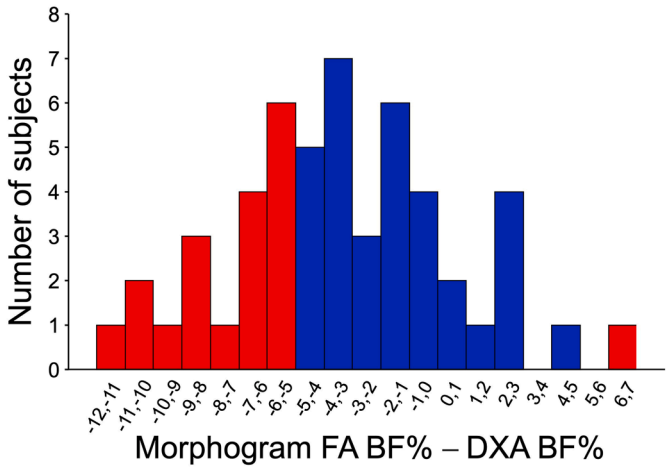

Fig. 6. *Distribution of Morphogram errors.* Frequency distribution of Morphogram FA minus DXA differences of body fat percentage (BF%) estimates. Red bars denote the number of subjects with differences equal, greater or smaller than 5 %.

participants with over-estimation discrepancies (positive bias) could not be addressed because this group was very small (1 FA, 3 SA) and consisted of overweight individuals caused by excessive lean mass. Therefore, we report here the analysis of FA data from the 18 participants, which include all participants analyzed with Morphogram SA exhibiting a negative bias.

Among the 18 discrepancies equal or greater than 5 %, 11 participants (4 males and 7 females; 21.1 % of all participants) were within 5 % and 8 %, with 7 participants exhibiting a BMI between 25 and 30 kg/m^2. The remaining 7 participants (4 males and 3 females; 13.5 % of all participants) exhibited discrepancies between 8 % and 11.4 %, with 5 participants exhibiting a BMI between 30 and 34.9 kg/m^2. The discrepancies (≥ -5 %) in BF% estimated by Morphogram versus DXA were equally distributed among male and female participants. Most discrepancies (14/18, 78 %) were associated with a fat mass index above the 90th percentile. Seven of these participants also exhibited a fat-free mass index below the 25th percentile, denoting a condition of relative sarcopenia. These percentiles are based on the work by Coin (2008) [32].

Examination of DXA parameters of the ratios between (1) android and gynoid fat (A/G), trunk and leg fat (Trunk/Leg), and trunk and limb fat (Trunk/Limb) provided further insights into the factors underlying the discrepancies in BF% estimation by Morphogram and DXA. These DXA parameters allow the characterization of fat distribution as android or gynoid according to their percentiles (10th – 50th and 50th – 90th percentile, respectively). For A/G, Trunk/Leg and Trunk/Limb percentiles, we used the work by Imboden (2017) [33]. According to the DXA percentiles reported by that work, 7 out of the 18 participants (39 %) with the largest discrepancies had an extreme android fat distribution (10th-20th percentile), 6/18 participants (33 %) were characterized by an extreme gynoid fat distribution (80th-90th percentile), and the remaining 5/18 participants (28 %) had a mixed fat distribution (between 30th and 70th percentile). This evaluation identified the main factors underlying the largest (≥−5 %) Morphogram − DXA BF% estimation discrepancies as follows:

1) For participants exhibiting strong android fat distribution, BF% under-estimation by Morphogram is caused by the coexistence of subcutaneous fat and pendulous abdomen, both of which cannot be estimated by using only body segment circumferences.
2) For participants exhibiting strong gynoid fat distribution, particularly in the arms and thighs, circumference measurements alone cannot evaluate the amount of subcutaneous fat;
3) BF% under-estimation by Morphogram occurs also in participants with excessive fat mass and relative lean mass deficits.

3.4. Assessment of metabolic syndrome risk

To evaluate the usefulness of the MSR scoring system, we compared it with the risk levels identified by WC, WHR, WHtR, and BF%. We found that WC, whose correlation with risk of cardiac and metabolic diseases in the general population has been clearly demonstrated, identifies “high” risk subjects – which would prompt clinical intervention – but cannot correctly identify the individual risk (Fig. 7A). This happens because the height and hip circumference of individual subjects are not considered, even though these two parameters significantly reduce the number of subjects identified as having high risk of cardiac and metabolic diseases [34]. As a result, WC over-estimates (3-fold) the number of subjects characterized by high risk for metabolic syndrome relative to Morphogram.

BF% over-estimates the number of subjects with high risk for metabolic syndrome (6-fold) relative to Morphogram and to a greater extent than WC because it does not consider the distribution of fat mass [35–37] (Fig. 7B). Regarding WHtR, this ratio over-estimates the moderate risk level while under-estimating the low risk level relative to Morphogram (Fig. 7C). These differences are due to the fact that WHtR does not consider variation in hip circumference.

The classification of metabolic syndrome risk based on WHR was closer to that performed by Morphograrm (Fig. 7D) relative to WC, BF%, and WHtR. However, WHR under-estimated the number of subjects with high risk because it does not integrate the height of each subject. This issue, which is not found in the MSR score computed by Morphogram, prevents the use of WHR for monitoring the stage of risk. Linear regression analysis revealed that the MSR score computed by Morphogram significantly correlates with WC, WHR, WHtR, BMI and BF%, with the strongest and weakest variance accounted for being WHtR and WHR (82 % and 21 %,

Table 2
Linear relations between DXA parameters, anthropometric variables, and risk of metabolic syndrome scores. MSR: metabolic syndrome risk; A/G: android/gynoid; T/Leg: Trunk/leg; T/Limb: Trunk/limb; BMI: body-mass index; WC: waist circumference; WHR: waist-hip ratio; WHtR: waist-height ratio; BF%: Body fat percentage. Asterisks denote statistically significant relations (*p < 0.05; ***p < 0.001).

Correlation analyses	R^2
A/G ratio vs. MSR	0.09*
T/Leg ratio vs. MSR	0.03
T/Limb ratio vs. MSR	0.04
WC vs. MSR	0.57***
WHR vs. MSR	0.21***
WHtR vs. MSR	0.82***
BMI vs. MSR	0.44***
BF% vs. MSR	0.43***

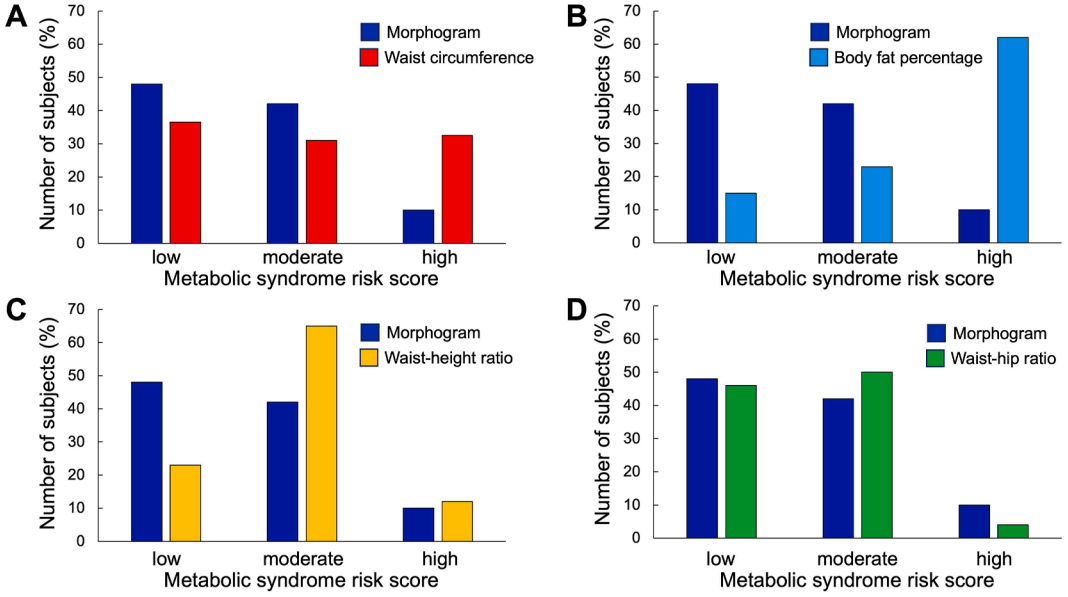

Fig. 7. *Metabolic syndrome risk scores.* The metabolic syndrome risk scores computed by Morphogram is plotted in each panel with the scores computed using waist circumference (A), body fat percentage, (B), waist-height ratio (C), and waist-hip ratio (D) across subjects expressed as percentage of the total number of subjects.

respectively; Table 2). In contrast, the MSR score was weakly correlated with parameters of adiposity obtained by DXA (Android/Gynoid, Trunk/Leg, and Trunk/Limb ratios) (Table 2).

4. Discussion

The present study examined the usefulness of an anthropometry-based method, Morphogram, for estimating body composition and quantifying individual stages of metabolic syndrome risk. As expected, BF% and LM% were under-estimated and over-estimated by Morphogram, respectively, relative to DXA, even though a good correspondence was found in most study participants. Furthermore, our study proposes a new methodology aimed at computing an individual score of risk of metabolic syndrome. We discuss our results in the context of the clinical potential of anthropometric analysis as an effective tool for the gradation and monitoring of cardiac and metabolic risk factors.

We found that the Smart Analysis' ability to estimate body composition is like that exhibited by FA (Figs. 3–5). Importantly, SA is simple to administer as it uses fewer variables than the Full Analysis (FA), i.e., only 3 body segment circumferences instead of 8 circumferences (Fig. 1). Therefore, SA can be considered particularly useful for screening, monitoring, and self-monitoring. We note that self-measurement of waist circumference is recommended to increase the population's awareness of the risk of central adiposity [13], while several studies also underscore its accuracy and reliability [38–40].

4.1. Estimation of body composition by Morphogram

The usefulness of the Morphogram algorithm is its ability to estimate BF% through changes in fat that occur at three body segment circumferences (waist, abdomen, hips), with the goal of capturing approximately 90 % of the fat changes that occur throughout the body [17]. This consideration underlies our hypothesized under- and over-estimation of BF% and LF%, respectively, by Morphogram relative to DXA. Specifically, as Morphogram weighs the circumferences of variations in waist, abdomen, and hip circumferences to estimate BF% (see *Introduction*), we expected Morphogram to under-estimate BF% and, therefore, over-estimate LM%. This hypothesis was statistically supported by our results (Fig. 3). Nevertheless, when comparing body composition estimated by Morphogram versus DXA, a good match was found in BF% and LM% in most study participants (Figs. 4 and 5). Specifically, the discrepancy in BF% estimation between the two techniques was below 5 % in 65 % of our study participants (Fig. 6).

The larger discrepancies in BF% under-estimation by DXA and Morphogram (between 5 % and 11 %; Fig. 6) were caused by Morphogram's inability to measure subcutaneous fat and estimate the amount of lean mass of the limbs. Consequently, this limitation causes a greater BF% underestimation especially in male, overweight, and sarcopenic subjects. Furthermore, for the same reasons, Morphogram under-estimates BF% also in people with obesity who have pendulous fat or significant subcutaneous fat.

We should emphasize that the imprecision exhibited by Morphogram in estimating BF% in subjects with gynoid fat distribution and pendulous abdomen does not affect Morphogram's ability to screen, grade and monitor subjects with cardio-metabolic risks (see section *Morphogram as a screening tool for metabolic syndrome risk*). This is because in subjects with gynoid fat distribution, the risk for metabolic syndrome is reduced [41,42]. However, in subjects with pendulous abdomen, part of the fat mass is missed by measuring abdomen, waist, and hip circumferences, but the risk of abdominal obesity is nevertheless accurately detected by the integrated score based on all risk indicators (WC, WHR and WHtR).

In sum, variations in body segment circumferences used by Morphogram simultaneously capture abdominal volume and anthropometric risk factors of central adiposity. Therefore, these body segment circumferences are both reliable indicators for estimating BF% and tools for metabolic screening and monitoring. Even though body composition estimation by Morphogram was reliable in most study participants, skin fold measurement should also be used to integrate monitoring of changes in subcutaneous fat while confirming or correcting fat estimation by Morphogram. This integrated approach is desirable in general, but it is essential in cases where the body fat mass is mostly represented by subcutaneous fat or in conditions of mixed obesity. In these cases, the subcutaneous fat component is associated with the abdominal-visceral component.

4.2. Morphogram as a screening tool for metabolic syndrome risk

Metabolic syndrome is a complex of risk factors interrelated with cardiovascular disease (CVD) and diabetes that include hyperglycemia, hypertension, hypertriglyceridemia, low high-density lipoprotein levels, and central adiposity. Although various diagnostic criteria have been proposed, a Joint Scientific Statement established that WC remains a useful, although not mandatory, preliminary screening tool (using national or regional cut-offs) and that diagnosis should be made using three abnormal results out of the above-mentioned five risk factors [43,44]. This work further confirmed that defining WC thresholds for abdominal obesity is problematic. Specifically, there is no universally accepted system for evaluating metabolic syndrome risk because this varies non only as a function of race, but also of ethnicity, sex, height and fat distribution. Nevertheless, WC is a modifiable risk factor. In fact, the International Atherosclerosis Society and the International Chair on Cardiometabolic Risk Working Group recommends that WC should be routinely included as an important “vital sign” in clinical practice [45].

The anthropometric measures currently used for clinical purposes (BMI and WC) have been widely used in population studies, but they lack sensitivity and specificity. Therefore, BMI and WC have obvious limitations in grading clinical decisions in individuals and, therefore, are perceived as having of low degree of clinical usefulness [34]. Lack of attention to the management of central adiposity leads to a progressive increase in diabetes and cardiovascular diseases, thus ignoring the ongoing epidemic [46–49].

The recognition of the many limitations of WC has led to the proposition of the WHR as a very useful indicator for the evaluation of body fat distribution [50]. However, when the WHR is used to monitor changes in risk, its usefulness is limited when the value of the numerator and denominator change in response to treatment [45]. In contrast, the simultaneous use of WC and WHR leads to a stronger association with metabolic syndrome and cardiovascular risks [50,51].

Recently, the 2022 NICE Guidelines recommended using the WHtR to grade abdominal obesity below a BMI of 35 kg/m^2 [13]. WHtR is a very sensitive indicator in adolescents and because, for a given WC, the risk increases with shorter heights [52]. Furthermore, WHtR can identify 11 % of males and 6 % of females who fall within the normal BMI but are characterized by normal weight obesity. Therefore, WHtR is considered as a more useful metric than WC for scrutinizing cardiometabolic risk factors [53,54]. Nevertheless, in clinical practice, it is difficult to phenotypically classify a patient using a single indicator. This is because, at the population level, a single anthropometric metric – WC, WHtR, or

WHR – can correlate with metabolic syndrome risk [13,55–58] but cannot identify *individual risks* because it does not consider the *integrated combination of variations* of several individual parameters, e.g., height, WC, and HC. These observations confirm the logic of the MSR score used by Morphogram.

We note that the MSR algorithm is not a diagnostic criterion of metabolic syndrome, but rather a scientific criterion to overcome the known limitations of WC through the contextual evaluation of WHR and WHtR. This evaluation weighs and grade individual risk using the degree of correlation of the individual anthropometric measurements with adverse health events, while implementing a criterion of systematization and use of existing data in the literature.

There are studies that have demonstrated that some anthropometric indicators correlate with adverse health outcomes. Nevertheless, it remains unclear which indicator should be used as the best predictor and how to use a given indicator to grade individual risk. The Golestan study examined 50,045 people aged between 45 and 75 years and tested BMI, WC, WHtR, WHR, and hip-corrected WC as predictors of cardiovascular mortality [59]. In that work, the association of these indicators with intermediate outcomes was also studied, including hypertension, glycemia, dyslipidemia, and visceral abdominal fat. The follow-up of study participants lasted 10.9 years. This work identified visceral adiposity as having the strongest predictive power on both intermediate outcomes and mortality when both WC – as a risk factor –, and hip circumference – as a protective factor –, are considered individually and simultaneously.

The work of Jayedi and colleagues [60], a meta-analysis of 72 prospective cohort studies with 2,528,297 participants, confirmed that central adiposity indices, including WC, WHR, WHtR, and waist-to-thigh ratio (WTR), were positively and significantly associated with higher all-cause mortality risk independent of overall adiposity, whereas the risk decreased with increasing hip and thigh size. The risk of metabolic syndrome computed by Morphogram (Fig. 7) addresses the above-mentioned limitations associated with the use of individual anthropometric measure and can therefore identify more realistically individual risk.

Recently, an international commission involving 56 world experts from a wide range of medical specialties redefined clinical obesity and its diagnostic criteria [61]. The experts recommended moving away from diagnosing obesity based on BMI alone, except in people with BMI >40 kg/m^2, in whom excess body fat can be empirically presumed. They also recommend confirming the presence of excess body fat and studying its body distribution, through at least (a) one body measurement (WC, WHR or WHtR) in addition to BMI, (b) two of these body measurements regardless of BMI, or (c) with direct measurement of body fat through DXA regardless of BMI. Thus, clinical and pre-clinical obesity can be distinguished based on the following considerations: Clinical obesity should be classified as a chronic disease determined by the direct effect of excess adiposity on the function of organs and tissues, and reduced ability to carry out normal daily activities. Pre-clinical obesity, in addition to having a variable risk of developing Clinical Obesity, should be followed and supported to reduce the risk of potential pathologies, primarily diabetes and cardiovascular diseases [61].

In this renewed context, Morphogram allows to define excess body fat by using both BMI and estimated BF%, confirming excess fat and its distribution through WC, WHR and WHtR, and grading and monitoring cardiometabolic risk through the integrated MSR score. We note that the MSR score uses the cut-off values for “low”, “moderate” and “high” risk established in the literature [41,42,53,54,62–70] based on WC, WHR and WHtR. As such, the MSR risk score offers a valid and immediate support to the management of Pre-clinical Obesity.

It could be argued that the WC cut-offs may have different references, as they are based on ethnicity and regional differences. Nevertheless, the other two indicators are sufficient to highlight the increase in abdominal adiposity, while the total score can be modified using the cut-offs validated by ethnicity or region.

5. Conclusion

Morphogram opens new avenues for the prevention and monitoring of Pre-Clinic and Clinical Obesity, offering a simple, low cost and accurate approach. The possibility of relying on multiple parameters of abdominal adiposity monitoring (excess abdominal volume, WC, WHR, WHtR, and an integrated MSR score) can be proposed for the monitoring of pharmacological therapies of obesity and diabetes, e.g., GLP-1 and GLP-1/GIP agonists. However, the present study, while indicating that Morphogram has a strong potential and solid scientific basis for the screening and monitoring of obesity and metabolic syndrome risk, did not monitor longitudinal changes in the metabolic status of subjects. Further work on a larger population of subjects is therefore needed to confirm the usefulness of Morphogram as a monitoring tool.

Author contribution

MS, ADC, PDC: Conceptualization; BB, LK, MS, PDC: Data curation; MS, JS, PDC: Formal analysis; MS: Funding acquisition; All authors: Investigation; MS, ADC, PDC: Methodology; MS, JS: Project administration; MS, ADC: Software; MS, PDC: Supervision; All authors: Writing (original draft); All authors: Writing (review and editing).

Data sharing plan

Data described in the manuscript will be made available upon request pending.

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Declaration of competing interest

A patent application on the Morphogram technology reported here has been submitted (WO 2023/069605). P. De C., A. De C., and M.S. are co-authors on the patent application. P. De C. and A. De C. are co-authors on an Italian copyright on the Morphogram technology. The remaining authors declare no competing interests.

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Appendix A. Supplementary data

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