MRI-based strain measurements reflect morphological changes following myocardial infarction: A study on the UK Biobank cohort

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Abstract

In a porcine experimental model of myocardial infarction, a localised, layer-specific, circumferential left ventricular strain metric has been shown to indicate chronic changes in ventricular function post-infarction more strongly than ejection fraction. This novel strain metric might therefore provide useful prognostic information clinically. In this study, existing clinical volume indices, global strains, and the novel, layer specific strain were calculated for a large human cohort to assess variations in ventricular function and morphology with age, sex, and health status. Imaging and health data from the UK Biobank were obtained, including healthy volunteers and those with a history of cardiovascular illness. In total 710 individuals were analysed and stratified by age, sex, and health.

Significant differences in all strain metrics were found between healthy and unhealthy

populations, as well as between males and females. Significant differences in basal circumferential strain and global circumferential strain were found between healthy males and females, with males having smaller absolute values for both (all $p \leq 0.001$). There were significant differences in the functional variables left ventricular ejection fraction, end systolic volume, end systolic volume index, and mid-ventricular circumferential strain between healthy and unhealthy male cohorts aged 65-74 (all $p \leq 0.001$).

These results suggest that while regional circumferential strains may be useful clinically for assessing cardiovascular health, care must be taken to ensure critical values are indexed correctly to age and sex, due to the differences in these values observed here.

Abbreviations

ACS	Apical circumferential strain
ANOVA	Analysis of variance
BCS	Basal circumferential strain
BMI	Body mass index
BSA	Body surface area
CMR	Cardiovascular magnetic resonance
ED	End diastole
EDV	End diastolic volume
ESV	End systolic volume
ESVi	End systolic volume index
GCS	Global circumferential strain
HF	Heart failure
HR	Heart rate
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MCS	Mid-circumferential strain
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NSTEMI	Non-ST-elevation myocardial infarction
STE	Speckle tracking echocardiography
STEMI	ST-elevation myocardial infarction

1 Introduction

Left ventricular (LV) strain is a useful tool for the prediction of outcome following myocardial infarction (MI) and other cardiovascular illness (Rademakers and Nagel 2017; Gavara et al. 2017; Moen et al. 2011; Koos et al. 2013). It can provide supplementary information about changes to LV function alongside other standard clinical indices derived from medical imaging. These indices may provide morphological information such as changes to end diastolic volume (EDV) and end systolic volume (ESV), and functional information such as stroke volume and left ventricular ejection fraction (LVEF). Other factors used in such an assessment of MI include the infarct size, age, sex, and body size. There is a need to understand the links between age, sex, or cardiovascular health status, and typical strain values for these populations, as well as how these strain values relate to indices currently used clinically. This would provide scientific insights into differences in cardiac function between sub-groups and provide a firm basis for the use of strains in clinical practice.

Cardiovascular magnetic resonance imaging (CMR) is the gold standard for imaging of cardiovascular morphology and function but expensive and time-consuming when compared with echocardiography, which is fast, inexpensive, and ubiquitous in healthcare clinics. For these reasons, large-scale studies on cardiovascular function are often performed using echocardiography. Due to difficulties associated with speckle tracking echocardiography (STE), such as poor spatial resolution, and operator induced errors in transducer positioning, it is preferable to use CMR. Large scale studies on strain have been conducted (Støylen et al. 2019), but fewer have used CMR, with studies often having an upper limit of 150-200 participants (Augustine et al. 2013; Mangion et al. 2016; Andre et al. 2015; Koos et al. 2013; Rodriguez-Palomares et al. 2019). Many studies also focus primarily on longitudinal strain, as there is evidence it is a strong prognosticator (Gavara et al. 2017). Indeed, it has often been found to be a stronger prognosticator than circumferential or radial strains, with Rademakers & Nagel explaining that while some have argued that this is because it is more affected by the damage caused by MI as longitudinal fibres are more prevalent at the endocardium (Streeter et al. 1969), in their view this is unlikely as the majority of fibres throughout the myocardium are obliquely oriented across the wall (ibid.), thus contributing to both longitudinal and circumferential strains (Rademakers and Nagel 2017). An alternative explanation is that longitudinal strain is no more representative than short-axis strain but that poor imaging and contouring in the short-axis can have a larger impact on the reproducibility and outcome (ibid.). Through-plane motion is another factor that may affect short-axis strains more than long-axis based measures (Claus et al. 2015).

The particular strain calculation approach used also affects this; imaging methods such as feature tracking, tagged MRI, strain-encoded CMR, speckle tracking are used, and then whether myocardial strain or layer-specific strains are calculated is also of concern. Due to these differences in results caused by differing imaging modalities, imaging machines, and even research centre practices, no overarching consensus values or reference ranges for strains have been reached. It has been noted that relationships between strain and other factors such as age or body size would more likely be universal across these imaging modalities (Støylen et al. 2019). Furthermore, there are few large-scale studies which include both healthy and unhealthy populations, with many studies opting for either only healthy populations, or studying only a specific illness.

In previous works (Doyin S. Mansell et al. 2020; D. S. Mansell et al. 2021) a localised, layer-specific, circumferential left ventricular strain metric was developed, using porcine imaging data. The reproducibility of this strain metric was demonstrated across different users and software packages and compared favourably to that of standard clinical metrics such as global strains and ejection fraction (Doyin S. Mansell et al. 2020). Its ability to characterise acute changes to left ventricular function post myocardial infarction was similar to volume metrics such as ejection fraction. However, in that study it was found that these changes in strain also persisted to the chronic period more strongly than changes in ejection fraction, suggesting that strains may provide additional information on ventricular remodelling and function (D. S. Mansell et al. 2021).

The aim of this study was to determine if there are differences in strain, as quantified by the novel layer-specific circumferential strain metric, between different population subgroups stratified by age, sex, and cardiovascular health status, and assess how these functional differences compare to morphological differences between groups. To achieve this aim, strains and other clinical metrics were calculated for a large population of volunteers within the UK Biobank.

2 Methods

2.1 Data Source

Cardiovascular MRI and relevant patient history data were obtained from the UK Biobank, a large-scale biomedical database containing health information for over half a million UK participants (`https://www.ukbiobank.ac.uk`). Permission was obtained to access data for use in this project (application number 52530 (Odunmbaku-

Mansell 2020)). Ethical implications associated with this study were considered in line with university regulations (EIRA1 number 2920). Further information about UK Biobank ethics can be found online (Biobank 2007).

2.2 CMR protocol

For cardiac function, the UK Biobank's CMR acquisitions included three long-axis cines (2-, 3-, and 4-chamber orientations), and a complete short-axis stack covering the left (and right) ventricle (Petersen, Matthews, et al. 2016). Imaging was performed in Cheadle, United Kingdom, using a 1.5 T scanner (MAGNETOM Aera, Syngo Platform VD13A, Siemens Healthcare, Erlangen, Germany). The acquisition parameters of interest to this study were as follows: slice thickness of 8 mm, slice gap of 2 mm, temporal resolution of 31.56 ms.

2.3 Image Analysis and Segmentation

CVI42 (Release 5.11.2, Circle Cardiovascular Imaging Inc., Calgary, Canada) was used to extract endocardial contours automatically using the in-built machine learning based segmentation algorithm. Contour lengths and enclosed areas were extracted from the segmentation at the locations corresponding to imaging slice positions. All contours were checked by an experienced reader, with only 636 of the 29826 segmented contours (2.13%) needing manual correction.

2.4 Deformation Analysis

The novel method for calculating strains proposed by Mansell *et al.* (Doyin S. Mansell et al. 2020; D. S. Mansell et al. 2021) was used here. Endocardial circumferential strains, ϵ_n were calculated from the perimeter length data extracted from the segmentations produced by CVI42, using the definition in Equation 1:

$$\epsilon_n = \frac{L_n - L_0}{L_0} \tag{1}$$

where L_0 is the endocardial perimeter reference length at end diastole (ED), and L_n is the endocardial perimeter length at time n throughout the cardiac cycle for a given cine slice. The short-axis slices were divided into three 'vertical' regions in the LV: apex, mid-ventricle, and base. The number of slices in each region varied depending on the total number of slices for a given patient. The minimum total number of slices

was 6 and the maximum 10. Correspondingly, the minimum number of slices in a region was 2 and the maximum 4. The mean of the circumferential strains in each region were then calculated. Global circumferential strain (GCS) was also calculated as the mean of the circumferential strains from all slices (Doyin S. Mansell et al. 2020).

Though volumetric measures could have also been calculated using the enclosed areas of the contours and known slice thickness, these values had been calculated and verified in other studies and supplied to the UK Biobank. As such, the values from the UK Biobank were used.

2.5 Data Selection

2.5.1 Study Population

Participants in the UK Biobank database who had short-axis CMR images were assessed. Participants with non-white British or Irish background, diabetes, current or ex-tobacco smokers, with BMI outside of the range 18.5 - 30 kg/m^2, and aged outside of the range 45-74 years old were excluded from the analysis. The comorbidities listed were similar (though less restrictive) to those from a study which investigated reference ranges in baseline cardiovascular health of the population (Petersen, Aung, et al. 2017) and comorbidities such as hypertension, respiratory disease, and renal disease. These exclusions were chosen mainly to allow a more direct comparison with the results of Petersen et al. Exclusions based on ethnicity were unfortunately necessary due to insufficient numbers of patients with non-white background included in the Biobank dataset for statistically significant conclusions to be drawn. Altogether, these exclusions resulted in 12,398 potential participants being identified.

Participants were split into groups by sex, age (45-54, 55-64 or 65-74 years) and health status (those with known cardiovascular illnesses and those without) to give 12 groups in total. These age ranges were chosen to enable easy comparison with similar studies. Cardiovascular illnesses were defined as STEMI (ST-elevation myocardial infarction), NSTEMI (non-ST-elevation myocardial infarction), and HF (heart failure) as documented in the UK Biobank data, though the degree to which HF had progressed was not specified in the dataset. Those without cardiovascular illnesses gave a revised total of 12,866 participants to choose from, and were distributed by age ranges as shown in Table 1. As there was a sufficiently large pool of data, 100 participants were randomly selected from each of the three age groups for both males and females. The group of volunteers with known cardiovascular illnesses gave a total of 136 participants, and were distributed by age ranges as shown in Table 1. Of

Table 1: Number of healthy and unhealthy (British white and Irish) potential participants in the UK Biobank repository in each age range by sex, and numbers of participants selected for this study.

Age Range	Total N		N Males		N Females	
	N Biobank	N Study	N Biobank	N Study	N Biobank	N Study
Healthy Cohort						
45-54	1988	194	828	100	1160	94
55-64	5133	190	2099	96	3034	94
65-74	5191	190	2324	97	2867	93
Unhealthy Cohort						
45-54	7	6	5	5	2	1
55-64	31	28	25	24	6	4
65-74	98	97	82	82	16	15

those participants, 56 had suffered STEMI (50 males, 6 females), 64 had suffered from NSTEMI (50 males, 14 females), and 12 had suffered heart failure (8 males, 4 females).

2.6 Statistical Analysis

Statistical analyses were run on all variables of interest: apical circumferential strain (ACS), mid-circumferential strain (MCS), basal circumferential strain (BCS), GCS, LVEF, EDV, ESV, end systolic volume index (ESVi), and body surface area (BSA).

To assess the hypothesis that there is a change in functional metrics (strain and volumetric measures) between healthy and unhealthy groups, as well as the hypothesis that there is a difference in the metrics between men and women, statistical analyses were performed. An initial set of Student's t-tests were performed for all variables (ESV, EDV, LVEF, ESVi, BSA, ACS, MCS, BCS, GCS), and data was grouped simply: all healthy vs. all unhealthy volunteers (men and women), and all male vs. all female volunteers (irrespective of health status). $p \leq 0.05$ was considered to be statistically significant.

A further hypothesis was that there would be changes in the metrics between age groups within the sexes for both healthy and unhealthy populations. An initial one-way ANOVA was conducted for each variable (ESV, EDV, LVEF, ESVi, BSA, ACS, MCS, BCS, GCS). If the results of the ANOVA gave indication that there was some statistical significance to $p = 0.05$, further tests were conducted to see where

the differences lay. Planned contrasts between selected subgroups were performed to avoid unnecessary comparisons being performed. These planned contrasts were Female Healthy 45-54 vs. Female Healthy 55-64, Female Healthy 45-54 vs. Female Healthy 65-74, Female Healthy 55-64 vs. Female Healthy 65-74, Female Healthy 45-54 vs. Male Healthy 45-54, Female Healthy 55-64 vs. Male Healthy 55-64, Female Healthy 65-74 vs. Male Healthy 65-74, Male Healthy 45-54 vs. Male Healthy 55-64, Male Healthy 45-54 vs. Male Healthy 65-74, Male Healthy 55-64 vs. Male Healthy 65-74, Male Healthy 65-74 vs. Male Unhealthy 65-74, Female Healthy 65-74 vs. Female Unhealthy 65-74, Male Healthy 55-64 vs. Male Unhealthy 55-64, Male Unhealthy 55-64 vs. Male Unhealthy 65-74, All Males Healthy vs. All Females Healthy, All Females Healthy vs. All Females Unhealthy, All Males Healthy vs. All Males Unhealthy, and All Females Unhealthy vs. All Males Unhealthy. To account for any non-orthogonal contrasts and in order to control the familywise Type I error rate, a Bonferroni correction was used meaning that $p \leq 0.003$ was defined as significant. Bootstrapping was employed during these analyses, as it is a robust method of estimating properties of the sample distribution from the sample data.

Outliers were defined as being outside ± 2.7 standard deviations from the mean. In two cases, it was evident that values for the data were unphysical in nature (LV volumes which were 8-10 times greater than expected), and had been inputted incorrectly by the UK Biobank. After removing five outlier individuals, means, medians, standard deviations, and 95% confidence intervals were calculated for all groups. Final numbers of participants used in the study are presented in Table 1. Not all data from the UK Biobank came with all entries included, and as such the values listed in this table is the maximum possible N for any group for any variable.

Pearson correlation coefficients between all variables of interest (EDV, ESV, ESVi, LVEF, ACS, MCS, BCS, GCS) and both age and BSA were calculated via linear regression. For these correlations, participants were 'lumped' into their larger groups, i.e. all healthy females, all healthy males, all unhealthy females, and all unhealthy males. A $p \leq 0.05$ was considered to be statistically significant and bootstrapping was again used to analyse the results from the correlations.

All statistical analyses were conducted using IBM SPSS (IBM SPSS Statistics for Windows, Version 25.0, Armonk, NY, IBM Corp.).

Table 2: Characteristics for all healthy and unhealthy participants stratified by age group.

Characteristic	Age Group (years)					
	45-54		55-64		65-74	
	Healthy	Unhealthy	Healthy	Unhealthy	Healthy	Unhealthy
N	194	6	190	28	190	97
Age (years)	52.0 (±2.0)	53.0 (±1.0)	60.0 (±3.0)	61.0 (±3.0)	69.0 (±3.0)	69.0 (±3.0)
Male Gender (N(%))	100 (51.5%)	5 (83.3%)	96 (50.5%	24 (71.4%)	97 (51.1%)	82 (69.1%)
HR (bpm)	59.9 (±8.0)	53.6 (±11.2)	61.1 (±9.4)	57.0 (±10.4)	62.7 (±9.6)	57.0 (±9.2)
BMI (kg/m^2)	25.4 (±2.6)	27.3 (±2.1)	24.8 (±2.7)	25.0 (±2.5)	25.1 (±2.6)	25.6 (±2.3)
Weight (kg)	74.9 (±12.1)	76.7 (±6.2)	72.4 (±11.9)	75.9 (±8.9)	72.1 (±10.7)	75.9 (±10.5)
ESV (mL)	58.7 (±15.1)	59.3 (±13.7)	54.6 (±14.9)	67.1 (±24.3)	52.1 (±14.5)	67.2 (±26.4)
EDV (mL)	151.6 (±31.1)	170.6 (±22.8)	141.2 (±30.9)	169.8 (±25.6)	136.3 (±30.9)	158.8 (±41.6
LVEF (%)	56.2 (±5.0)	53.4 (±6.2)	56.8 (±5.3)	52.0 (±7.4)	55.9 (±5.8)	50.4 (±8.1)
ESVi (mL/m^2)	35.4 (±7.5)	43.7 (±10.9)	33.1 (±7.3)	43.4 (±12.3)	33.0 (±8.1)	42.3 (±15.4)
BSA (m^2)	1.9 (±0.2)	1.8 (±0.1)	1.8 (±0.2)	1.9 (±0.1)	1.8 (±0.2)	1.9 (±0.2)
ACS (%)	-41.7 (±7.4)	-36.7 (±10.3	-41.9 (±8.0)	-40.2 (±14.6)	-41.6 (±8.1)	-37.8 (±13.8)
MCS (%)	-28.5 (±3.6)	-29.0 (±5.2)	-29.6 (±4.3)	-28.3 (±8.4)	-30.0 (±4.4)	-26.8 (±6.8)
BCS (%)	-31.6 (±5.0)	-30.5 (±3.9)	-31.5 (±3.9)	-29.2 (±5.8)	-31.8 (±4.8)	-29.3 (±8.0)
GCS (%)	-33.4 (±3.9)	-31.6 (±5.9	-33.7 (±4.4)	-31.6 (±8.2)	-33.8 (±4.6)	-30.6 (±7.7)

3 Results

3.1 Population Characteristics

Characteristics for all participants are provided in Table 2. More detailed baseline characteristics, which are stratified by gender and health status, are presented in Supplementary Tables 5 - 8. For the unhealthy groups the mean time since first cardiac event (any damage done to cardiac tissue) is shown in Supplementary Table 9.

3.2 Statistical Analysis

Results from the Student's t-test were all statistically significant to $p \leq 0.05$ (see Table 1), with all volume indices, BSA, BCS, and GCS, particularly strongly significant. For auxiliary data from the t-tests please see Supplementary Tables 2 and 3.

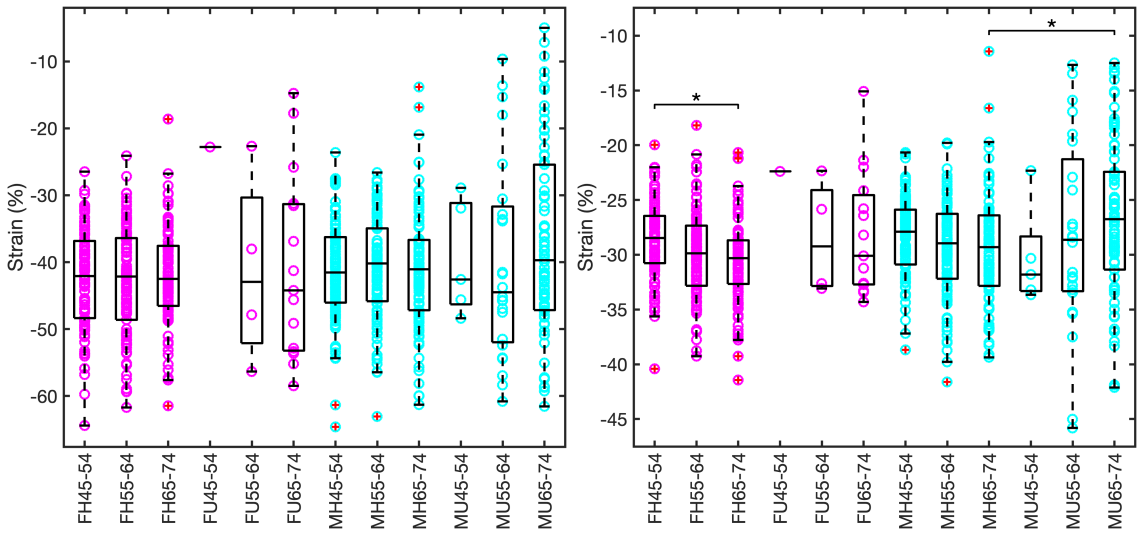
The results from the one-way ANOVA suggested that all metrics required further

investigation with planned comparisons, as all p-values were less than the critical value of 0.05. In the text and on the x-axis of Figure 1 and figures in the Supplementary, comparisons between sex and age groups are abbreviated and should be read as such: F=female, M=male, H=healthy, U=unhealthy. The following four numbers XX-YY, are the age brackets for each group, with XX being the lower age limit, and YY being the upper age limit.

BCS had three statistically significant planned comparisons (Supplementary Table 10: FH45-54 vs MH45-54, FH65-74 vs MH65-74, and all MH vs all FH all $p \leq 0.001$), these are shown in Figure 1c. MCS had a statistically significant result for MH65-74 vs MU65-74, see Figure 1b), and for FH45-54 vs FH65-74 (both $p \leq 0.002$). For GCS all MH vs all FH was statistically significant ($p = 0.001$, see Figure 1d). ACS had no planned comparisons that returned statistically significant results. Broadly these results suggest that only differences in basal and global circumferential strains exist between the sexes, with no significant differences found for apical or mid-circumferential strain.

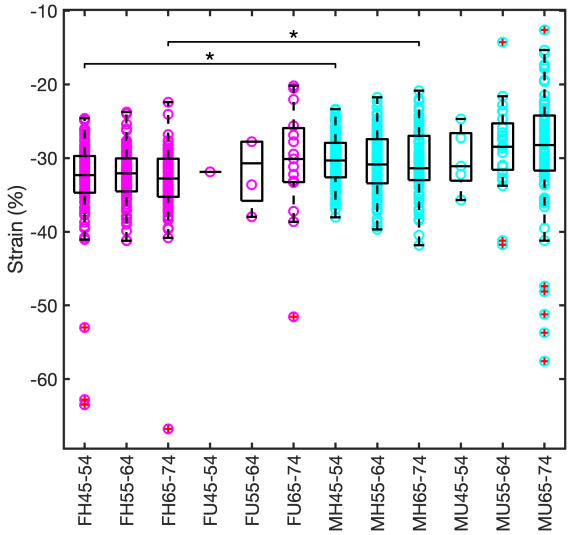
The volume metrics EDV, ESV, and ESVi all had multiple instances of being statistically significant (see Supplementary Table 11). Planned comparisons corresponding to the three age range comparisons between the healthy sexes were all statistically significant for EDV, ESV, and ESVi (all $p \leq 0.001$), suggesting differences in volumes between the sexes (see Supplementary Figures 1 - 3). Additionally, for EDV, FH45-54 vs FH55-64, FH45-54 vs FH65-74, MH45-54 vs MH65-74, all MH vs all FH, and all MU vs all FU were also statistically significant (all $p \leq 0.003$, see Supplementary Table 11). MH45-54 vs MH65-74, MH65-74 vs MU65-74, all MH vs all FH were statistically significant for ESV (all $p \leq 0.003$). For ESVi, MH65-74 vs MU65-74 and all MH vs all FH were both also statistically significant (both $p \leq 0.001$). LVEF had only two comparisons result in statistically significant differences, MH65-74 vs MU65-74 and all MH vs all FH (both $p \leq 0.001$, see Supplementary Figures 5). BSA had multiple instances of comparisons being statistically significant; the three age range comparisons between the healthy sexes, MH45-54 vs MH 65-74, all MH vs all FH, and all MU vs all FU (all $p \leq 0.001$, see Figure 4).

A list of all statistically significant planned comparisons is shown in Table 3.

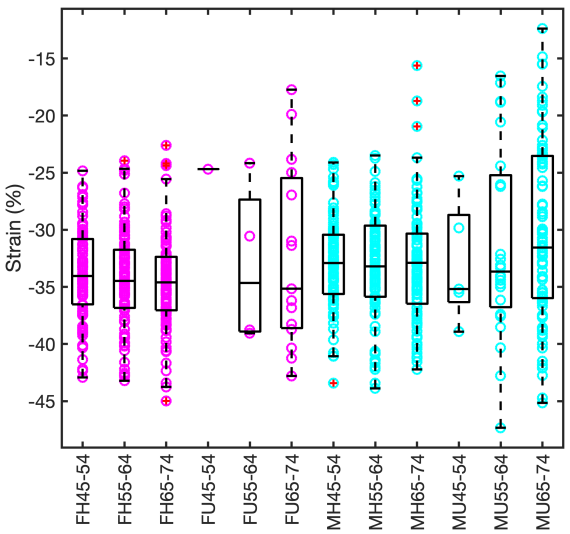


(a) ACS boxplots for all groups.

(b) MCS boxplots for all groups.



(c) BCS boxplots for all groups.



(d) GCS boxplots for all groups.

Figure 1: Strain boxplots for all groups: M = Male; F = Female; H = Healthy; U = Unhealthy; XX-YY = age range. Pink data points represent females and blue data points represent males. Groups with statistically significant differences found in planned comparisons are denoted by an overhead bar and star (both here and in the supplement). Data points with a red cross enclosed are outliers greater than the third quartile plus 1.5 times the interquartile range (both here and in the data supplement). (a) No groups were found to have statistically significant differences when analysed by the planned comparisons. (b) Only one group was found to have statistically significant differences. (c) One further planned comparison was statistically significant that could not be represented on this plot: all healthy females vs. all healthy males. (d) One further planned comparison was statistically significant that cannot be represented on this plot: all healthy females vs. all healthy males.

Table 3: List of all planned comparisons which had statistically significant results to $p \leq 0.003$.

Comparison	Variable	p-value
Female Healthy 45-54 vs Female Healthy 55-64	EDV	0.003
Female Healthy 45-54 vs Female Healthy 65-74	MCS	0.002
	EDV	0.002
Female Healthy 45-54 vs Male Healthy 45-54	BCS	0.001
	EDV	0.001
	ESV	0.001
	ESVi	0.001
	BSA	0.001
Female Healthy 55-64 vs Male Healthy 55-64	EDV	0.001
	ESV	0.001
	ESVi	0.001
	BSA	0.001
Female Healthy 65-74 vs Male Healthy 65-74	BCS	0.001
	EDV	0.001
	ESV	0.001
	ESVi	0.001
	BSA	0.001
Male Healthy 45-54 vs Male Healthy 65-74	EDV	0.001
	ESV	0.003
	BSA	0.001
Male Healthy 65-74 vs Male Unhealthy 65-74	MCS	0.001
	LVEF	0.001
	ESV	0.001
	ESVi	0.001
All Male Healthy vs All Female Healthy	BCS	0.001
	GCS	0.001
	LVEF	0.001
	EDV	0.001
	ESV	0.001
	ESVi	0.001
	BSA	0.001
All Female Unhealthy vs All Male Unhealthy	EDV	0.003
	BSA	0.001

3.2.1 Correlations

For healthy males and females, all correlations for both EDV and ESV with both age and BSA were statistically significant, apart from the correlation of age and ESV for healthy females (all $p \leq 0.05$, Supplementary Tables 14 and 12). Also for healthy males and females, correlations between MCS and age were found, and for males a correlation of MCS with BSA was also found (all $p \leq 0.05$, Supplementary Tables 14 and 12). Furthermore, a statistically significant correlation between age and ESVi for healthy males was found (all $p = 0.028$, Supplementary Table 14). No further significant correlations between age or BSA were found for the healthy groups.

For the unhealthy cohorts, fewer statistically significant correlations were found. For unhealthy females, the only significant correlation found was that between age and EDV ($p = 0.039$, Supplementary Table 13). For unhealthy men significant correlations were found between age and LVEF, and between BSA and EDV (both $p \leq 0.41$, Supplementary Table 15). No other significant correlations between age or BSA were found for the unhealthy groups.

The only correlation where the bootstrapped 95% CIs suggested that statistical significance found by the correlation was incorrect was for unhealthy females between age and EDV (Supplementary Table 13). This was most likely due to the low n for this group. All other 95% CIs corroborated the statistical significant p-values for the correlations. While the spread of the data allowed line fits to be made and statistically significant p-values in several of the analyses, the Pearson correlation coefficients did not indicate that any of the correlations were strong, with Pearson r values ranging from -0.49 to 0.482. These data are detailed in Supplementary Tables 12 - 15.

4 Discussion

The present study aimed to investigate clinically relevant age- and sex-specific LV values for healthy and unhealthy Caucasian adults, derived from CMR. A cohort of 710 individuals taken from the UK Biobank population was used.

4.1 Male to Female Comparisons

Significant differences were found for all strain measures when comparing all males to all females, regardless of health status or age group (see Table 1). Comparing only all healthy males to all healthy females showed that BCS and GCS remained statistically

different (both $p \leq 0.001$, Table 10),with males having lower absolute values of both BCS and GCS, indicating there may be a difference in function between the sexes, which, as discussed in more detail below, may reflect the fact that while volumes are larger for males, ejection fractions are lower. For age-range paired comparisons significant differences were only found for BCS in the youngest and eldest groups (both $p = 0.001$, Table 10).

These results confirm previous work where differences in GCS were found between males and females, with some studies reporting statistically significant differences (Andre et al. 2015; Mangion et al. 2016), and one reporting differences, but not of significance (Augustine et al. 2013). Stoylen *et al.* however, found no difference in endocardial strains, but did find differences in epicardial strains (Støylen et al. 2019). These different conclusions may arise in part due to differences in the accuracy of the different imaging modalities used, as Mangion *et al.* found differences in strain using both 1.5 T and 3 T MRI (Mangion et al. 2016). Given that cardiovascular MR affords greater spatial and contrast resolution than echo, regardless of patient body habitus, it is more appropriate for our layer-specific strain measure, which requires clear endocardial definition throughout the cardiac cycle. This higher endocardial resolution may explain why statistically significant differences in some endocardial strains were found here, but not in the study by Stoylen *et al.* which used echocardiography.

Statistically significant differences were also found for all volumetric measures and BSA when comparing all males to all females, regardless of health or age (see Table 1). Statistically significant differences for EDV, ESV, ESVi and BSA were found between all four healthy male to female comparisons, with males having higher mean values than females (see Supplementary Figures 1, 2, 3, and 4). These results were expected as males are larger than females on average and similar differences have been previously reported (Petersen, Aung, et al. 2017). For LVEF, the only comparison found to be statistically significant was that between all healthy males to all healthy females with healthy males having a slightly lower LVEF on average ($p = 0.001$, Table 11), agreeing with a result found by Petersen *et al.* (ibid.). This lowered LVEF accords with the lower average strain values for males which, when coupled with the larger ventricular volumes for males, appear to create sufficient blood flow in males.

4.2 Healthy Age Group Comparisons

The only strain metric to have any significant differences when comparing within-sex age ranges for healthy populations was MCS, it was found to be significant for the

comparison between the youngest and oldest healthy female groups ($p = 0.002$, Table 10).

MCS was also the only strain metric which showed statistically significant correlations to either age or BSA for healthy groups. A significant correlation was found between MCS in healthy females and age (Table 12) and also between MCS in healthy males and both age and BSA (Table 14). Two previous studies also found no correlation between global endocardial circumferential strain (Støylen et al. 2019; Andre et al. 2015), though Mangion *et al.* did find correlations relating global strains to age (Mangion et al. 2016). The mean ages of the cohorts used in these three studies were all different and all lower than in the present study, preventing a like-for-like comparison. In addition, the circumferential strain measurement technique used by Stoylen *et al.* was mid-wall only and not a global measure (Støylen et al. 2019). Mid-wall circumferential is thought to be most closely related to mean GCS and often used in its place for reasons of speed and ease (Lee et al. 2019; Støylen et al. 2019). The study by Stoylen *et al.* also derived circumferential strains from geometrical considerations combined with LV blood pool diameters (Støylen et al. 2019), likely a less accurate method than the MR-derived layer specific method of this study that uses endocardial perimeter lengths. Given that only MCS was found to vary significantly, it is possible that when the underlying change is included within the GCS calculation it is obscured by noise or is too small to discern in a statistically significant manner.

The significant MCS correlations with age for both females and males, and the significant result for healthy females aged 45-54 versus aged 65-74 potentially indicate a change in function with age, to accompany the changes seen with the volumetric measures EDV, ESV and ESVi. Sex- and age-specific patterns of LV remodelling have been reported by Hung *et al.*, with females exhibiting pronounced changes in LV torsion, and a tendency towards greater LV concentricity (Hung et al. 2017), which may relate to the positive correlation of MSC with age.

There were statistically significant differences between age groups for healthy males. EDV and ESV for healthy males aged 45-54 versus 65-75 were significantly different (both $p \leq 0.003$, see Supplementary Table 11). EDV, for healthy males aged 45-54 versus 55-64 was just above the threshold for statistical significance ($p = 0.005$ Supplementary Table 11 respectively) matching the results reported by Petersen *et al.* (Petersen, Aung, et al. 2017). Overall, these results for ventricular volumes align with the findings in Petersen et al. that both absolute and indexed measures of LV end-diastolic volumes and stroke volumes were lower with increasing age. For ESVi and LVEF, no differences between age groups for healthy males were found.

Differences in EDV were significant between healthy females aged 45-54 and both the 55-64 and 65-74 groups (both $p \leq 0.003$, Supplementary Table 11), agreeing with findings reported by Petersen *et al.*, who also found that both absolute and indexed measures of EDV, ESV and stroke volume were smaller with increasing age in females. For ESV, ESVi and LVEF, no differences between age groups for healthy females were found.

There were statistically significant, but weak correlations between age and EDV for both healthy males and females (Supplementary Tables 12 and 14). There was also a statistically significant correlation between ESV and age in healthy males (r = -0.192, $p = 0.001$, Supplementary Table 14), while for females the relationship was almost significant (r = -0.120, $p = 0.054$, Supplementary Table 12). Petersen *et al.* (Petersen, Aung, et al. 2017) found similar correlations. The BSA correlation results also suggest that the data is following the same trends reported by Petersen *et al.*, with EDV and ESV both increasing with BSA (Supplementary Tables 12 and 14).

4.3 Healthy to Unhealthy Population Comparison

In comparing all healthy participants to all unhealthy participants (irrespective of sex or age), all strain measures were found to be statistically significant (see Table 1). This suggests an overall difference in strain between the two populations, with healthy hearts exhibiting larger strain magnitudes than unhealthy hearts, in agreement with studies showing strains may be useful in predicting outcomes following MI (Rademakers and Nagel 2017; Gavara et al. 2017; Moen et al. 2011; Koos et al. 2013). In addition, all volumetric measures and BSA were also found to be statistically significant (see Table 1), with unhealthy participants having larger hearts (larger ESV and EDV) and smaller LVEF, when comparing all healthy with all unhealthy participants. Taken together these results suggest a link between morphological and functional changes occurring due to disease. It is likely that diseased myocardium that has underdone negative remodelling and ventricular dilatation, leading to larger end diastolic volumes, is then unable to generate sufficient stress through myocardial contraction to overcome the higher resultant fluid loading. This means strain magnitudes will be lower than in healthy hearts, which from geometric considerations implies a smaller stroke volume and LVEF.

When comparing strains in age and sex matched healthy and unhealthy groups, the only statistically significant difference was for MCS in males age 65-74 ($p = 0.001$, Supplementary Table 10), with strains lower in magnitude for the unhealthy group. In addition to MCS, several volumetric measures (LVEF, ESV and ESVi) and BSA

were also significantly different between healthy and unhealthy males 65-74, with LVEF lower, but ESV and ESVi larger, in the unhealthy group, thus explaining the lowered LVEF. However, there were no significant differences between any volume metrics for any other matched groups.

4.4 Links Between MI and Strains

In Mansell *et al.* (D. S. Mansell et al. 2021), strain metrics were shown to be sensitive to MI location in the acute and early-chronic phases post-MI. Unfortunately, while strains do appear to indicate a difference between healthy and unhealthy heart function, such detailed links between MI and strains are hard to draw in this study for several reasons. Firstly, the time since cardiac event in the previous study was in the order of days, as opposed to years, and the disease status of the unhealthy UK Biobank cohort was more complex than in the animal experiments, comprising those having suffered STEMI, NSTEMI, and HF. Secondly, the precise location of the infarct was unknown in the UK Biobank data, meaning any correlation between infarct location and regional strain could not be determined. To definitively test the ability of the strain metric to localise myocardial infarcts in humans a targeted study with appropriate patient recruitment would be required.

4.5 Limitations

Despite more than 12,000 UK Biobank participants fulfilling the inclusion criteria, sample sizes for the unhealthy cohorts, particularly in the lower age ranges, remained small, affecting both the power of the statistics and statistical analyses. The disease state of these unhealthy groups was also heterogeneous due to varying elapsed time since cardiac event and possible medical interventions, though all unhealthy participants were still reasonably healthy. This limitation may be difficult to overcome in future studies due to the heavily skewed prevalence of myocardial infarction with increasing age (Dhingra and Vasan 2012; Rodgers et al. 2019). Furthermore, all members of the unhealthy cohorts were also survivors of MI and HF, potentially introducing a survivorship bias into the data, as those with potentially worse cases of MI and HF would not be included.

In Mansell et al. (D. S. Mansell et al. 2021), strain metrics were shown to be sensitive to MI location in the acute and early-chronic phases post-MI. Unfortunately, such detailed links between could not be assessed in this study since the length of time since MI was of the order of years, the precise location of the infarct was unknown, and the varying diagnoses (STEMI, NSTEMI and HF) indicate a range of infarct

severities, including the possibility of no MI in some cases of HF.

Finally, a BMI of up to 30 kg/m^2 was used as one of the inclusion criteria. While BMIs at the top of this range is technically considered to be overweight, and obesity has been shown to affect cardiac structure and function in an otherwise healthy population (Rider, Francis, et al. 2009; Rider, Petersen, et al. 2011), other studies have also used these same inclusion criteria based on the fact that this BMI represents a 'new normal' for the population, with 58% of females and 65% of males in the UK having a BMI of more than 25 kg/m^2 in 2014 (Petersen, Aung, et al. 2017; Støylen et al. 2019; HSCIC 2016). Thus, we argue, that those with a BMI of up to 30 kg/m^2 should be included when statistics on the average healthy population are required.

5 Conclusions

This aim of this study was to characterise changes in LV standard clinical and strain metrics in both sexes, and to identify changes between healthy and unhealthy groups for both sexes, using imaging data from the UK Biobank. The main findings were that left ventricular function as measured by basal and global circumferential strains differed between healthy males and females, with males having lower absolute values of these strains. Furthermore, both functional and morphological variables differed between healthy and unhealthy participants, particularly males aged 65-74, which showed increased MCS, reduced LVEF, and increased ESV and ESVi, in that unhealthy group. Finally, some data suggested that MCS may correlate positively with age, but additional data is required to confirm this.

These results suggest that if regional circumferential strains are to be used clinically for assessing cardiovascular health, due care must be taken to ensure critical values are indexed correctly to age and sex, whilst also validating the measurements against different imaging modalities, scanners, strain methods, and research centres. Future studies should also investigate whether changes in strain values are observed for other cardiovascular diseases such as myocarditis and early stage heart failure. Finally, as these results apply only to British and Irish white adults, future work should study larger cohorts of age-ranged and specific ethnic groups to assess whether these conclusions apply more generally and to determine the corresponding population-level statistics.

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Data Availability Statement

The raw data for this study is available currently to registered users of the UK Biobank (`https://www.ukbiobank.ac.uk/`). Restrictions apply to the availability of these data, which were used under license for this study. The data generated that support the findings of this study will be returned to the UK Biobank, which may then make them available to registered users.

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Online Supplementary Materials

Table 1: Results from Student's t-test for all males vs. all females, as well as all healthy vs. all unhealthy participants. All results were statistically significant.

Variable	All Males vs All Females p-values	All Healthy vs All Unhealthy p-values
ESV	0.001	0.001
EDV	0.001	0.001
LVEF	0.001	0.001
ESVi	0.001	0.001
BSA	0.001	0.005
ACS	0.002	0.006
MCS	0.003	0.001
BCS	0.001	0.001
GCS	0.001	0.001

Table 2: Further data for the Student's t-test for all male vs. all female volunteers. Where the Variance p-value is less than 0.05, the data shown assumes that the variances between the groups was not equal.

Variables	Variance p-value	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
				Lower	Upper
ESV	0	-22.5	1.3	-25.2	-19.9
EDV	0	-38.9	2.1	-43.0	-34.9
LVEF	0.002	3.3	0.5	2.4	4.2
ESVi	0	-7.3	0.7	-8.7	-6.0
BSA	0.06	-0.3	0.01	-0.3	-0.2
ACS	0.03	-2.1	0.7	-3.4	-0.8
MCS	0	-1.1	0.4	-1.8	-0.4
BCS	0.2	-2.6	0.4	-3.4	-1.8
GCS	0.001	-1.8	0.4	-2.6	-1.1

Table 3: Further data for the Student's t-test for all healthy vs. all unhealthy volunteers. Where the Variance p-value is less than 0.05, the data shown assumes that the variances between the groups was not equal.

Variables	Variance p-value	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
				Lower	Upper
ESV	0	-17.9	2.8	-23.4	-12.4
EDV	0.07	-18.3	3.3	-24.9	-11.8
LVEF	0	5.4	0.8	3.9	6.9
ESVi	0	-8.7	1.4	-11.4	-6.0
BSA	0.003	-0.05	0.02	-0.08	-0.01
ACS	0	-3.5	1.2	-5.9	-1.0
MCS	0	-2.1	0.6	-3.4	-0.9
BCS	0	-2.3	0.7	-3.7	-1.0
GCS	0	-2.8	0.7	-4.2	-1.4

Table 4: Results from the initial one-way ANOVAs. All p-values were less than the required 0.05.

ANOVA	p-value
ESV	0.001
EDV	0.001
LVEF	0.001
ESVi	0.001
BSA	0.001
ACS	0.019
MCS	0.001
BCS	0.001
GCS	0.001

Table 5: Baseline characteristics for healthy females of all ages.

Measure	n	Mean	Median	St. Dev.	Lower 95% CI	Upper 95% CI
BMI (kg/m^2)	281	24.53	24.38	2.78	24.2	24.86
HR (bpm)	260	62.09	61	9.22	60.95	63.23
Weight (kg)	281	65.51	64.7	8.34	64.51	66.51
Age (years)	281	60.17	61	7.58	59.27	61.07
ESV (mL)	260	52.92	52	11.6	51.49	54.35
EDV (mL)	260	124.2	124	21.2	121.5	126.8
LVEF (%)	260	57.42	58	4.91	56.81	58.03
ESVi (mL/m^2)	260	31.01	30.09	6.4	30.22	31.8
BSA (m^2)	260	1.71	1.7	0.12	1.7	1.72
ACS (%)	281	-42.43	-42.17	7.68	-43.35	-41.51
MCS (%)	281	-29.68	-29.74	3.9	-30.15	-29.21
BCS (%)	281	-32.8	-32.42	5.01	-33.4	-32.2
GCS (%)	281	-34.29	-34.4	4.09	-34.78	-33.8

Table 6: Baseline characteristics for unhealthy females of all ages.

Measure	n	Mean	Median	St. Dev.	Lower 95% CI	Upper 95% CI
BMI (kg/m^2)	20	24.85	24.73	2.84	23.58	26.12
HR (bpm)	18	61.56	58	10.9	56.43	66.69
Weight (kg)	20	63.6	64.25	7.28	60.34	66.86
Age (years)	20	66.85	68.5	5.03	64.6	69.1
ESV (mL)	18	58.11	57	17.7	49.75	66.47
EDV (mL)	18	126.6	129	24	115.3	137.9
LVEF (%)	18	54.56	56	8.18	50.7	58.42
ESVi (mL/m^2)	18	34.66	34.13	10.5	29.73	39.59
BSA (m^2)	18	1.67	1.69	0.1	1.62	1.72
ACS (%)	20	-39.97	-42.74	13.9	-46.18	-33.76
MCS (%)	20	-27.98	-29.15	5.44	-30.41	-25.55
BCS (%)	20	-30.94	-30.64	7.16	-34.14	-27.74
GCS (%)	20	-32.13	-33.26	7.65	-35.55	-28.71

Table 7: Baseline characteristics for healthy males of all ages.

Measure	n	Mean	Median	St. Dev.	Lower 95% CI	Upper 95% CI
BMI (kg/m^2)	293	25.65	25.9	2.42	25.37	25.93
HR (bpm)	274	60.32	60	8.86	59.25	61.39
Weight (kg)	293	80.45	80.4	9.5	79.34	81.56
Age (years)	293	60.35	60	7.87	59.43	61.27
ESV (mL)	274	72.4	70	16.8	70.37	74.43
EDV (mL)	274	161.4	159	29	157.9	165
LVEF (%)	274	55.3	56	5.59	54.62	55.98
ESVi (mL/m^2)	274	36.56	35.98	7.85	35.61	37.51
BSA (m^2)	274	1.98	1.97	0.14	1.96	2
ACS (%)	293	-41.08	-40.86	7.9	-42	-40.16
MCS (%)	293	-29.08	-28.67	4.35	-29.59	-28.57
BCS (%)	293	-30.53	-30.73	3.89	-30.98	-30.08
GCS (%)	293	-32.99	-32.99	4.44	-33.51	-32.47

Table 8: Baseline characteristics for unhealthy males of all ages.

Measure	n	Mean	Median	St. Dev.	Lower 95% CI	Upper 95% CI
BMI (kg/m^2)	111	25.68	25.78	2.28	25.25	26.11
HR (bpm)	101	56.02	54	9.04	54.22	57.82
Weight (kg)	111	78.19	78.3	8.65	76.55	79.83
Age (years)	111	66.8	68	5.36	65.78	67.82
ESV (mL)	101	84.88	78	28.8	79.14	90.62
EDV (mL)	101	167.9	161	37	160.5	175.2
LVEF (%)	101	50.25	51	7.68	48.72	51.78
ESVi (mL/m^2)	101	44	40.51	14.8	41.06	46.94
BSA (m^2)	101	1.93	1.93	0.13	1.9	1.96
ACS (%)	111	-37.97	-41.54	13.8	-40.6	-35.34
MCS (%)	111	-27.1	-27.81	7.4	-28.5	-25.7
BCS (%)	111	-29	-28.28	7.45	-30.41	-27.59
GCS (%)	111	-30.61	-32.14	7.75	-32.08	-29.14

Table 9: Mean time in years since initial cardiac event. * There was only one participant in this group.

Unhealthy Group	Mean time (years)
Females 45-54	14.7*
Females 55-64	2.8
Females 65-74	4.3
Males 45-54	4.6
Males 55-64	5.9
Males 65-74	7.7

Table 12: Age and BSA correlations with other variables of interest for all healthy females. Statistically significant p-values are highlighted in green. The 95% CIs are taken from the bootstrapping analysis.

Variable	Age Correlations				
	n	Pearson	p-value	95% CIs	
				Lower	Upper
EDV	260	-0.193	0.002	-0.303	-0.069
ESV	260	-0.120	0.054	-0.243	-0.003
LVEF	260	-0.059	0.344	-0.189	0.068
ESVi	260	-0.120	0.054	-0.242	0.008
ACS	281	0.046	0.442	-0.089	0.175
MCS	281	-0.163	0.006	-0.272	-0.029
BCS	281	-0.006	0.918	-0.114	0.134
GCS	281	-0.041	0.490	-0.156	0.090
Variable	BSA Correlations				
EDV	260	0.443	0.000	0.341	0.542
ESV	260	0.318	0.000	0.202	0.425
LVEF	260	0.065	0.300	-0.070	0.190
ESVi	260	-0.017	0.786	-0.137	0.109
ACS	260	-0.046	0.459	-0.165	0.074
MCS	260	-0.063	0.308	-0.208	0.071
BCS	260	0.054	0.384	-0.065	0.153
GCS	260	-0.007	0.917	-0.136	0.117

Table 10: P-values for all strain and strain rate metrics. Results highlighted in green with bold text and *, indicates results which are statistically significant to $p \leq 0.003$.

Planned Comparison	ACS	MCS	BCS	GCS
Female Healthy 45-54 vs. Female Healthy 55-64	0.556	0.041	0.462	0.439
Female Healthy 45-54 vs. Female Healthy 65-74	0.816	**0.002***	0.785	0.226
Female Healthy 55-64 vs. Female Healthy 65-74	0.412	0.272	0.245	0.669
Female Healthy 45-54 vs. Male Healthy 45-54	0.321	0.569	**0.001***	0.066
Female Healthy 55-64 vs. Male Healthy 55-64	0.078	0.376	0.004	0.051
Female Healthy 65-74 vs. Male Healthy 65-74	0.449	0.153	**0.001***	0.015
Male Healthy 45-54 vs. Male Healthy 55-64	0.839	0.098	0.505	0.682
Male Healthy 45-54 vs. Male Healthy 65-74	0.969	0.069	0.709	0.824
Male Healthy 55-64 vs. Male Healthy 65-74	0.860	0.763	0.762	0.865
Male Healthy 65-74 vs. Male Unhealthy 65-74	0.033	**0.001***	0.118	0.01
Female Healthy 65-74 vs. Female Unhealthy 65-74	0.725	0.145	0.266	0.311
Male Healthy 55-64 vs. Male Unhealthy 55-64	0.790	0.563	0.147	0.303
Male Unhealthy 55-64 vs. Male Unhealthy 65-74	0.436	0.369	0.857	0.569
All Males Healthy vs. All Females Healthy	0.060	0.061	**0.001***	**0.001***
All Females Healthy vs. All Females Unhealthy	0.437	0.248	0.305	0.283
All Males Healthy vs. All Males Unhealthy	0.299	0.513	0.207	0.228
All Females Unhealthy vs. All Males Unhealthy	0.948	0.719	0.288	0.877

Table 11: *P*-values for all strain and strain rate metrics. Results highlighted in green with bold text and *, indicates results which are statistically significant to $p \leq 0.003$.

Planned Comparison	LVEF	EDV	ESV	ESVi	BSA
Female Healthy 45-54 vs. Female Healthy 55-64	0.252	**0.003***	0.004	0.010	0.196
Female Healthy 45-54 vs. Female Healthy 65-74	0.872	**0.002***	0.024	0.040	0.315
Female Healthy 55-64 vs. Female Healthy 65-74	0.209	0.693	0.711	0.781	0.843
Female Healthy 45-54 vs. Male Healthy 45-54	0.020	**0.001***	**0.001***	**0.001***	**0.001***
Female Healthy 55-64 vs. Male Healthy 55-64	0.005	**0.001***	**0.001***	**0.001***	**0.001***
Female Healthy 65-74 vs. Male Healthy 65-74	0.017	**0.001***	**0.001***	**0.001***	**0.001***
Male Healthy 45-54 vs. Male Healthy 55-64	0.755	0.005	0.150	0.053	0.048
Male Healthy 45-54 vs. Male Healthy 65-74	0.516	**1.00E-03***	**0.003***	0.039	**0.001***
Male Healthy 55-64 vs. Male Healthy 65-74	0.357	0.070	0.392	0.701	0.071
Male Healthy 65-74 vs. Male Unhealthy 65-74	**0.001***	0.018	**0.001***	**0.001***	0.886
Female Healthy 65-74 vs. Female Unhealthy 65-74	0.351	0.962	0.499	0.346	0.074
Male Healthy 55-64 vs. Male Unhealthy 55-64	0.031	0.008	0.013	0.008	0.111
Male Unhealthy 55-64 vs. Male Unhealthy 65-74	0.485	0.094	0.734	0.632	0.701
All Males Healthy vs. All Females Healthy	**0.001***	**0.001***	**0.001***	**0.001***	**0.001***
All Females Healthy vs. All Females Unhealthy	0.202	0.248	0.209	0.206	0.574
All Males Healthy vs. All Males Unhealthy	0.044	0.151	0.074	0.052	0.004
All Females Unhealthy vs. All Males Unhealthy	0.263	**0.003***	0.012	0.090	**0.001***

Table 13: Age and BSA correlations with other variables of interest for all unhealthy females. Statistically significant p-values are highlighted in green. The 95% CIs are taken from the bootstrapping analysis.

Variable	Age Correlations				
	n	Pearson	p-value	95% CIs	
				Lower	Upper
EDV	18	-0.49	0.039	-0.790	0.012
ESV	18	-0.319	0.196	-0.243	-0.003
LVEF	18	0.005	0.984	-0.517	0.672
ESVi	18	-0.269	0.281	-0.781	0.351
ACS	20	-0.187	0.431	-0.682	0.390
MCS	20	-0.165	0.487	-0.613	0.365
BCS	20	0.093	0.697	-0.149	0.506
GCS	20	-0.123	0.606	-0.567	0.370
Variable	BSA Correlations				
EDV	18	0.428	0.076	-0.148	0.721
ESV	18	0.307	0.216	0.202	0.425
LVEF	18	-0.155	0.538	-0.594	0.526
ESVi	18	0.157	0.534	-0.525	0.642
ACS	18	0.113	0.656	-0.358	0.470
MCS	18	0.131	0.605	-0.403	0.552
BCS	18	0.053	0.834	-0.477	0.471
GCS	18	0.131	0.605	-0.390	0.506

Table 14: Age and BSA correlations with other variables of interest for all healthy males. Statistically significant p-values are highlighted in green. The 95% CIs are taken from the bootstrapping analysis.

Variable	Age Correlations				
	n	Pearson	p-value	95% CIs	
				Lower	Upper
EDV	274	-0.280	0.000	-0.399	-0.152
ESV	274	-0.192	0.001	-0.316	-0.063
LVEF	274	-0.047	0.439	-0.171	0.082
ESVi	274	-0.133	0.028	-0.249	-0.003
ACS	293	-0.026	0.657	-0.186	0.062
MCS	293	-0.160	0.006	-0.308	-0.072
BCS	293	-0.033	0.569	-0.139	0.088
GCS	293	-0.048	0.411	-0.201	0.050
Variable	BSA Correlations				
EDV	274	0.482	0.000	0.390	0.567
ESV	274	0.395	0.000	0.293	0.484
LVEF	274	-0.049	0.420	-0.168	0.070
ESVi	274	0.100	0.097	-0.012	0.207
ACS	274	0.075	0.217	-0.029	0.183
MCS	274	0.170	0.005	0.049	0.283
BCS	274	0.092	0.130	-0.044	0.210
GCS	274	0.108	0.074	-0.008	0.226

Table 15: Age and BSA correlations with other variables of interest for all unhealthy males. Statistically significant p-values are highlighted in green. The 95% CIs are taken from the bootstrapping analysis.

Variable	Age Correlations				
	n	Pearson	p-value	95% CIs	
				Lower	Upper
EDV	101	-0.114	0.256	-0.315	0.065
ESV	101	0.049	0.626	-0.159	0.200
LVEF	101	-0.204	0.041	-0.374	-0.026
ESVi	101	0.048	0.632	-0.151	0.215
ACS	111	0.089	0.351	-0.049	0.339
MCS	111	0.148	0.120	-0.064	0.342
BCS	111	0.020	0.835	-0.131	0.192
GCS	111	0.101	0.293	-0.056	0.320
Variable	BSA Correlations				
EDV	101	0.312	0.001	0.138	0.471
ESV	101	0.165	0.100	-0.001	0.339
LVEF	101	0.074	0.465	-0.107	0.266
ESVi	101	-0.039	0.697	-0.197	0.150
ACS	101	-0.169	0.092	-0.342	0.013
MCS	101	-0.112	0.263	-0.315	0.098
BCS	101	-0.128	0.201	-0.329	0.091
GCS	101	-0.160	0.109	-0.343	0.024

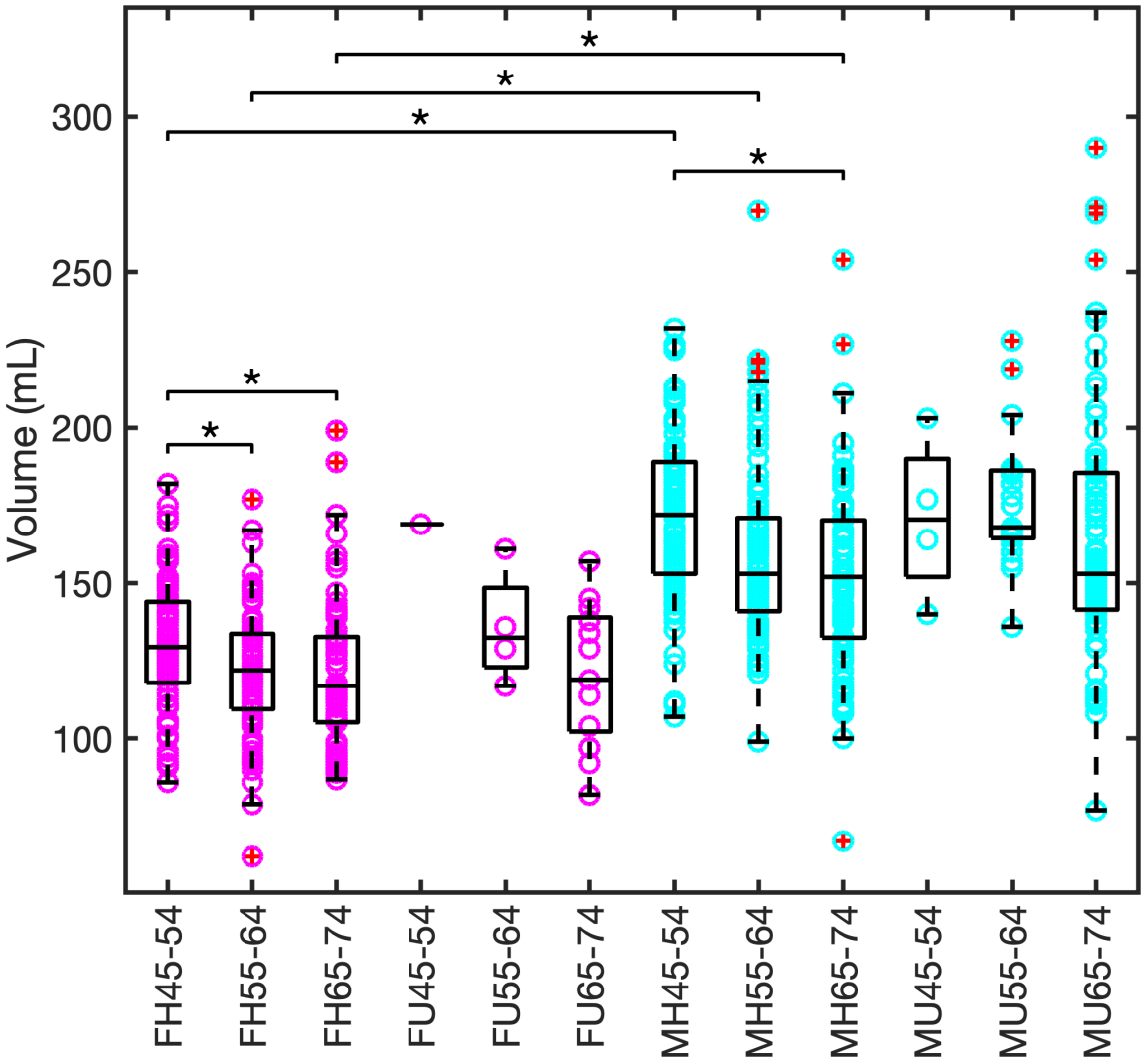

Figure 1: EDV boxplots for all groups: M = Male; F = Female; H = Healthy; U = Unhealthy; XX-YY = age range. Two further planned comparisons were statistically significant that could not be represented: all healthy females vs. all healthy males, and all unhealthy females vs. all unhealthy males.

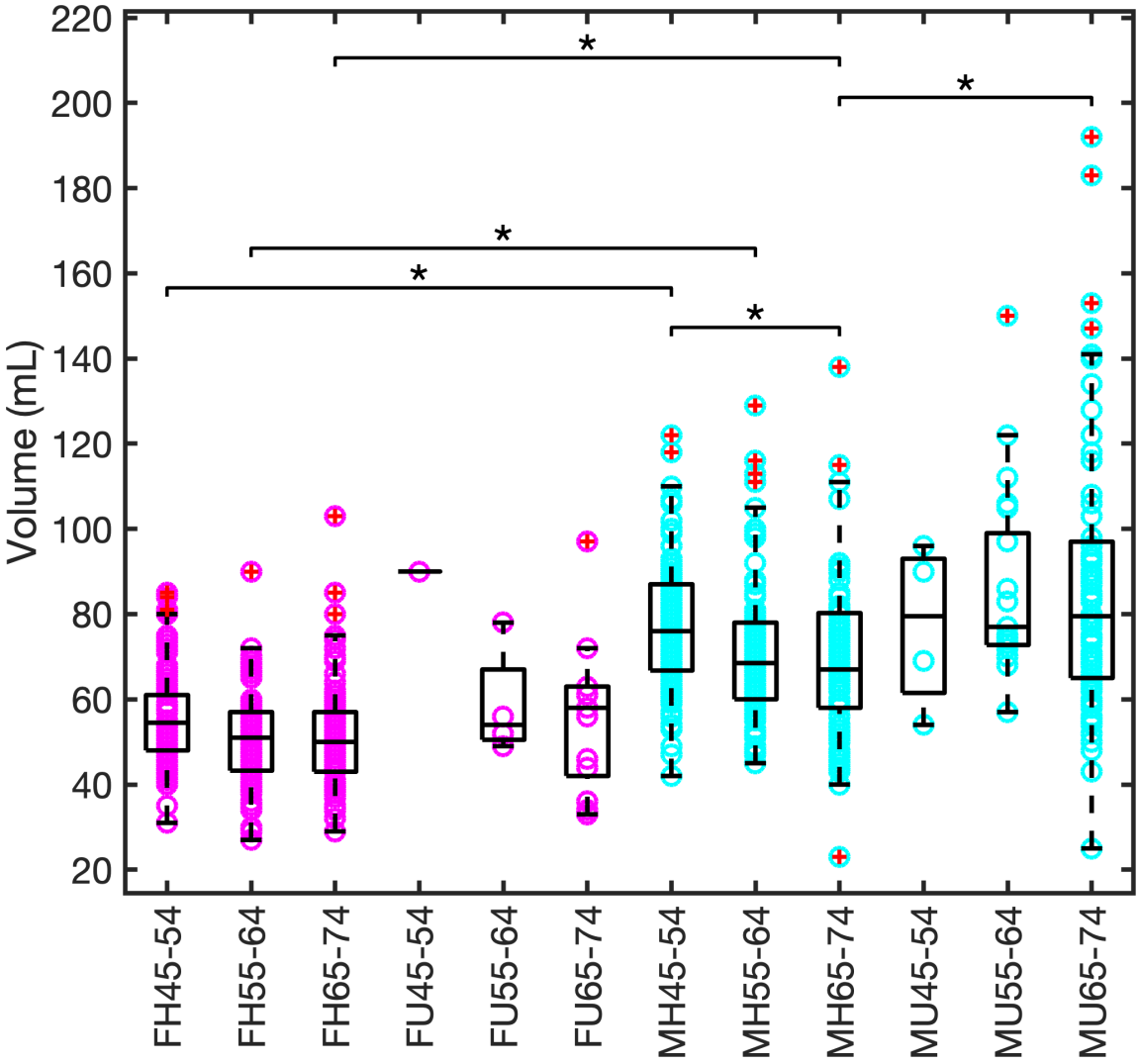

Figure 2: ESV boxplots for all groups: M = Male; F = Female; H = Healthy; U = Unhealthy; XX-YY = age range. One further planned comparison was statistically significant that could not be represented on this plot: all healthy females vs. all healthy males.

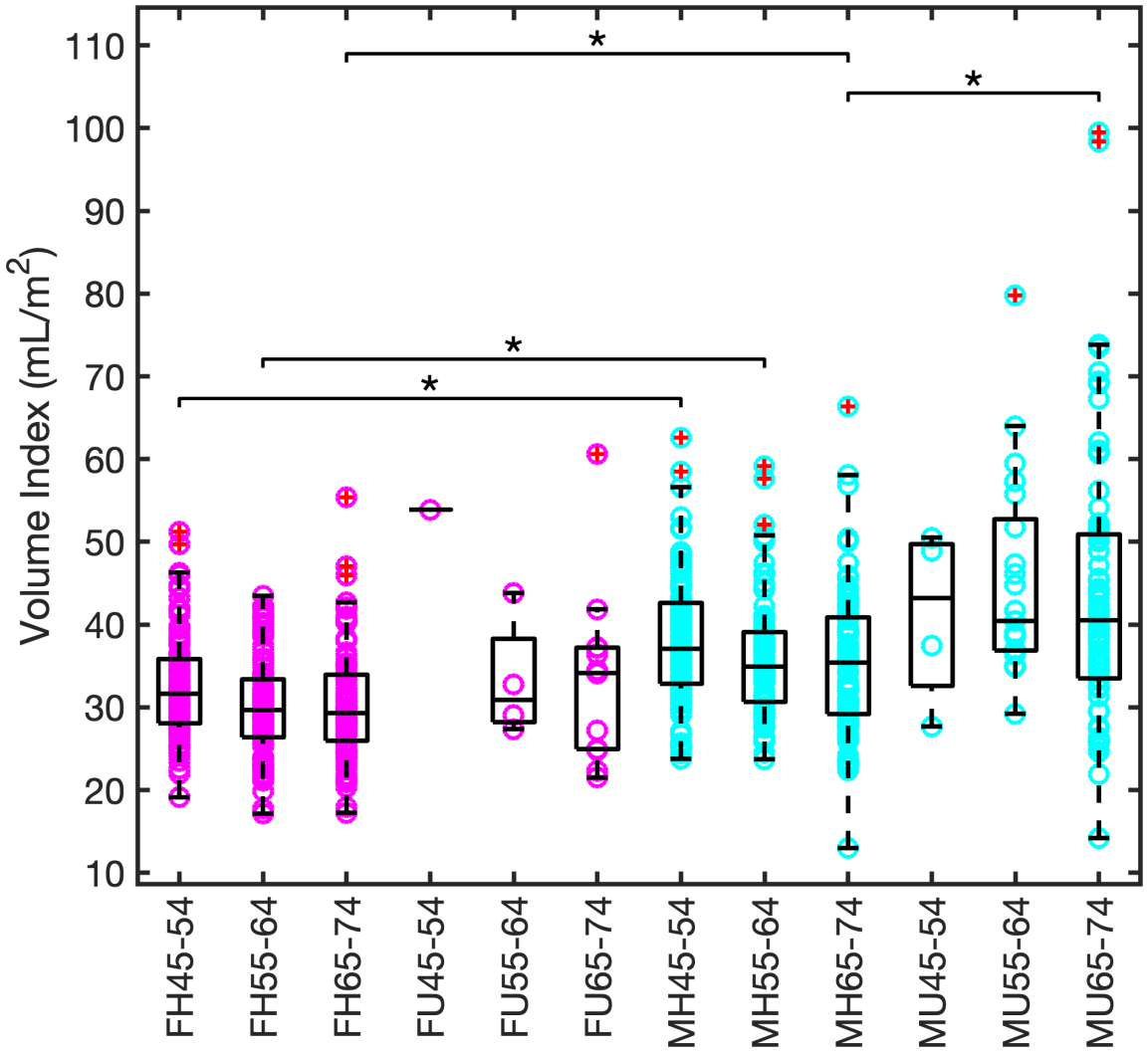

Figure 3: ESVi as boxplots for all groups: M = Male; F = Female; H = Healthy; U = Unhealthy; XX-YY = age range. One further planned comparison was statistically significant that could not be represented on this plot: all healthy females vs. all healthy males.

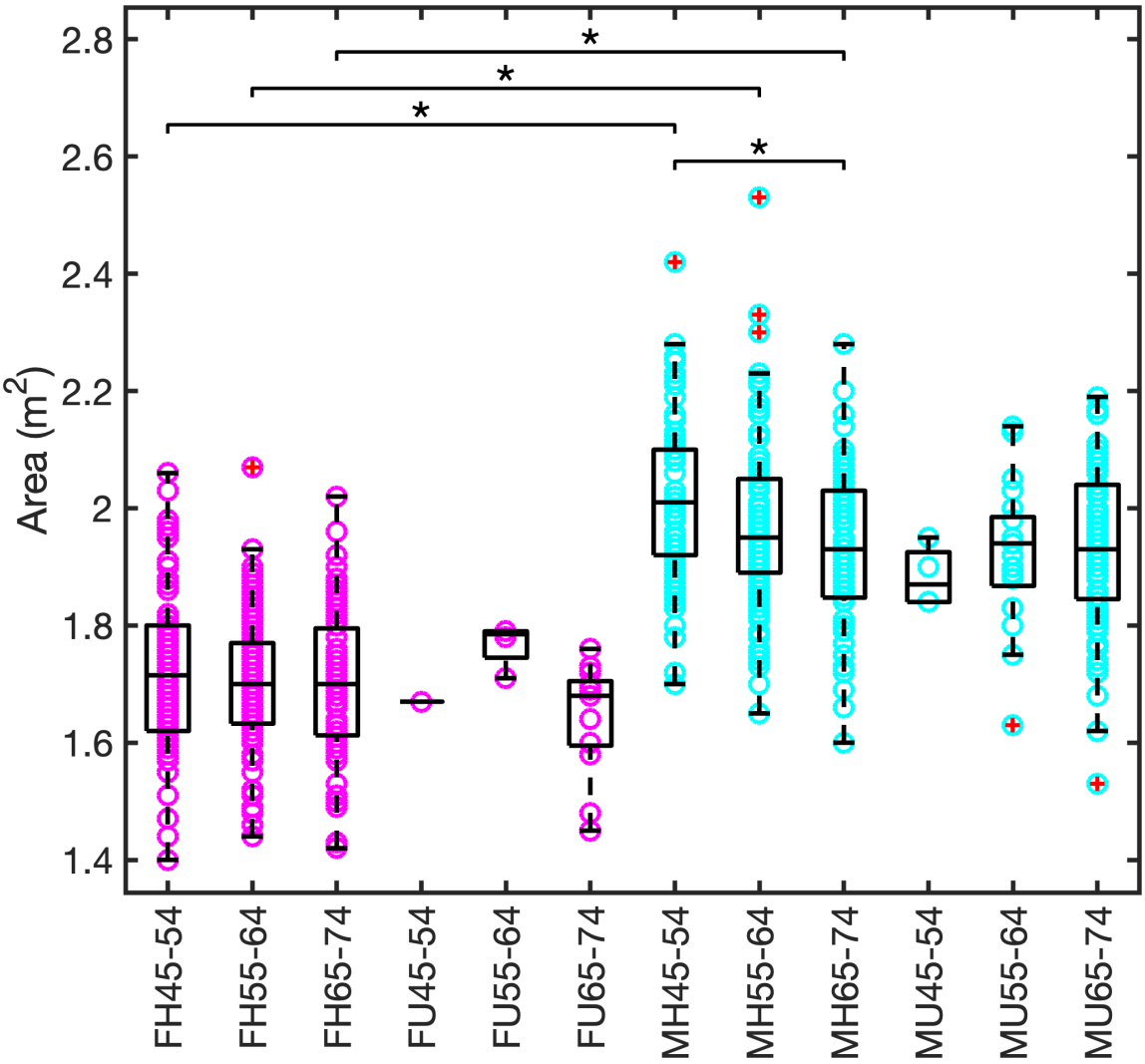

Figure 4: BSA as boxplots for all groups: M = Male; F = Female; H = Healthy; U = Unhealthy; XX-YY = age range. Two further planned comparisons were statistically significant that could not be represented on this plot: all healthy females vs. all healthy males, and all unhealthy females vs. all unhealthy males.

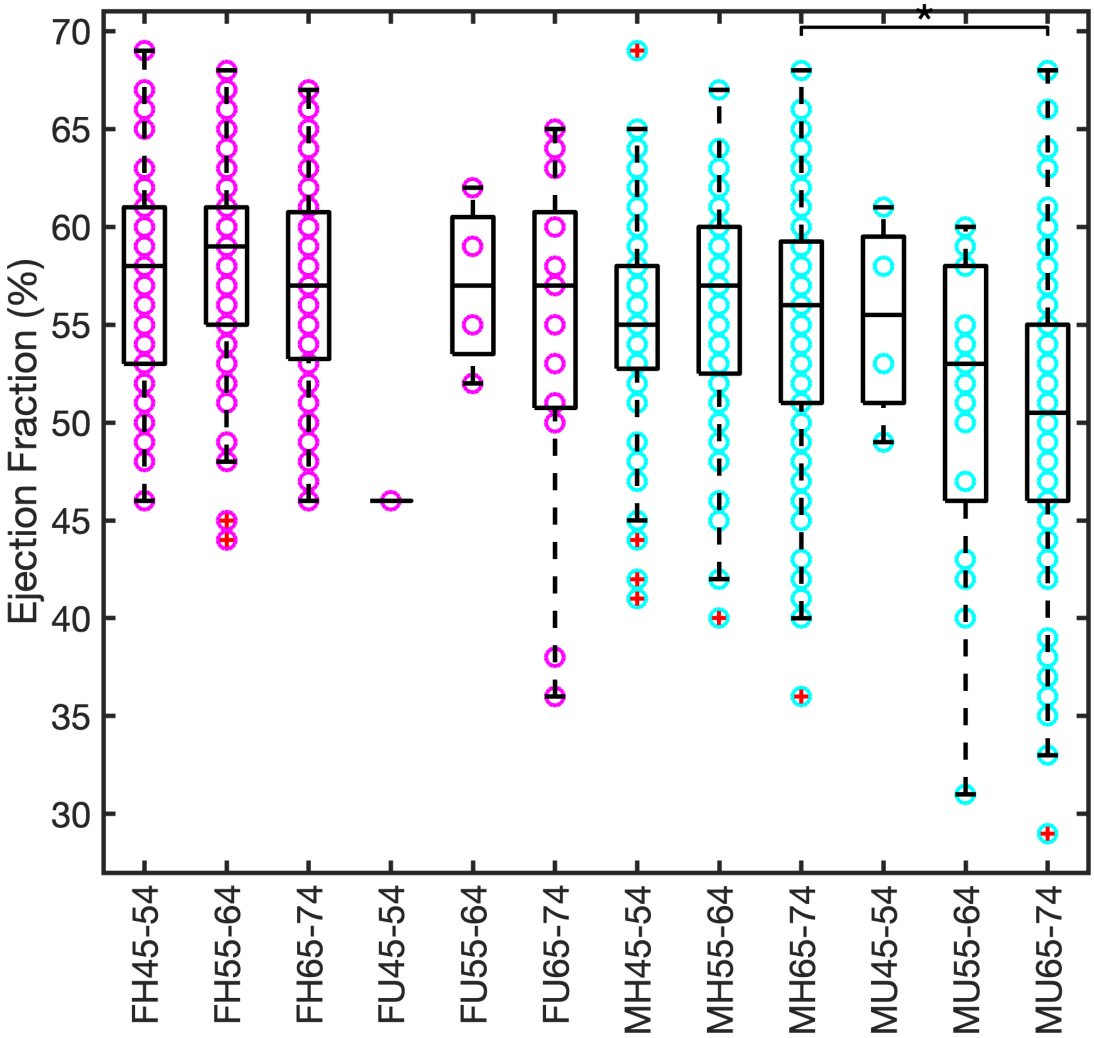

Figure 5: LVEF boxplots for all groups: M = Male; F = Female; H = Healthy; U = Unhealthy; XX-YY = age range. One further planned comparison was statistically significant that cannot be represented on this plot: all healthy females vs. all healthy males.