Validation of Cardiovascular Magnetic Resonance-Derived Equation for Predicted Left Ventricular Mass using the UK Biobank Imaging Cohort: Tool for donor-recipient size matching

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Abstract

Background:

Current guidance from International Society for Heart and Lung Transplantation (ISHLT) recommends using body weight for donor-recipient size matching for heart transplantation. However, recent studies have shown that predicted heart mass, using body weight, height, age and gender, may represent a better method of size matching. We aim to validate a cardiovascular magnetic resonance (CMR)-derived equation for predicted left ventricular mass (LVM) in a cohort of normal individuals in the UK.

Methods and Results:

This observational study was conducted in 5,065 middle-aged (44-77 years old) UK Biobank participants who underwent CMR imaging in 2014-2015. Individuals with cancer diagnosis in the previous 12 months or history of cardiovascular disease were excluded. Predicted LVM was calculated based on participants' gender, height, and weight recorded at the time of imaging. Correlation analyses were performed between the predicted LVM and the LVM obtained from manual contouring of CMR cine images. 3,398 participants (age 61.5 ± 7.5 years, 47.8% males) were included for analysis. Predicted LVM was considerably higher than CMR-derived LVM (mean ± standard deviation of 138.8 ± 28.9g vs 86.3 ± 20.9g). However, there was a strong correlation between the two measurements (Spearman's correlation coefficient 0.802, $p < 0.0001$).

Conclusions:

Predicted LVM calculated using a CMR-derived equation that incorporates height, weight and gender has a strong correlation with CMR LVM in large cohort of normal individuals in the UK. Our findings suggest that predicted heart mass equations may be a valid tool for donor-recipient size matching for heart transplantation in the UK.

Non-standard Abbreviations and Acronyms

bSSFP balanced steady-state free precession

CMR cardiovascular magnetic resonance

GRE gradient-echo

HES Hospital Episode Statistics

ICD International Classification of Diseases

ISHLT International Society for Heart and Lung Transplantation

LV left ventricular

LVM left ventricular mass

MESA Multi-Ethnic Study of Atherosclerosis

PHM predicted heart mass

UNOS United Network for Organ Sharing

Clinical Perspective

What is new?

- In this large cohort study, we demonstrated that predicted left ventricular (LV) mass using sex, height and weight has strong correlation with LV mass measured by cardiovascular magnetic resonance (CMR) imaging.
- The correlation of CMR-measured LV mass with predicted LV mass (Spearman's rho = 0.802, $p < 0.0001$) is stronger compared with weight (Spearman's rho = 0.665, $p < 0.0001$) or height (Spearman's rho = 0.684, $p < 0.0001$).
- There is poor absolute numerical agreement between predicted LV mass and CMR-measured LV mass (absolute difference in mean values = 62g for men, 44g for women).

What are the clinical implications?

- Our findings challenge the clinical practice of using weight or height alone for donor-recipient size matching in heart transplantation.
- Predicted heart mass using CMR-derived equations appears to offer a better technique for donor-recipient size matching than using height or weight alone.
- The equations for predicted heart mass, which were derived from a multi-ethnic group, are translatable to a predominately Caucasian population.
- Further studies are warranted to determine the optimal metric for donor-recipient size matching and guide future clinical recommendations in heart transplantation.

Introduction

Size matching is an important consideration in heart transplantation. At a simplistic level, a recipient should receive a donor heart that is large enough to generate adequate cardiac output and overcome recipient pulmonary vascular resistance, but small enough to fit into the mediastinal space and allow the chest to be closed. Current guidelines for donor-recipient size matching are based on body weight alone. The International Society for Heart and Lung Transplantation (ISHLT)[1] recommends a) that it is safe to use hearts from donors whose body weight is <30% below that of the recipient, b) that a heart from a male donor of average body weight (70kg) is acceptable for all recipients, and c) that in cases where the donor is female, then her body weight should not be >20% lower than a male recipient. These recommendations are based on expert consensus opinion and small observational studies from the early 1990s[2,3].

It is recognized that body weight is not a good marker of heart mass. This is a particular concern with the rising prevalence of obesity in the 21st century[4,5]. Ventricular mass varies significantly with age and gender[6–8]. Equations to predict left and right ventricular heart mass (PHM) have been derived from regression models of cardiovascular magnetic resonance (CMR) imaging using a large subset of participants in the American, population based, Multi-Ethnic Study of Atherosclerosis (MESA) cohort[9,10]. These equations incorporate height, weight, age and gender in order to determine PHM. Total PHM has been proposed as an alternate method to evaluate donor-recipient size matching for heart transplantation.

Total PHM as a tool for size matching in heart transplantation has been explored in the United Network for Organ Sharing (UNOS) dataset. There was no association between post-transplant survival and under-sizing by body weight difference, but there was lower post-transplant survival with under-sizing by PHM difference. PHM difference appeared to modulate the lower post-transplant survival associated with female donor into male recipient gender mis-matching[11,12]. In addition, under-sizing by PHM

difference appears to be associated with higher rates of severe primary graft dysfunction after heart transplantation[13].

Although PHM equations are a promising tool for size-matching in heart transplantation, PHM equations were not derived for this purpose and there is no data to support the validity of this approach outside the United States[11]. In addition, PHM equations were derived from a single study based in the United States and have not been externally validated. This study aims to validate a CMR-derived equation for predicted left ventricular mass (LVM) in a large population of normal individuals within the UK Biobank imaging study.

Methods

Data access

The data used in this study are available to all bona fide researchers via application to the UK Biobank in accordance with their approval criteria. Information for the detailed access procedure can be found at https://www.ukbiobank.ac.uk/using-the-resource/.

Study participants

The first 5,065 participants from the UK Biobank imaging substudy (https://imaging.ukbiobank.ac.uk) enrolled between 2014 and 2015 were included. These participants were initially part of the 500,000+ men and women aged 40-69 years recruited in 2006-2010 into the UK Biobank study, which is a large prospective study with a wealth of physical, genetic and clinical data for health-related research. The imaging substudy aims to assess over 100,000 participants for a range of imaging including CMR by 2023[14]. The UK Biobank study was approved by the North West Multi-Centre Research Ethics Committee and written informed consent was obtained from all individuals at recruitment in order to participate in the UK Biobank study. All methods were carried out in accordance with the relevant guidelines and regulations.

Exclusion criteria

Participants with a history of angina, myocardial infarction, stroke and atrial fibrillation were excluded. We also excluded those with a reported diagnosis of cancer in the previous 12 months prior to CMR imaging. These data were collected based on self-reported questionnaires and nurse-led verbal interviews on past and current medical conditions. In addition, diagnoses were captured from Hospital Episode Statistics (HES) records according to the *International Classification of Diseases Ninth and Tenth Revisions (ICD-9 and ICD-10)*[15]. We also utilized the algorithmic definitions for myocardial infarction[16] and stroke[17] developed by UK Biobank that incorporates data from hospital admissions and

death registries. No-one declared to be pregnant at the time of imaging. Finally, individuals who weighed more than 135kg were excluded.

CMR acquisition and derived parameters

The UK Biobank CMR imaging protocol and image analysis have been described in detail previously[18,19]. Briefly, CMR examinations were performed with a 1.5 Tesla scanner (MAGNETOM Aera, Syngo Platform VD13A, Siemens Healthcare, Erlangen, Germany) in a single dedicated centre for UK Biobank imaging in Cheadle, UK. The manual analyses of CMR images were previously performed using cvi42 post-processing software (Version 5.1.1, Circle Cardiovascular Imaging Inc., Calgary, Canada) between eight readers located in two core laboratories based on standard operating procedures for analysis. The end-diastolic frame was nominally defined as the first frame of the image series. Papillary muscles were included as blood pool and excluded from mass. The derived left ventricular (LV) parameters included: end-diastolic volume, end-systolic volume, stroke volume, mass and ejection fraction. A healthy sub-cohort was previously used to derive normal reference ranges[19] and provided cut-offs for our study whereby individuals with LV parameter values outside their gender-specific reference ranges were removed.

Predicted left ventricular mass

Predicted LVM was calculated using the equation developed from MESA[9]: a x (height in meters)$^{0.54}$ x (weight in kilograms)$^{0.61}$, where a = 6.82 for women and 8.25 for men. Physical measurements were recorded on the day of imaging with height being measured to the nearest centimeter in a barefoot standing position using a Seca 202 device (Seca, Birmingham, UK). Body weight was measured, to the nearest 0.1 of a kilogram, using a Tanita BC-418MA body composition analyzer. Participants were asked to remove their shoes and heavy outer clothing before weight measurements were taken.

Statistical analyses

LVM was assessed for normality using histograms and quantile-quantile plots. Continuous variables were summarized as mean ± standard deviation or median (interquartile range) whilst categorical data

were displayed as absolute counts (percentages). Linear regression analysis was performed to compare predicted LVM and CMR LVM. Bland-Altman plot using log-transformed predicted LVM and log-transformed CMR LVM were used to assess for bias and limits of agreement. Log-transformation was performed in order to adjust for the relative difference that exists between the derived LVM in MESA and UK Biobank. R (version 3.5.1) software[20] was used for all statistical analyzes and $p < 0.05$ was considered statistically significant.

Results

Baseline demographics

Of the 5,065 participants, we initially excluded those with either no available images or non-analyzable images (n = 172). We excluded individuals with LV parameters that lie outside the normal ranges (n = 1,234). We excluded three individuals who weighed more than 135kg. A further 258 participants were excluded due to a history of cardiovascular disease or a diagnosis of cancer in the preceding 12 months. After these exclusions, a total of 3,398 individuals (age 61.5 ± 7.5 year, 47.8% males) were included in our study (Figure 1) and their characteristics are summarized in Table 1. The median (interquartile range) body mass index was 25.3 (5.0) kg/m^2. The mean LVM obtained from the manual analysis of CMR images was 102.9 ± 16.4g for men and 71.1 ± 10.4g for women, whilst the mean predicted LVM in the same cohort was 165.0 ± 16.3g for men and 114.8 ± 12.3g for women.

Correlation between predicted LVM and CMR LVM

The predicted LVM calculated using the equation has strong positive correlation with the measured LVM from CMR images in our cohort (Figure 2). The Spearman's correlation coefficient was 0.802 ($p < 0.0001$) between predicted LVM and CMR LVM. The sex-specific correlation for men and women between these two masses were more modest with coefficients of 0.431 ($p < 0.0001$) and 0.401 ($p < 0.0001$) respectively (Figure 1 in Data Supplement).

Bland-Altman analysis showed generally excellent agreement between the observed with predicted LVM with mean log-transformed difference of 0.48 ± 0.15g (Figure 3). The 95% limits of agreement between the two log-transformed measurements were between 0.19g and 0.77g. The 95% CI of the lower and upper limits of agreement were 0.186g to 0.203g and 0.757g to 0.774g, respectively.

Correlation between height/weight and CMR LVM

Given that height or weight alone is used in current clinical practice for donor-recipient size matching in heart transplantation, we therefore also report the correlation of these measures with CMR LVM. In our studied population, both height and weight were found to have strong positive correlations with CMR-measured LVM (Figure 4). The Spearman's correlation coefficients for these measures with CMR LVM were 0.684 ($p < 0.0001$) for height and 0.665 ($p < 0.0001$) for weight respectively. However, the correlations are greatly reduced when we derived for males and females. For males, the Spearman's correlation coefficients were 0.235 ($p < 0.0001$) for height and 0.427 ($p < 0.0001$) for weight (Figures 2 and 3 in Data Supplement). For females, the Spearman's correlation coefficient were 0.199 ($p < 0.0001$) for height and 0.389 ($p < 0.0001$) for weight (Figures 2 and 3 in Data Supplement).

Discussion

We have validated an equation for prediction of LV mass in 3,398 participants of the UK Biobank study. We have demonstrated that predicted LVM has a strong correlation with CMR-measured LVM, performed by manual contouring of short-axis cine images, in our study population. This finding is encouraging with regard to the use of predicted heart mass equations for donor-recipient size matching in heart transplantation.

There was a significant difference between the absolute values of predicted LVM and CMR-measured LVM (absolute difference in mean values = 62g for men, 44g for women). This is an expected finding due to differences in the imaging protocols and analysis technique between the MESA and UK Biobank studies. The mean LVM in the MESA cohort that was used to derive the PHM equations, but without traditional cardiovascular risk factors, was 163.8 ± 35.8g for men and 113.6 ± 24.2g for women[7]. However, the mean LVM in the UK Biobank healthy subset was lower (103 ± 21g for men, 70 ± 13g for women) and therefore much of the absolute difference may represent differences in imaging and analysis techniques. Calculated LVM has been previously shown to be greater when measured from traditional gradient-echo (GRE) images, which was used in the MESA study, compared with images acquired using balanced steady-state free precession (bSSFP) imaging sequence[21].

Although the age and sex ratio are comparable between the MESA and UK Biobank cohorts, there are a number of baseline characteristics that would also account for the higher LVM seen in the MESA cohort. Firstly, the MESA cohort was ethnically diverse, with 39% Caucasian, 26% Hispanic, 26% African-American and 13% Chinese-American participants. In contrast, 96.8% of participants in the UK Biobank study were Caucasian and this may have contributed to lower measured LV mass. Secondly, in our studied populations, the MESA participants had higher body mass index (mean 28 ± 5 vs 26 ± 4 kg/m^2) and thirdly, the proportion of current smokers was 12% in MESA cohort compared with just 4% amongst UK Biobank participants.

Clinical implications

It would appear that predicted heart mass equations are well correlated with a 'real world' measurement of heart mass in a large population of normal individuals; the type of individuals who might become organ donors in unfortunate circumstances. It is important to note that the absolute value of predicted heart mass is less important than the correlation between predicted heart mass and a 'real world' measurement of heart mass. When using an equation to predict both donor and recipient matching, one is trying to judge the relative difference between donor and recipient heart mass, rather than the absolute heart mass.

Predicted heart mass equations may become a useful tool for size matching in heart transplantation. All required variables are available when decisions about donor-recipient suitability are being made. Predicted heart mass is relatively straightforward to calculate. In addition, it would be amenable to automate calculations using an online or mobile app and this could be incorporated with a decision support tool for healthcare professionals. Such a tool might help clinicians avoid under-sizing and therefore reduce the risk of primary graft dysfunction and post-transplant mortality in the recipient. In particular, the equations may help clinicians to identify the 'hidden' under-sizing that is associated with gender mis-matching of female donor hearts into male recipients.

Further work is required to determine whether size matching by PHM is the optimal metric for donor-recipient size matching in heart transplantation and whether a 'cut-off' exists for an acceptable level of under-sizing. This may require complex statistical analysis of other factors that may interact with under-sizing, such as ischemic time, donor age and recipient pulmonary vascular resistance.

Strength and limitations

The main strengths in this study lie in the fact that it is performed in a large cohort and CMR data has been collected and analyzed using defined protocols to produce highly accurate and reproducible data. However, we do acknowledge some limitations in our study. The UK Biobank participants are

predominately middle-aged Caucasians and so the findings may not be applicable to other age and ethnic groups. Cancer diagnoses and the year (or age) of diagnosis were self-reported. Therefore, we may not have captured all cancer diagnoses within 12 months of CMR imaging. Finally, we could only validate predicted LVM as right ventricular mass was not manually derived from the UK Biobank CMR images.

Conclusions

In a large middle-aged Caucasian cohort, we have demonstrated a strong correlation between LVM predicted by a CMR-derived equation and LVM measured by CMR in a large population of normal individuals in the United Kingdom. Our findings support ongoing study of predicted heart mass equations as a tool for donor-recipient size matching in heart transplantation.

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Disclosures

Professor Petersen provides consultancy to Circle Cardiovascular Imaging Inc., Calgary, Canada. The other authors have no conflicts of interest to declare.

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Figure titles and legends

Figure 1. UK Biobank participant selection flowchart. CMR = cardiovascular magnetic resonance; LV = left ventricular; MI = myocardial infarction; HF = heart failure; AF = atrial fibrillation.

Figure 2. Correlation of predicted LVM and CMR LVM. A strong correlation between the predicted LVM calculated using a CMR-derived equation and CMR-measured LVM was found with a Spearman's correlation coefficient 0.802 ($p < 0.0001$). LVM = left ventricular mass; CMR = cardiovascular magnetic resonance.

Figure 3. Bland-Altman plot for the differences between log-transformed predicted LVM and CMR LVM. Blue line represents the mean of the differences between log-transformed predicted LVM and CMR LVM. Red lines denote the upper and lower limits of agreement (mean difference +/- [1.96 x SD]), where SD is the standard deviation of the differences. LVM = left ventricular mass; CMR = cardiovascular magnetic resonance

Figure 4. Correlation of CMR LVM with height (A) and weight (B). Strong correlations were found for height and weight (Spearman's correlation coefficient 0.684 and 0.665 ($p < 0.0001$ for both) respectively) but the magnitude of these correlations is less compared to the correlation between predicted LVM and CMR LVM. LVM = left ventricular mass; CMR = cardiovascular magnetic resonance.

Tables

Table 1 UK Biobank participants characteristics

	All participants (n = 3398)
Age (years)	61.5 ± 7.5
Males	1623 (47.8)
Caucasian	3288 (96.8)
Height (cm)	169.6 ± 9.3
Weight (kg)	74.2 ± 14.0
Body mass index (kg/m^2)	25.7 ± 3.9
Higher education	2063 (60.7)
Employment	1494 (44.4)
Current smoker	137 (4.1)
Regular alcohol	1529 (45.4)
Systolic blood pressure (mmHg)	135.7 ± 17.9
Diastolic blood pressure (mmHg)	78.6 ± 9.9
Heart rate (beats/minute)	70.4 ± 11.2
Hypertension	898 (26.4)
Hypercholesterolaemia	695 (20.5)
Diabetes mellitus	129 (3.8)
CMR left ventricular end-diastolic volume (ml)	139.1 ± 27.2
CMR left ventricular end-systolic volume (ml)	56.4 ± 14.1
CMR left ventricular mass (g)	86.3 ± 20.9
CMR left ventricular ejection fraction (%)	59.7 ± 4.8

Data are expressed as mean ± standard deviation or as numbers (percentage).

CMR = cardiovascular magnetic resonance

Figures

Figure 1

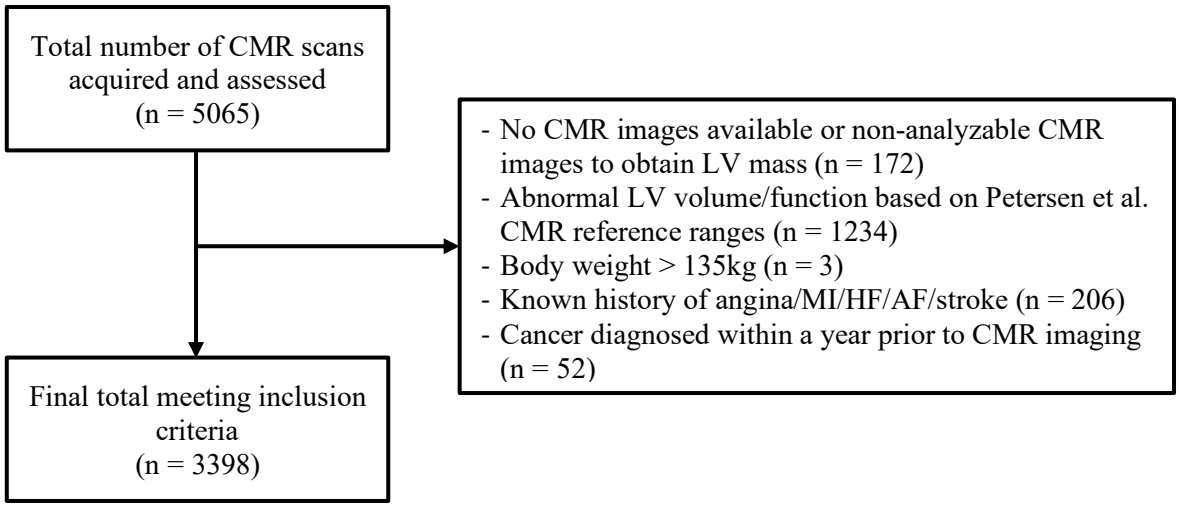
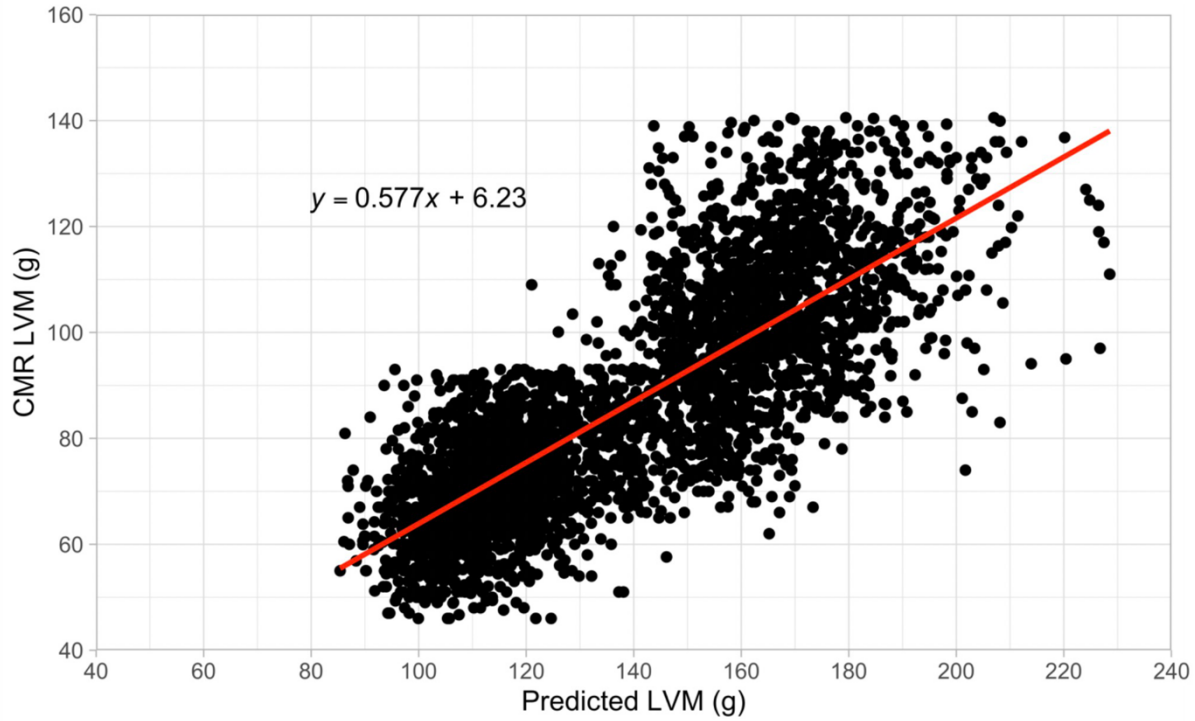


Figure 2


y = 0.577x + 6.23
CMR LVM (g)
Predicted LVM (g)
160
140
120
100
80
60
40
40
60
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140
160
180
200
220
240

Figure 3

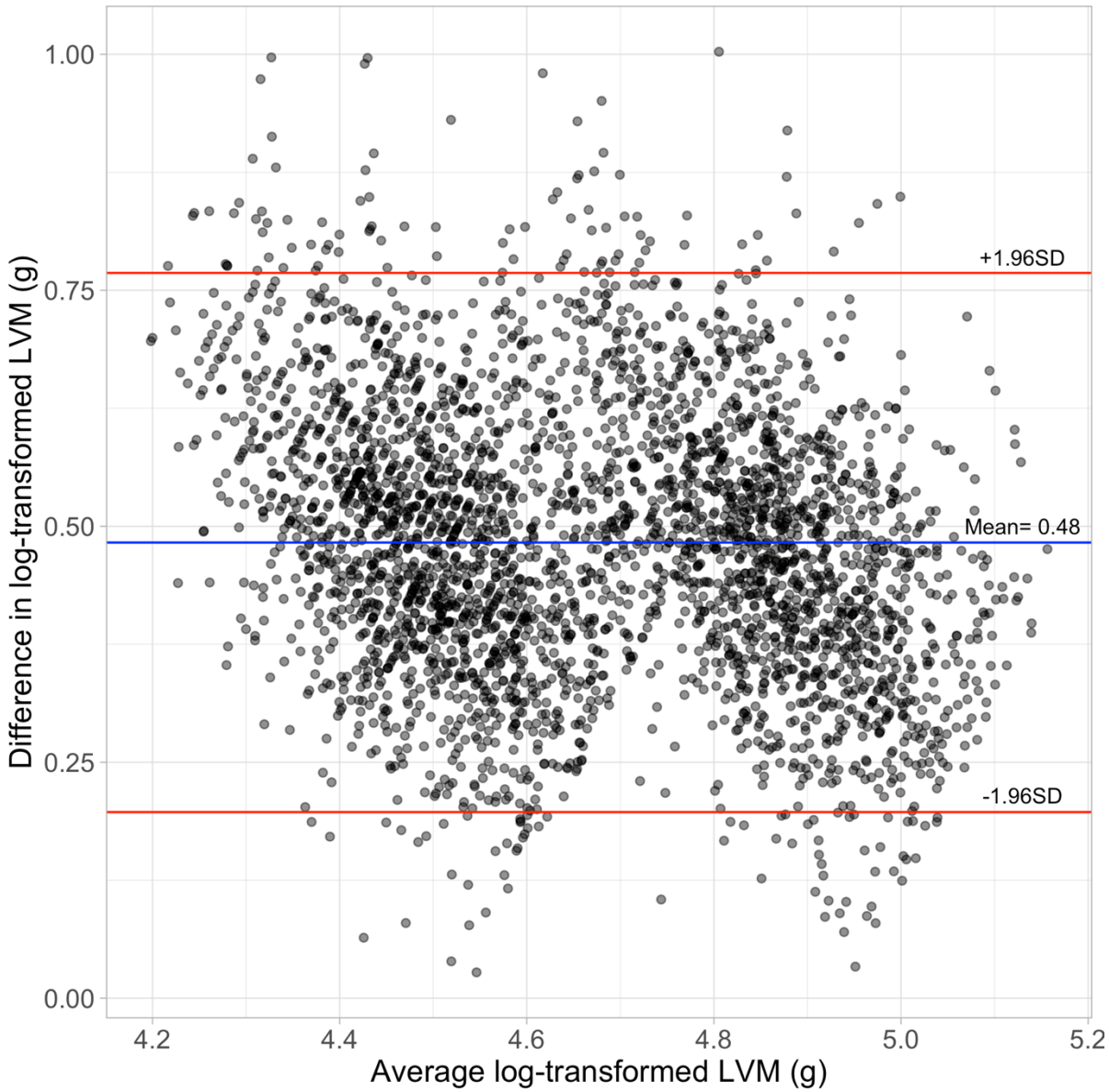
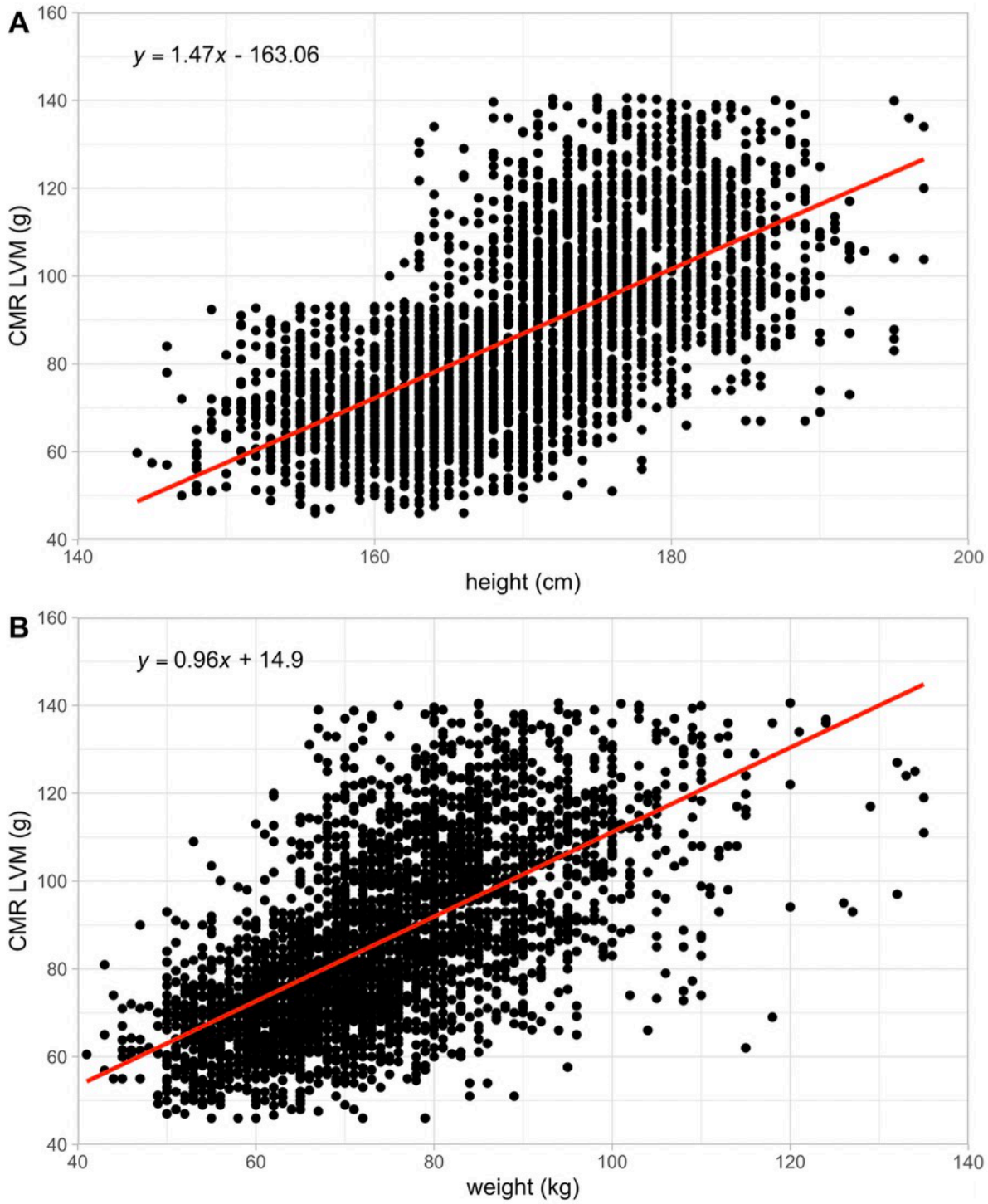

1.00
0.75
0.50
0.25
0.00
Difference in log-transformed LVM (g)
+1.96SD
Mean= 0.48
-1.96SD
4.2
4.4
4.6
4.8
5.0
5.2
Average log-transformed LVM (g)

Figure 4


A
y = 1.47x - 163.06
CMR LVM (g)
height (cm)
B
y = 0.96x + 14.9
CMR LVM (g)
weight (kg)