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Defining left ventricular remodeling using lean body mass allometry: a UK Biobank study.

Defining Left Ventricular Remodeling using Lean Body Mass Allometry, A UK Biobank Study

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ABSTRACT

Purpose: The geometric patterns of ventricular remodeling are determined using indexed left ventricular mass (LVM), end-diastolic volume (LVEDV) and concentricity, most often measured using the mass to volume ratio (MVR). The aims of this study were to validate lean body mass (LBM) based allometric coefficients for scaling and to determine an index of concentricity that is independent of both volume and LBM.

Methods: Participants from the UK Biobank who underwent both CMR and dual-energy x-ray absorptiometry (DXA) during 2014-2015 were considered (n=5064). We excluded participants aged ≥70 years or those with cardiometabolic risk factors. We determined allometric coefficients for scaling using linear regression of the logarithmically transformed ventricular remodeling parameters. We further defined a multiplicative allometric relationship for LV concentricity (LVC) adjusting for both LVEDV and LBM.

Results: A total of 1638 individuals (1057 female) were included. In subjects with lower body fat percentage (<25% in males, <35% in females, n= 644), the LBM allometric coefficients for scaling LVM and LVEDV were 0.85±0.06 and 0.85±0.03 respectively (R^2= 0.61 and 0.57, P<0.001) with no evidence of sex-allometry interaction. While the MVR was independent of LBM, it demonstrated a negative association with LVEDV in (females: r= -0.44, P<0.001; males: -0.38, P< 0.001). In contrast, LVC was independent of both LVEDV and LBM [LVC = LVM / ($LVEDV^{0.40}$ × $LBM^{0.50}$)] leading to increased overlap between LV hypertrophy and higher concentricity.

Conclusions. We validated allometric coefficients for LBM based scaling for CMR indexed parameters relevant for classifying geometric patterns of ventricular remodeling.

Key words: Ventricular remodeling, LV hypertrophy, scaling, allometry, body composition, adiposity, obesity, visceral fat.

ABBREVIATIONS

BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
CMR	Cardiac magnetic resonance
CO	Cardiac output
DXA	Dual-energy X-ray absorptiometry
MESA	Multiethnic Study of Atherosclerosis
MVR	Mass-to-volume ratio
LAV	Left atrial volume
LBM	Lean body mass
LVC	Left ventricular concentricity, by multiplicative allometry
LVE	Left ventricular enlargement
LVEF	Left ventricular ejection fraction
LVEDV	Left ventricular end-diastolic volume
LVESV	Left ventricular end-systolic volume
LVH	Left ventricular hypertrophy
LVM	Left ventricular mass

INTRODUCTION

Scaling of left ventricular mass (LVM) and end-diastolic volume (LVEDV) plays a central role when evaluating left ventricular hypertrophy (LVH) or chamber enlargement enabling better comparison across the spectrum of body size (Jain et al. 2011; Gaasch and Zile 2011; Marwick et al. 2015). Concentricity, which is an internally scaled measure of ventricular mass and volume, when combined to indexed LVM and LVEDV, is essential for the classification of geometrical patterns of ventricular remodeling (Jain et al. 2011; Gaasch and Zile 2011; Marwick et al. 2015). Gaasch and Zile (2011) proposed a subdivision of LV remodeling which classifies LV geometry into eight geometric patterns (**Figure 1A**) i.e. normal LV geometry, physiological (adaptative) hypertrophy, maladaptive hypertrophic profiles (concentric, mixed, dilated and eccentric) and remodeling patterns (concentric to eccentric). Physiological or adaptative hypertrophy is usually defined by the combination of mild LVH in the presence of normal concentricity.

From a mathematical perspective, scaling can be accomplished by simply dividing a clinical variable with a measure of body size (ratiometric scaling) or by elevating the body size metric to a specific power (allometric scaling). Several criteria are used to determine whether scaling is optimal for clinical practice. First, it is important to determine whether scaling leads to body size independent indexing, i.e. removes any residual relationship between the indexed variable and the body size metric. Second, indexing should not lead to unequal variance across the spectrum of body size (heteroscedasticity) as this could lead to higher or lower values in smaller or larger body size. Finally, indexing should not introduce bias in obesity, which consequently would underestimate the prevalence of LVH or LV enlargement (LVE) in obesity as to individuals with normal weight. Compared to ratiometric scaling, allometry may allow for better dimensional consistency, and may help adjusting for linear relationships not crossing the origin, which would create unequal variance and residuals across the spectrum of body size.

While scaling to body surface area (BSA) remains the most commonly used indexing in clinical practice, de Simone et al. and others have clearly demonstrated that indexing to BSA leads to a paradoxical lower prevalence of LV hypertrophy in obesity (Simone et al. 1992, 1995; de Simone and Galderisi 2014). For this reason, scaling allometrically to height (where the coefficient is raised to a power of 1.7 or 2.7) or to lean body mass (LBM) is preferred when assessing ventricular remodeling patterns (Simone et al. 1992; Hense et al. 1998; Kuch et al. 2000; George et al. 2001; Chirinos et al. 2010; Kuznetsova et al. 2016). Compared to height, LBM has the advantage of considering body composition. For LVM, studies in young fit male subjects or athletes have shown that LVM scales allometrically to LBM raised to a power of approximately 0.9 (George et al. 2001; Giraldeau et al. 2015; Martinho et al. 2020). While concentricity is most often defined using the LVM to LVEDV ratio (mass-to-volume ratio, MVR), Khouri et al. (2010) introduced the concept of allometric concentricity, where LVM is scaled to LVEDV raised to the 2/3 power yielding a more volume independent relationship. This exponent was chosen based on the relationship between LVM and LV area. In fact, mathematically, LVM is approximated by area * wall thickness. While ventricular equals to LVEDV $^{2/3}$, assuming a spherical geometry of the heart (area of a sphere = $(\pi^{1/3})$ *(6*volume of a sphere)$^{2/3}$).

To date, few studies have validated the allometric coefficients of LVM or LVEDV based on LBM using a well-defined reference group defined by its body composition. In addition, no studies have defined concentricity allometrically to derive a metric that is independent of both volume and body size or determined its impact on defining geometric patterns of remodeling. The population-based UK Biobank study offers a unique possibility to analyze allometric scaling of cardiac measurements, as it includes both measures from cardiac magnetic resonance (CMR) and body composition data based on dual-energy X-ray absorptiometry (DXA) (Petersen et al. 2017). In the current analysis of data from the UK biobank, we first sought to validate LBM based allometric coefficients for LVM and LVEDV in a well-defined reference group with “normal” body fat composition. We then sought to determine a novel multiplicative allometric index of concentricity

that would be independent of both ventricular volume and LBM. Finally, we assessed the impact of LBM based scaling on geometrical patterns of ventricular remodeling. **Figure 1B** summarizes the objectives of the study.

METHODS

The UK Biobank is a large-scale biomedical database and research resource which investigates the contribution of genetic predisposition and environmental exposure to the development of disease. We considered individuals who participated in the first imaging visit including CMR and DXA, which occurred between August 2014 and August 2015 (n=5064) (Petersen et al. 2017). To minimize confounding effects of race and older age, we focused on 4896 subjects of white ancestry, aged between 45 to 70 years old. We applied strict exclusion criteria to identify a subgroup of 1638 healthy individuals including 1057 females and 581 males (**Figure 2**).

Exclusion criteria included: (1) surgical (OPSC4) and/or diagnoses (ICD10), (2) anthropomorphic or body exclusion criteria or (3) CMR guided data. Surgical or diagnostic codes for exclusion included the following: hypertension, hyperlipidemia, pre-diabetes, current smoker, diabetes mellitus, coronary artery disease, coronary intervention, pulmonary disease, other heart disease, heart failure and kidney disease. Hypertension was defined as either of (a) a mean systolic blood pressure (BP) or mean diastolic BP ≥140 or ≥90 mmHg, respectively, at the time of imaging and at one more UK biobank visit; (b) a medical diagnosis of arterial hypertension; (c) self-reported use of any anti-hypertensive medication. Hyperlipidemia was defined as either of (a) an inpatient diagnosis of hyperlipidemia; (b) self-reported use of cholesterol lowering medication; (c) recorded

use of statins. Diabetes mellitus was defined as any of (a) an HbA1c-value ≥ 48 mmol/mol or fasting plasma glucose ≥ 7 mmol/L at any of the two possible visits preceding the imaging visit; (b) recorded use of metformin, sulfonylurea, acarbose, prandial, thiazolidinediones or insulin; (c) an inpatient diagnosis of diabetes mellitus; (d) self-reported diabetes mellitus. Pre-diabetes was defined (in subjects not fulfilling any criteria for diabetes mellitus) as an HbA1c-value ≥ 39 mmol/L or fasting plasma glucose ≥ 5.6 mmol/L at any of the two possible visits preceding the imaging visit.

From the remaining 1881 subjects, we excluded 123 subjects with either a body mass index (BMI) ≤17 or ≥40 kg/m², LBM ≤30 kg or missing data on height, weight or LBM. We excluded extreme obesity from the analysis as these individuals have a much higher probability of undiagnosed metabolic disease. Finally, 120 subjects with either left ventricular ejection fraction (LVEF) < 50% (n=66), missing CMR data on LVM (n=43) or extreme outliers defined as three times the inter quartile range above 75th or under 25th percentile in LV mass or end-diastolic volume values (n=11) were excluded.

Cardiac magnetic resonance and body composition analysis

Details on the specific CMR imaging protocols have been previously published (Petersen et al. 2013, 2015, 2017), and are available at https://www.ukbiobank.ac.uk/. For the analysis of cardiac remodeling profiles, we first focused on LVM, LVEDV and the MVR. Other CMR variables

analyzed included LVEF, left ventricular end-systolic volume (LVESV), LV stroke volume, cardiac output (CO) and left atrial volume (LAV). DXA based measurements included LBM (including both total LBM as well as the "trunk" LBM related to the neck, chest, abdominal and pelvic areas), fat mass, fat mass percentage and visceral fat mass. Height and weight were collected at the time of the visit and BMI was calculated.

Reference group for defining allometric coefficients

Allometric coefficients were derived in individuals with body fat percentage lower than 25% for males and lower than 35% for females. These thresholds were based on the study of Gallagher et al. (2000). In this reference group, we derived reference limits for allometrically indexed LVM and LVEDV using the 2.5th and 97.5th percentiles.

Overfat and obese categories were also defined based on the study of Gallagher et al. (2000), as a body fat percentage between 25-30% (overfat) or above 30% (obese) for male and between 35-40% (overfat) or above 40% (obese) for female. Since we excluded individuals with BMI ≤17 kg/m², we did not consider an underfat category; among the reference group, no male had a body fat percentage < 8% and 16 females (1.5%) had body fat percentage < 21% (Gallagher et al. 2000).

Statistical analysis

Analysis was performed using Python version 3.9 and MedCalc® Statistical Software version 20.014 (MedCalc Software Ltd, Ostend, Belgium). Continuous variables were presented as mean ± standard deviation. We selected standard deviation as the metric of dispersion, since outlier values were rare in the dataset (**Supplemental table 3**) and compared to interquartile range. Outliers (outside values) were defined using the Tukey method defined as excluding values above

the first or below the third quartile ranges. Categorical variables were presented as count and percentages. Student's t-test or Mann-Whitney U test were used to compare group mean differences in continuous variables, while the Chi-square test was used for group differences in categorical variables.

Allometry of CMR parameters of LV remodeling and concentricity

To determine the allometric coefficients for body size metrics, linear regression models of the logarithmically transformed variables were fitted to predict the different CMR variables, as shown in **Table 1.** For all models we used backward regression, variables with p-value < 0.05 were entered and then removed if p> 0.1. Sex was added to these models as a covariable. In the absence of a sex-allometry interaction, a single allometric coefficient was used for both males and females. Significant sex-allometry interaction was defined as an interaction coefficient greater than two standard deviations of the allometric coefficient. Multiplicative models for LVM were also considered entering both LBM and height; in these models age was also considered as a co-variable. To define left ventricular concentricity, we first developed a model where ln(LVM) was entered as the dependent variable and ln(LVEDV), ln(LBM) and sex were entered as the independent variables. In the absence of significant sex-allometry interaction, then a single model can be used for both male and female. The multiplicative concentricity would, then, be expressed as LVM/ ($LVEDV^{a} * LBM^{b} * e^{c\ *sex}$), were the sex factor would be a conditional multiplicative constant. This index would have the theoretical advantage to be independent of LVEDV, LBM and sex. We then tested to whether including individuals with overfat or obese composition as part of the reference group would yield different allometric coefficients for scaling. Finally, we derived allometric coefficients for the other CMR variables.

Several criteria were used to evaluate whether a scaling metric was adequate: (1) body size independence, i.e. no significant relationship between the indexed parameters and the body size metric (a relationship was considered significant if Pearson r >0.10 with a P<0.01 in

correlation analysis); (2) absence of heteroscedasticity and (3) absence of bias in obesity, i.e. paradoxical lower prevalence of LVH and concentric remodeling associated with higher body fat percentage (Batterham et al. 1997; Kuznetsova et al. 2016). For concentricity metrics (MVR and LVC), independence from body size and volume was assessed. To compare correlation coefficients, we used a *z*-test on Fisher *z*-transformed correlation coefficients as described by Hinkel and colleagues.

Left Ventricular Remodeling profile analysis

Using reference limits for indexed LVM, LVEDV and concentricity (defined as their 2.5th or 97.5th percentile in the reference group), we classified LV geometric patterns of remodeling in the entire population based on the scheme proposed by Gaasch and Zile (Gaasch and Zile 2011; Marwick et al. 2015). We created plots representing the different LV geometric patterns of remodeling using either LBM or height-based indexing. We further compared the geometric patterns of remodeling between allometric concentricity and the MVR. A multivariable regression model including age, sex, height, weight, arterial pulse pressure, visceral fat composition (visceral fat to LBM ratio), was used to identify the standardized odds ratios for presenting LBM indexed definitions of LVH or concentricity.

RESULTS

The baseline characteristics of the cohort of 1638 participants (64.5% female) are summarized in **table 2**. A BMI > 30 kg/m^2 was present in 10.8% of females and 12.0% of males.

Part A. Body composition defined reference groups

The distribution of body fat percentage stratified by sex is presented in **Figure 3a**. The full cohort was divided into three groups: “normal fat” (n=644), “overfat” (n= 485) or “obese” (n=521) according to the classification of Gallagher et al. (2000) (**supplemental table 1)**. Body fat

percentage was strongly related to visceral fat indexed to LBM and followed a non-linear relationship (quadratic) with r= 0.86, P< 0.001 for females and r=0.80, P<0.001 for males (**Figure 3b)**. A steeper increase in visceral fat mass content occurred when fat percentage exceeded the limits proposed by Gallagher et al. (2000) (25% in males and 35% in females). Since LBM was previously reported to increase with obesity, we quantified to which extend body fat percentage was related to indexed LBM. We only found a modest non-linear relationship between body fat percentage and LBM index in both males (R^2 =0.045, P<0.001) and females (R^2 =0.023, P<0.001) (**Supplementary Figure 1**). For this analysis, LBM scaled to height to the power 1.9 in both male and female as this coefficient led to a height independent metric.

Part B. Allometric based coefficients for scaling LV mass and volumes

Regression analysis showed that LVM and LVEDV were more strongly associated with LBM than height (R^2 = 0.61 vs. 0.50, P<0.001) but not statistically different from scaling to BSA (R^2 = 0.61 vs. 0.57, P=0.28) in the reference group. The allometric coefficients are summarized in **Table 3a.** A sex-allometry interaction was only noted when scaling LVM to BSA. In contrast to LVM and LVEDV, the MVR was independent of body size.

For both LVM and LVEDV, we found an allometric coefficient based on LBM of 0.85 (0.85 ± 0.06 for LVM and 0.85 ± 0.03 for LVEDV). When based on height, the allometric coefficient for indexing LVM was 1.23 ± 0.18 and 1.78 ± 0.16 for LVEDV. When using height to the 1.7 power (guideline recommended)(Marwick et al. 2015), scaling of LVM to height only showed a weak association in female (P = 0.014) but no significant correlation in male (P = 0.24) (**Supplemental Figure 2)**. In contrast, when using height to the 2.7 power, LVM index remained dependent on height with a correlation coefficient of -0.33, P<0.001 in females and -0.27, P=0.002 in males. Males had on average 9% higher LVM (when indexed to $LBM^{0.85}$) and MVR than females. The sex difference was greater when indexing to height (32% higher LVM and 17% higher for LVEDV for males compared to females).

Next, we tested whether considering both LBM and height could improve the prediction of LVM (multiplicative model). The allometric coefficient for height in the model with LBM was -0.69±0.21 (negative coefficient). Although both LBM and height were retained in the model, the increase in the coefficient of determination was small (from 0.61 to 0.62) (**Table 3B**).

Left ventricular concentricity

While the MVR was independent of LBM, we found a significant relationship with LVEDV (volume dependent) with a correlation coefficient of -0.44, P<0.011 for females (n=444) and -0.38, P< 0.001 for males (n=188) (**Figure 4**). The concentricity index of Khouri ($LVM/LVEDV^{2/3}$) was independent of LVEDV, but retained a significant relationship with LBM (r=0.28, P=0.001 for males and r= 0.14, P=0.002 for females). In our cohort, LVM was allometrically related to volume with a coefficient of 0.60 ± 0.03 (**Table 3c)** with a small sex-allometry interactions. Similar to the index of Khouri et al., $LVM/LVEDV^{0.6}$ retained a relationship with LBM in males (r=0.33, P < 0.001) and in females (r= 0.19, P < 0.001).

Using multiplicative allometry, LVM was related to both LVEDV (with an allometric coefficient of 0.40±0.04) and LBM (with an allometric coefficient of 0.49±0.06) with an R^2 = 0.67, P<0.001 **(Table 3c)**. As shown in **Figure 4c**, the multiplicative concentricity index (LVC) was independent of both LVEDV (P=0.92) and LBM (P=0.57). In contrast to the MVR, the upper limits of LVC (97.5^{th} percentile) were well distributed across the spectrum of LVEDV (**Figure 4c**). Multiplicative concentricity based on LVEDV and height is presented in **Table 3d**.

The influence of body fat percentage on allometric coefficients for LVM

When derived in groups including the overfat or obese thresholds, the allometric coefficients for indexing LVM based on LBM were 0.95±0.04 and 0.98±0.03, respectively, higher than the coefficients derived in the reference group with lower body fat percentage.

LBM compartment and its importance in LVM indexing

The DXA quantified the total LBM as well as the "trunk" LBM associated with the neck, chest, abdominal and pelvic areas. The difference between the total LBM and trunk LBM represent an indirect measure of appendicular (arm and leg) LBM. In the entire cohort of healthier individuals included in this cohort, trunk LBM was strongly associated with total LBM in both males (R^2=0.90, p<0.001) and females (R^2=0.88, p<0.001) with an average ratio between truncal and non-trucal LBM of 0.91 ± 0.06 in males and 0.97 ± 0.07 in females. Including both truncal and non-truncal LBM into the LVM scaling model led to a similar R^2 of 0.61 (p< 0.001), where truncal LBM having showed a greater contribution (r partial of 0.26 vs. 0.12).

Allometric coefficients for other CMR measures

While stroke volume was strongly related to body size, a weaker relationship was noted for cardiac output and left atrial volume (P<0.001 for all comparisons). The allometric coefficient differed according to the different CMR variable (**Table 4)**. For example, cardiac output had the lower allometric coefficient of 0.55±0.04. LVEF was body size independent with males having a relative 4.2% lower value in males.

Part C. Geometric patterns of Ventricular Remodeling Across the Spectrum of Body composition

The prevalence of LV hypertrophy and high concentricity in the normal, overfat and obese subgroups is summarized in **Figure 5a and b**. For LVM, scaling metrics included BSA, $LBM^{0.85}$ or $height^{1.7}$ and for concentricity indices included the MVR or LVC. These thresholds were derived based on reference limits in the lower fat composition group (**Table 5).** When scaled to BSA,

there was a paradoxical decrease in the prevalence of LVH with individuals with higher body fat percentage (P=0.019 for female and 0.032 for male, **Figures 5.A and 5.B**). Indexing to height showed a higher prevalence of LVH in the overfat and obese groups; using both MVR and LVC, higher concentricity was noted in the overfat and obese group. A trend for LVH based on $LBM^{0.85}$ was also noted in the female group.

Geometric patterns of remodeling can be obtained by using allometrically indexed LVM, LVEDV and a measure of concentricity. Figures 5c and d summarizes the geometric pattern of LV remodeling for females using multiplicative concentricity and LV mass to volume ratio, respectively. The geometric pattern of remodeling for males is shown in supplemental Figure 3a and b. Supplemental Figure 4 depicts the pattern of remodeling using allometrically indexed height.

As shown in Figure 5c, the majority of females had normal geometry (94.7%), while concentric hypertrophy was noted in 2.3%, concentric remodeling in 2.1% and physiological (adaptative) hypertrophy in 0.9% of these participants. As shown in supplementary Figure 3a, the majority of males had normal geometry (96.4%) while concentric hypertrophy was noted in 1.4%, concentric remodeling in 1.9% and physiological (adaptative) hypertrophy in 0.3% of them. Using the LV mass to volume ratio instead of multiplicative concentricity, a higher proportion of individuals have physiological hypertrophy and concentric remodeling, while a lower proportion have concentric hypertrophy. The concentric remodeling pattern also becomes more prevalent in individuals with low LVEDVI (arrow in Figure 5d and Figure 5e, f). On multivariable analysis, higher LVC (including concentric remodeling and concentric LVH) was independently associated with higher visceral fat content (in both male and female) and higher pulse pressure in females (**Supplemental Table 2**). Pulse pressure but not visceral fat content was significantly associated with LVH (indexed to LBM) in females.

DISCUSSION

Leveraging data from the UK Biobank, our study has three main findings. First, we validate the allometric coefficients for LBM based scaling of ventricular mass and volume in a well-defined reference group. Second, we described a novel index of concentricity (LVC) that is both volume and body size independent. When defined using LVC, there was a greater overlap between hypertrophy and concentricity with obesity and as expected an appropriate decrease in physiological hypertrophy. Finally, we demonstrated that allometric coefficients can't be uniformly applied to all CMR metrics; for example, the LBM allometric coefficient for scaling cardiac output is significantly lower than the coefficient for indexing LVM.

Our study validates the allometric coefficients for scaling LV mass and volume based on height and LBM (Schmidt-Nielsen 1975; Nevill and Holder 1995; Gaasch and Zile 2011). Consistent with the studies of DeSimone et al. (1992) and Kuznetsova et al. (2016), we demonstrate that ratiometric scaling to BSA leads to a paradoxical decrease in the prevalence of LVH with obesity. We further validate that scaling to height is best accomplished with a lower coefficient; in this UK Biobank analysis indexing to 1.7 was associated with body size independent scaling (for clinical purposes) in contrast to scaling with a coefficient of 2.7 (Simone et al. 1992, 1995, 2005; Chirinos et al. 2010; de Simone and Galderisi 2014; Marwick et al. 2015). This is consistent with recent findings from the Multiethnic Study of Atherosclerosis (MESA) and the Asklepios Study which conducted sex-specific analysis (Chirinos et al. 2010). The negative coefficient for height (coefficient of -0.69±0.21) suggests that individuals of taller stature have lower LVM when adjusted for LBM. This could be related to a lower reflected arterial wave observed in taller individuals consistent with the work of Mitchell and colleagues. In their population based study, which focused on artery tonometry measurements of ca. 500 individuals of the Framingham Heart Study offspring cohort who were free from clinical cardiovascular disease, height was negatively associated with wave augmentation index and reflected pressure waves. Our analysis also confirms that scaling to LBM is best accomplished with a coefficient of 0.85 when derived from a reference group with normal body composition. This is in agreement

with previous smaller studies which have found an allometric coefficient close of 0.9 (George et al. 2009; Giraldeau et al. 2015; Krysztofiak et al. 2019; Martinho et al. 2020; Shea et al. 2020) . Compared to other body size metrics, LBM was more strongly associated with LVM and LVEDV and therefore had the lowest coefficient of variation. Indexing to LBM addresses a different question than indexing to height as it adjusts for the increase in LBM associated with obesity(Hense et al. 1998; Bella et al. 1998). Although the increase is small as our study has quantified (<2kg/$m^{1.9}$), this could explain the slightly lower prevalence of LVH when indexing to LBM compared to height-based indexing (Palmieri et al. 2001).

Ventricular remodeling not only contemplates LVM and LVEDV to derive geometric patterns of remodeling, but also requires the definition of LV concentricity. In the original framework of Gaasch and Zile, the majority of hypertrophy in non-dilated ventricles would be concentric in nature and only a small percentage of non-athletes would have physiological hypertrophy. By developing a novel index of LV concentricity that is independent of both LVEDV and LBM, we were able to increase the overlap between hypertrophy and concentricity. The commonly used MVR implicitly assumes that the relationship between LVM and LVEDV passes through the origin yielding a ratio with unequal variance across the spectrum of volume. When applied to ventricular remodeling graphs, this will increase the proportion of individuals with hypertrophy and normal concentricity, a feature of physiological hypertrophy. In our study, this would yield to the counterintuitive conclusion that overfat and obesity is associated with more physiological hypertrophy than individuals with normal body composition. While the allometric concentricity index proposed by Khouri et al. (LVM/ $LVEDV^{0.66}$) was volume independent, as expected, it retained a relationship with LBM(Khouri et al. 2010b). The rationale of Khouri was based on the fact that LVM = LV area * wall thickness and that LV area relates to $LVEDV^{0.66}$ assuming a spherical geometry of the left ventricle; in this reasoning LVM/ $LVEDV^{0.66}$ will be related to wall thickness which itself is associated with LBM. In our study, we observed an allometric coefficient when LVM to LVEDV slightly lower than 2/3 in keeping with the elliptic shape

of the heart. If further validated, LVC can be valuable for differentiating adaptative from maladaptive remodeling across the spectrum of health and disease. Interestingly, similar findings on the geometric patterns of remodeling were also observed when defining LVC based on LVEDV and height base indices. While the analysis of concentricity in this paper focuses on the mass and volume relationships, the RWT is most commonly used in echocardiography. Gaash et al. has previously described the non-linear relationship between RWT and LV mass to volume ratio. Analyzing the extent by which RWT is independent of LV size and body size will be subject of future work.

While not the primary objective of our study, our analysis also led to important findings on the scaling of other CMR metrics as well as on observation relevant to body composition and visceral fat. Our study highlights that allometric coefficients cannot be uniformly applied across CMR variables. For example, the lower scaling coefficient for cardiac output is in keeping with the allometric coefficient of resting energy expenditure and resting oxygen consumption with a coefficient close to 2/3 when defined across the spectrum of BMI (White and Seymour 2003). In addition, we found that body size only accounts for a small part of the biological variability of LAV which scales “poorly” compared to other metrics.

Our study also underlines the association between LV concentricity and visceral adipose tissue. The visceral fat mass appears to increase more steeply when individual exceed the “normal” body fat percentage thresholds proposed by Gallagher et al. (2000). Based on the Dallas Heart Study, Neeland et al. have previously shown that visceral adipose tissue, a marker of central adiposity, was independently associated with concentric LV remodeling and adverse hemodynamics (Neeland et al. 2013). Furthermore, a recent study by van Hout et al. (2020) based on the UK Biobank study population also showed that visceral obesity was associated with a smaller LVEDV and subclinical lower LV systolic function in men.

The current study has several limitations. The current study has several limitations. First, due to the largely healthy collective of participants underlying the UK Biobank cohort with

predominantly caucasian ancestry, we focused on subjects of that ethnicity and excluded common cardiovascular comorbidities to avoid bias in our results. Continuing this line of work and the preliminary results by the MESA study, future studies are needed to enable conclusions across ethnicities and concomitant cardiovascular conditions. Second, as it is known that physical activity has a short- and long-term impact in cardiac remodeling, it is possible that differences in physical activity would have implications in our results. Again, future larger studies are needed to explore this. Third, although our reference group was defined differently from the study of Petersen et al. (2017), we found similar reference limits for LV mass, volume and MVR. We also realize that LBM is not readily available clinically, and this study was intended to provide validation for coefficients previously derived in smaller studies.

In conclusion, our study validates allometric coefficients based on LBM and defined a new concentricity index that may improve the classification of geometric patterns of ventricular remodeling.

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FIGURE LEGENDS

Figure 1. Geometric patterns of LV remodeling profiles. Panel A summarizes the geometric patterns of LV remodeling, adapted from Gaasch and Zile by adding categories for low LV mass index and low LVEDV index. **Panel B** summarizes the three different parts of the study from defining a reference group based on body composition, to determining allometric coefficient for CMR based metrics as well as geometric patterns of LV remodeling. The last panel summarizes criteria for an optimal scaling metric.

Figure 2. Cohort selection for the study focused on a group of low risk individuals across the spectrum of body composition.

Figure 3. Body composition and relationship to visceral fat mass. Panel A. Highlights the criteria used to partition the groups according to body fat percentage according to the NHANES study of Gallagher et al.[18] **Panel B.** Non-linear relationship (fitted to quadratic equation) between body fat percentage and visceral fat component scaled to lean body mass. A steep transition in visceral fat content is noted when transitioning to the overfat category.

Figure 4. The concept of adjusted ventricular concentricity. Panel A. Concentricity relates ventricular mass and volume. Building on the relationship between ventricular mass, ventricular area and wall thickness, Khouri[14] proposed an allometric index of concentricity that would be volume independent. Ideally, an index should be independent of both volume and body size. This can be developed using multiplicative or stepwise regression analysis. **Panel B and C.** In the healthy subgroup of “reference” fat composition, the commonly used mass to volume ratio was not volume independent in contrast to LV concentricity index.

Figure 5. Scaling and patterns of geometrical remodeling in study cohort. Panel A and B demonstrate the prevalence of LV hypertrophy or high concentricity based on different metrics;

scaling to BSA underestimates LVH in obesity. **Panel C and D** compare pattern of geometric remodeling for allometric LBM based scaling in female using multiplicative concentricity or the MVR. With adjusted concentricity, there is a very high concordance between concentricity and LVH. **Panel E and F** present the prevalence of the different geometric pattern of remodeling according to multiplicative concentricity and MVR.