

1 **Ejection fraction as a statistical index of left ventricular systolic function: The**
2 **first full allometric scrutiny of its appropriateness and accuracy**

3

4 **Running head:** Modeling left ventricular volumes

5

6 Lorenzo Lolli¹, Alan M Batterham¹, Greg Atkinson¹

7

8 **Affiliations:**

9 ¹ Health and Social Care Institute, School of Health and Social Care, Teesside University,
10 Middlesbrough, United Kingdom.

11

12

13 **Corresponding author:**

14 Lorenzo Lolli

15 Health and Social Care Institute

16 School of Health and Social Care, Constantine Building

17 Teesside University, Middlesbrough, TS1 3BA, United Kingdom

18 Tel: +44 (0) 1642 342934

19 Email: L.Lolli@tees.ac.uk

20

21

22 **Word count: Manuscript:** 4647 words; **Summary:** 247 words

23 **Items:** 1 table; 2 figures; 2 supplemental tables

24

25

26

27 **Summary**

28 Left ventricular ejection fraction (EF) is a ratio that is deemed to accurately *normalize* stroke
29 volume (SV) to end-diastolic volume (EDV). Ratios are now well-recognised for not normalizing
30 the numerator, in this case SV, consistently for the denominator, EDV. We aimed to provide the
31 very first allometric-based scrutiny of the conventional assumptions that underpin the EF ratio. We
32 allometrically-modeled untransformed SV and EDV measurements from 112 preclinical heart
33 failure patients in the Multi-Ethnic Study of Atherosclerosis (MESA), and 864 chronic heart failure
34 patients in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone
35 Antagonist (TOPCAT) study. An information-theoretic approach was adopted to assess the relative
36 quality of twelve candidate models for normalizing SV to EDV. None of the conventional
37 underlying assumptions for accurate ratio normalization, e.g. an allometric exponent ≈ 1 , were
38 upheld for EF. A two-parameter power function with normal, heteroscedastic error was the best
39 model for scaling SV to EDV in both samples. The allometric exponent (95% confidence interval)
40 was 0.776 (0.682 to 0.869) in MESA, and 0.860 (0.857 to 0.864) in TOPCAT. EF was inversely
41 correlated with EDV in MESA ($r = -0.67$, 95%CI: -0.76 to -0.55) and TOPCAT ($r = -0.41$,
42 95%CI: -0.46 to -0.35). Consequently, for fundamental statistical reasons, EF was biased low for
43 people with generally larger EDVs, and *vice versa*. For the first time, we have demonstrated that EF
44 is an inaccurate statistic for scaling SV to EDV, leading to potential biased inferences for research
45 and individual patients.

46

47 **Key words:** ejection fraction; allometry; heart failure; left ventricle; normalization

48

49

50

51

52

53 **Introduction**

54 Left ventricular ejection fraction (EF) is typically calculated as the ratio of stroke volume (SV) to
55 end-diastolic volume (EDV) and expressed as a percentage statistic (Carabello 2002). Ejection
56 fraction represents a criterion measure used to inform clinical decisions in the diagnosis and
57 treatment pathways for heart failure (Dunlay *et al.*, 2017). Heart failure is a multifactorial clinical
58 syndrome resulting from pathological impairments in cardiac function and morphology (Abudiab *et*
59 *al.*, 2013) and is estimated to affect more than 37.7 million individuals worldwide (Ziaeeian &
60 Fonarow 2016). According to recent epidemiological data, hospital admissions due to heart failure
61 are expected to increase by more than 50% by 2035 (Ziaeeian & Fonarow 2016). In the United
62 Kingdom, there are approximately 493,000 people living with a definite diagnosis of heart failure
63 (Townsend *et al.*, 2015), which imposes a substantial economic burden on the UK's National
64 Health Service, accounting for 2.1% of its overall budget (Cook *et al.*, 2014).

65
66 Clinically, patients may often progress through a silent and asymptomatic phase of left ventricular
67 systolic dysfunction that characterizes the transition from preclinical to overt heart failure
68 (Goldberg & Jessup 2006). European guidelines for the diagnosis and treatment of acute and
69 chronic heart failure (Ponikowski *et al.*, 2016) differentiate patients with an EF < 40% as “heart
70 failure with reduced ejection fraction” (HFrEF), EF \geq 50% as “heart failure with preserved ejection
71 fraction” (HFpEF), and a ‘gray zone’ in the range from 40% to 49% (HFmrEF). It has been reported
72 that HF patients with a preserved EF have a 32% lower risk of mortality over a 3-year follow-up
73 period compared with HF patients with a reduced EF (Meta-analysis Global Group in Chronic
74 Heart 2012).

75
76 In a previous study, it was highlighted that “*in chronic, compensated heart failure with reduced EF,*
77 *the EF is reduced because the chamber size (denominator of EF equation) is larger, whereas the*
78 *stroke volume (numerator) is typically similar to that of normal controls”* (Borlaug & Redfield

79 2011, page 2008). In classical allometry, EF is a ratio size-scaling index, the accuracy of which is
80 reliant on SV varying as a constant proportion of EDV. Like many such ratio statistics, EF is a
81 statistically robust measure of systolic function only if this assumption and other related
82 assumptions are satisfied (Albrecht *et al.*, 1993; Curran-Everett 2013; George *et al.*, 2001; Tanner
83 1949). For example, recently-published studies have revealed that the percentage flow-mediated
84 dilation index can misrepresent the true size-scaling association between resting and hyperaemic
85 artery diameter, thereby entailing inaccurate inferences regarding human endothelial function
86 (Atkinson & Batterham 2015).

87

88 Since EF is the selected statistic for informing the diagnosis and treatment of patients with heart
89 failure (Dunlay *et al.*, 2017; Ponikowski *et al.*, 2016), we hypothesized that the true relationship
90 between the left ventricular systolic and diastolic volumes might not be directly proportional in
91 nature. It is this assumption which underpins the accuracy of the EF ratio statistic and, if false,
92 would lead to biased inferences in research and diagnoses for individual patients. While studies on
93 allometry and scaling in cardiovascular physiology have been traditionally conceived to standardise
94 measures of cardiac structure and function to body size (Dewey *et al.*, 2008), no previous study has
95 comprehensively scrutinised the inherent scaling properties of the EF index itself, i.e. the inherent
96 accuracy of how EF normalises stroke volume for differences in end diastolic volume.

97

98 Therefore, using a formal information-theoretic approach, we compared twelve candidate models
99 for scaling SV to EDV in terms of the potential implications for general clinical practice using two
100 samples of data (Studies 1 and 2). In study 1, we analysed data from preclinical heart failure
101 patients enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA), and, in study 2, we
102 analysed data from patients already with chronic HF involved in the Treatment of Preserved
103 Cardiac Function Heart Failure with and Aldosterone Antagonist (TOPCAT) echocardiographic
104 sub-study.

105 **Methods**

106

107 **Study 1 (MESA)**

108 **Participants**

109 A detailed study protocol of the MESA has been previously reported (Bild *et al.*, 2002). In brief, the
110 MESA is a prospective, population-based study on the prevalence, incidence, and progression of
111 subclinical cardiovascular disease (Bild *et al.*, 2002). For the present study, participants at the
112 baseline visit were selected based on the established diagnosis for incident heart failure after 8 years
113 of follow-up (Habibi *et al.*, 2014). The adjudication of a hard-cardiovascular event was established
114 by a committee that included a cardiologist, an epidemiologist, and a neurologist. Incident heart
115 failure was classified as definite, probable, or absent. The full criteria for the diagnosis of heart
116 failure in the MESA were also detailed in previous studies (Bluemke *et al.*, 2008; Yeboah *et al.*,
117 2012). The MESA was approved by the local institutional review boards of each study centre, and
118 participants provided written informed consent. The current study adhered to the ethics and research
119 governance procedures at Teesside University.

120

121 Demographic, medical history, metabolic and cardiovascular data for this study were obtained at the
122 MESA baseline examination. Resting blood pressure was determined as the average of the last two
123 measurements in the seated position using a Dinamap model Pro 100 automated oscillometric
124 sphygmomanometer (Critikon, Tampa, Florida). Hypertension was defined as systolic blood
125 pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, or the use of antihypertensive
126 medication. Fasting plasma glucose \geq 126 mg/dL or the use of anti-diabetic medications defined
127 diabetes mellitus. The glomerular filtration rate (eGFR) was estimated using the Chronic Kidney
128 Disease Epidemiology Collaboration (CKD-EPI) equation (Levey *et al.*, 2009). Smoking history
129 was determined via standardized questionnaires. Body mass index (BMI) was calculated as the ratio
130 of weight to height squared (kg/m^2). Lipid profiling from blood samples was performed after a 12-h

131 fast. Low-density lipoprotein cholesterol was estimated with the Friedewald equation (Friedewald
132 *et al.*, 1972).

133

134 **Cardiac magnetic resonance imaging**

135 The magnetic resonance imaging (MRI) protocol procedures and reliability of the global left
136 ventricular measurements have been outlined previously (Natori *et al.*, 2006). Briefly, the MRI
137 examination to quantify left ventricular functional and structural parameters consisted of a stack of
138 short- and long-axis echo cine images covering the base-to-apex distance of the left ventricle with a
139 temporal resolution of 50 ms (Natori *et al.*, 2006). The EDV and end-systolic volume (ESV) were
140 calculated using the Simpson's rule from endocardial and epicardial myocardial borders (Natori *et*
141 *al.*, 2006). Left ventricular mass was the resultant of the difference between epicardial and
142 endocardial areas times the slice thickness, section gap, and the specific gravity of the myocardium
143 (i.e. 1.05 g/mL) (Natori *et al.*, 2006). Papillary muscle mass was included in the left ventricular
144 cavity volume and excluded from left ventricular mass (Bluemke *et al.*, 2008). EF (%) was
145 conventionally calculated as SV divided by EDV \times 100.

146

147 **Study 2 (TOPCAT)**

148 **Study population and definitions**

149 TOPCAT is an intercontinental, double-blind, randomized, placebo-controlled, parallel-group study
150 involving 3445 HF patients recruited at 266 centres in United States, Canada, Russia, Republic of
151 Georgia, Argentina, and Brazil to test the efficacy and safety of an aldosterone antagonist to reduce
152 cardiovascular morbidity and mortality in patients with heart failure and an EF \geq 45% (Desai *et al.*,
153 2011). The present study examined participants enrolled in the TOPCAT echocardiographic sub-
154 study, a smaller sample from the TOPCAT trial (Shah *et al.*, 2014). Participants were eligible if
155 they had a technically-valid echocardiographic quantification of the left ventricular volumes derived
156 according to the modified biplane Simpson's rule, which represents the recommended method by

157 the American Society of Echocardiography (Lang *et al.*, 2015). The TOPCAT trial was funded by
158 the National Heart, Lung, and Blood Institute (NHLBI), and was approved by the local institutional
159 review boards of each study centre (Pitt *et al.*, 2014). The current study was compliant with the
160 ethics and research governance procedures at Teesside University.

161

162 At the baseline visit, each participant underwent record screening, which included self-reported
163 medical history and current medications, a physical examination (e.g. blood pressure, height,
164 weight), and laboratory data collection involving complete blood count, electrolytes, blood urea
165 nitrogen, creatinine, blood glucose, liver function assessment, and urine test for microalbuminuria.
166 (Pitt *et al.*, 2014; Shah *et al.*, 2014). Participants' chronological age, the inverse of serum creatinine,
167 sex, and ethnicity were obtained to derive eGFR using the four-variable Modification of Diet in
168 Renal Disease algorithm (Levey *et al.*, 1999).

169

170 **Echocardiography**

171 The echocardiographic assessments, procedures, and intra-observer measurement variability in the
172 TOPCAT echocardiographic sub-study have been described in detail previously (Shah *et al.*, 2014).
173 Each study centre submitted echocardiograms in digital or analog format to the core laboratory at
174 the Brigham and Women's hospital (Desai *et al.*, 2011). Left ventricular endocardial borders were
175 traced manually at the end of the diastolic and systolic phases in the 4- and 2-chamber apical views
176 (Shah *et al.*, 2014). The biplane method of disks (i.e. modified Simpson's rule) was adopted to
177 assess left ventricular volumes. Left ventricular mass estimation from linear dimension was
178 performed according to the American Society of Echocardiography equation (Lang *et al.*, 2015). Of
179 the 935 echocardiographic measurements that were analyzable quantitatively, left ventricular
180 volumes derived via the modified biplane Simpson's rule were available in 864 study participants.

181

182

183 **Statistical analyses and allometric modeling**

184 The MESA (n = 112) and TOPCAT (n = 864) samples were examined separately. Demographic and
185 clinical characteristics of participants at the baseline examination are presented as mean \pm standard
186 deviation (SD) for continuous variables and frequency or percentages for categorical variables.

187

188 To examine the scaling relationship between SV and EDV, we performed non-linear regression
189 analyses of untransformed measurements. We fitted three sets of four models, involving two
190 straight lines and two power functions, with multiplicative, log-normal, heteroscedastic error, and
191 additive, normal, homoscedastic or heteroscedastic error, respectively (Packard 2017). Parameter
192 estimates for each model were solved using an iterative protocol based on the Marquardt procedure
193 (Packard 2017). Participants' chronological age and sex (coded "0" for female, "1" for male) were
194 included as continuous and categorical covariates in the models, respectively. The commonality of
195 *b* exponent principle was tested to establish the presence of a common EDV exponent for both
196 sexes (Batterham *et al.*, 1997; Vanderburgh 1998). A substantial sex difference in the allometric
197 exponent, predefined as ± 0.1 in the present study, would reveal a fundamental difference in the
198 relationship between SV and EDV, thereby precluding meaningful comparisons between men and
199 women (Batterham *et al.*, 1997; Vanderburgh 1998).

200

201 The Akaike Information Criterion (AIC) was adopted to assess the relative quality of each model in
202 the set of candidates (Burnham *et al.*, 2011). The Akaike difference (Δ AIC) from the estimated best
203 model (i.e. the model with the lowest AIC value; Δ AIC = 0) was evaluated according to the
204 following scale: 0-2, essentially equivalent; 2-7, plausible alternative; 7-14, weak support; > 14, no
205 empirical support (Burnham *et al.*, 2011). Parameter estimates were interpreted from the
206 best/essentially equivalent models for the examined data. Regression coefficients were reported as
207 point estimates with 95% confidence intervals (CI). Statistical analyses were carried out using
208 SAS[®] software (PROC MODEL, Version 9.3; SAS Institute, Inc., Cary, NC, 2011), and figures

209 were produced using IBM Statistical Package for the Social Sciences (SPSS) Statistics v. 23.0
210 (SPSS, Chicago, IL, USA).

211

212 *Table 1 about here*

213

214 **Results**

215

216 **Allometric accuracy of the EF ratio in preclinical individuals (MESA)**

217 Among 5004 study participants with technically-valid measurements of the left ventricle obtained at
218 the baseline visit, 112 participants reported a subsequent diagnosis of heart failure at a median 7.2-
219 year follow-up. Of these participants, 43% were Caucasian (n = 48), 5% Chinese (n = 5), 31%
220 African-American (n = 35), and 21% Hispanic (n = 24). Table 1 shows the summary data of the 112
221 study participants stratified by sex.

222

223 Graphical and statistical criteria indicated that the EF ratio failed to meet underlying assumptions
224 for appropriate scaling. First, there was a large, negative correlation between the ratiometric index
225 and its denominator corresponding to $r = -0.67$ (95%CI: -0.76 to -0.55). This inconsistent
226 normalization for EDV is also shown in Fig. 1a. Second, the linear regression between SV and EDV
227 for the whole sample revealed a positive Y -intercept value of 44 mL (95%CI: 34 mL to 54 mL). Use
228 of a ratio would only be appropriate if the line describing the bivariate relationship passes through
229 the origin (Figure 1c). Accordingly, the ratio of the coefficient of variations (CV) for EDV to SV
230 was substantially different from the correlation coefficient describing the bivariate relationship
231 between the two variables ($1.31 \neq 0.68$). A ratio standard model is valid only if this ratio of CVs is
232 equal to the correlation coefficient between SV and EDV.

233

234 The AIC criteria revealed the two-parameter power function with normal, heteroscedastic error, of
235 the form $Y = a \cdot X^b$ (Figure 2a), to be the best of the twelve models (Supplemental Table 1). The
236 allometric exponent (b) describing the non-linear relationship between SV and EDV was 0.776
237 (95%CI: 0.682 to 0.869), with no main effects of chronological age and sex as predictor variables in
238 the model. The mean difference in the EDV exponent between men and women was 0.073 (95%CI:
239 -0.090 to 0.235). The EDV measurement spectrum ranged from 47 to 290 mL. Supplemental Table
240 1 shows the AIC values for each model in the set of candidates. In agreement with the AIC
241 outcomes, the raw residuals from the best model were well-behaved (Figure 2c).

242

243 **Allometric accuracy of the EF ratio in clinical individuals (TOPCAT)**

244 Among the 864 eligible study participants, 83% were Caucasian ($n = 714$), 13% were Black ($n =$
245 114), less than 1% Asian ($n = 4$), and 3% ($n = 30$) were defined as a minor mixed-ethnic group.
246 Demographic and cardiovascular functional parameters of the 864 study participants are illustrated
247 in Table 1.

248

249 The moderate, inverse association between the ratiometric EF and EDV corresponding to $r = -0.41$
250 (95%CI: -0.46 to -0.35) demonstrated that the conventional ratiometric EF index does not
251 consistently control for the effects of EDV (Figure 1b). Likewise, the positive Y -intercept value of
252 13 mL (95%CI: 11 mL to 14 mL) observed in the bivariate relationship between SV and EDV
253 indicated the failure of the ratiometric EF to meet another underlying assumption of ratio scaling
254 models (Figure 1d). In fact, the substantial difference between CV_x/CV_y and the observed
255 correlation coefficient between SV and EDV ($1.12 \neq 0.88$) provided additional evidence about the
256 inappropriateness of the EF ratio also for this data set. The two-parameter power function with
257 normal, heteroscedastic error, of the form $Y = a \cdot X^b$ (Figure 2b), emerged as the best model in the
258 pool of twelve candidates (Supplemental Table 2). The allometric exponent (b) describing the non-
259 linear relationship between SV and EDV was 0.860 (95%CI: 0.857 to 0.864), with a substantial

260 main effect of chronological age in the model. The mean difference in the EDV exponent between
261 men and women was 0.087 (95%CI: 0.080 to 0.093). The EDV measurements ranged from 27 to
262 233 mL for this TOPCAT sub-sample. The AIC values for each model in the set of candidates are
263 shown in the Supplemental Table 2. The raw residuals from the best model plotted against the
264 predicted values were found to be well-behaved (Figure 2d).

265

266 *Figure 1 about here*267 *Figure 2 about here*

268

269 **How the EF ratio can misdiagnose individuals**

270 In both MESA and TOPCAT, application of allometric scaling methods revealed a substantial
271 discrepancy between ratio and adjusted estimates of EF for some individuals on a between-subject
272 basis. For example, in MESA, a 64-year-old, Caucasian man with no history of hard cardiovascular
273 event, hypertension, a fasting glucose level of 87 mg/dl, and eGFR of 69.4 mL/min/1.73m², and a
274 blood pressure of 124/73 mmHg, presented an SV of 91 mL within the age-specific range. On the
275 other hand, left ventricular EDV (251 mL), ESV (160 mL), and mass (254 g) were markedly
276 outside the physiological parameters. Although the calculated EF ratio was 36%, use of the more
277 appropriate size-scaling model revealed an adjusted-EF of 41%. The allometric normalization of SV
278 for differences in EDV in MESA thus revealed an absolute underestimation of the relative systolic
279 function for this individual corresponding to 5%. In TOPCAT, ratio and allometric scaling
280 approaches were found to provide substantially different estimates of EF in a 77-year-old,
281 Caucasian woman with history of angina, hypertension, atrial fibrillation, a fasting glucose level of
282 91 mg/dl, an eGFR of 70.2 mL/min/1.73m², and on β -blockers therapy. The observed left
283 ventricular EDV, ESV, SV, and mass were 48 mL, 23 mL, 25 mL, and 256 g, respectively.
284 Notwithstanding the relatively small SV observed in this patient, the EF ratio of 52% indicated a
285 preserved systolic function. Conversely, the more appropriate adjusted-EF estimate of 47% revealed

286 a substantial 5% overestimation of the true EF. Accordingly, the most appropriate size-scaling
287 model provided a more sensible estimate of EF, ultimately in line with the abnormal global
288 longitudinal strain of -13% observed in this patient.

289

290 **Discussion**

291 For the first time, we report here that SV does not vary in direct proportion to EDV. The use of the
292 EF ratio must, as a fundamental assumption for accuracy, be used only when the association
293 between numerator and denominator is directly proportional in nature. This incompatibility of the
294 EF ratio has far-reaching implications, including the potential for biasing clinical and physiological
295 insights into the human left ventricular systolic function. Specifically, estimates of relative SV are
296 biased low for larger EDV measures, and *vice versa*. We contend that, although the EF ratio index
297 is simple to calculate, it can contribute to misdiagnoses in heart failure (Figure 2 a, b). Of the 23
298 patients who were found to have a reduced EF in the TOPCAT sample, 5 of these patients (22%)
299 were misclassified. In fact, the mean difference of 3.6% (95%CI: 2.6% to 4.5%) between the
300 ratiometric and allometrically-adjusted EF estimates indicated that these patients had a mid-range
301 EF. We also highlight the fact that, in the TOPCAT study, HFpEF patients were specifically
302 recruited (Desai *et al.*, 2011; Pitt *et al.*, 2014; Solomon *et al.*, 2016). As a consequence, only
303 approximately 3% of the patients in the TOPCAT sample had a reduced EF. This proportion would
304 be substantially larger in a random sample of HF patients, as would the range of measured EDVs.
305 For example, in the PREVEND study, at a median follow-up of 11.5 years, the reported proportion
306 of patients with HFpEF was 66% (Brouwers *et al.*, 2013). Therefore, a “reduced” misclassification
307 proportion of 22% could have wider ramifications in a random sample of HF patients.

308

309 In both the MESA and TOPCAT samples, the AIC criteria indicated that the two-parameter power
310 function with normal, heteroscedastic error was the superior model for describing left ventricular
311 systolic function rather than the EF ratio model of straight line with zero intercept (Supplemental

312 Table 1 and 2). The EDV scaling exponents observed in both MESA and TOPCAT samples
313 described unambiguously the negative allometric relationship ($b < 1$) between the volume of blood
314 pumped from the ventricle during each cardiac cycle and atrial filling at the end of the diastolic
315 phase both in preclinical and overt heart failure patients (Packard 2017). A simple ratio would have
316 empirical and physiological support only if these allometric exponents were found to be equivalent
317 to 1. Furthermore, as a potential solution to the scaling problems with EF ratio, the present study
318 provides a novel approach to derive EF measures adjusted properly for EDV differences working in
319 the raw arithmetic space and using the residuals from the best model (Albrecht *et al.*, 1993).

320

321 Our study findings also appeared to shed light on the reported sex differences in EF both in healthy
322 (Chung *et al.*, 2006; Yeon *et al.*, 2015) and diseased (Davies *et al.*, 2001; Martinez-Selles *et al.*,
323 2012) populations, whereby women typically show a higher EF compared with men. Yeon and
324 colleagues, who examined a large sub-population of the Framingham Heart Study Offspring Cohort
325 (n=1794) using cardiac MRI, reported a mean (\pm SD) EF of $68\% \pm 5$ in women and $66\% \pm 5$ in men
326 (Yeon *et al.*, 2015). Nevertheless, the observed EDV was found to be substantially smaller in
327 women than in men (Yeon *et al.*, 2015). Indeed, the mean sex-based differences we observed in
328 *absolute* EDV both in MESA and TOPCAT samples were in line with the current evidence (Gori *et*
329 *al.*, 2014; Salton *et al.*, 2002; Yeon *et al.*, 2015). The 95%CI for the mean EDV difference between
330 men and women was 23 mL to 59 mL in MESA, and 22 mL to 30 mL in TOPCAT. On the other
331 hand, application of allometric scaling methods revealed trivial sex-based differences in EF (Table
332 1). Specifically, in MESA, the observed mean difference of 5.7% (95%CI: 1.0% to 10.5%)
333 indicated that women had a substantially greater EF ratio than men. Conversely, there was a trivial
334 difference in EF of 1.6% (95%CI: -2.5% to 5.8%) between the sexes based on allometrically-
335 adjusted individual EF estimates. Likewise, trivial differences in the adjusted-EF were also
336 observed in the larger TOPCAT population. While EF ratio estimates indicated a substantial

337 difference of 2.6% (95%CI: 1.6% to 3.7%) between the sexes, the observed mean difference in the
338 adjusted-EF of 0.5% (95%CI: -0.5% to 1.5%) was again found to be trivial.

339

340 Not only did the procedures used for normalizing left ventricular SV relative to EDV unveil the
341 unappreciated potential of the EF ratio% to provide biased individual estimates, but they also permit
342 an accurate determination of properly normalized EF measures (Albrecht *et al.*, 1993; Laird 1983)
343 for new clinical patients showing hallmarks akin to the reference population. Conceptually, the sum
344 of a new heart failure patient's *individual* residual (Albrecht *et al.*, 1993), by definition the
345 difference between the observed and predicted EF, and the reference MESA sample mean EF of
346 63.7% can provide the clinician with a size-adjusted measure of EF for the new person examined in
347 the clinic. The prediction equation resulting from the best model parameter estimates in MESA
348 (Supplemental Table 1), with the EF ratio as the dependent variable, was $EF = 1.74298 \cdot$
349 $EDV^{-0.22326} \cdot \exp(\text{chronological age} \cdot 0.001831) \cdot \exp(\text{sex} \cdot -0.03121)$ and yields a predicted
350 estimate of EF. To illustrate further the importance of the proposed approach, we also re-examined
351 here the clinical case of a patient with a definite diagnosis of heart failure, known chronological
352 age, sex, and left ventricular functional parameters measured between 2010 and 2012 as part of the
353 fifth examination of MESA (Liu *et al.*, 2013). Demographic characteristics and parameters of
354 cardiac function were obtained for a 76-year-old, African-American woman with no history of
355 myocardial infarction or coronary heart disease, hypertension, treated diabetes, a blood pressure of
356 149/84 mmHg, an eGFR of 30.2 mL/min/1.73m², and on β -blockers therapy. Left ventricular EDV
357 (114 mL), ESV (51 mL), SV (63 mL), and mass (140 g) measures were within the physiological
358 parameters (Natori *et al.*, 2006). While the EF ratio of 55% was substantially above the threshold
359 *defining* HFpEF, the more appropriate adjusted-EF was a lower 49% and revealed a substantial
360 overestimation of the true relative systolic function corresponding to 6%. A similar trend was
361 observed in the case a follow-up assessment of a 64-year-old Caucasian man with a definite
362 diagnosis of heart failure in MESA (Liu *et al.*, 2013). The patient presented a history of myocardial

363 infarction, coronary heart disease, hypertension, sinus bradycardia, treated diabetes, a blood
364 pressure of 143/72 mmHg, an eGFR of 77.9 mL/min/1.73m², and was on β -blockers therapy. Left
365 ventricular EDV (235 mL), ESV (142 mL), and mass (233 g) measures were substantially elevated,
366 whereas the observed SV (93 mL) was within the physiological parameters (Natori *et al.*, 2006).
367 While the EF ratio of 39% allegedly suggested an HFrEF diagnosis (Ponikowski *et al.*, 2016), the
368 more appropriate allometrically adjusted-EF was a higher 47% and revealed a substantial
369 underestimation of the true relative systolic function corresponding to 8%. From a clinical
370 standpoint, the approach described herein is deemed superior to the traditional formulation of
371 power-function ratios (Y/X^b), which typically display distributional patterns dependent on the size of
372 the scaling variable (Albrecht *et al.*, 1993).

373

374 In a failing heart, it is well-established that changes in EDV are likely to affect EF to a much greater
375 extent than potential differences in SV, which typically tend to be of a smaller magnitude (Cohn *et*
376 *al.*, 2000). With use of the traditional EF ratio index, substantial and uncontrolled variations in EDV
377 have the unappreciated potential of generating artefactual variability in the estimated amount of
378 fractional volume that is ejected during each cardiac cycle, regardless of the observed SV (Konstam
379 2003). A landmark study on the pathophysiological characterization of heart failure revealed trivial
380 differences in SV between patients with chronic heart failure and healthy controls (Kitzman *et al.*,
381 2002). In contrast, the mean EF was substantially higher in people with HFpEF compared with the
382 observed values in both HFrEF patients and, paradoxically, healthy participants (Kitzman *et al.*,
383 2002). Similarly, the mean EF was found to be larger in patients with left ventricular hypertrophy
384 than healthy individuals despite significantly smaller left ventricular chamber dimensions
385 (Aurigemma *et al.*, 1995). Additionally, a recent study has demonstrated the unappreciated impact
386 of geometric confounders, primarily increased wall thickness and reduced EDV, hindering a
387 reliable interpretation of EF (Stokke *et al.*, 2017). Despite significant and proportional reductions in
388 SV and, more importantly, EDV which could result in a preserved EF, global longitudinal and

389 circumferential strain can yet be substantially impaired (Stokke *et al.*, 2017). This line of evidence,
390 alongside our study findings (Figure 1), appears to underline further the potential inadequacy of a
391 EF ratio for stratifying cardiovascular patients since, for example, the development of an increased
392 relative wall thickness could allow a preserved EF irrespective of a depressed myocardial
393 shortening (Aurigemma *et al.*, 1995). Since the physiological range of SV is finite, any substantial
394 increase in EDV would result in a consequent inflation of the ESV and concomitant reduction of EF
395 or vice versa (Li 1996). In relative terms, lack of adequate control for pathophysiological changes in
396 cardiac morphology influencing left ventricular cavity volume in diastole can bias the EF ratio and,
397 ultimately, lead to misclassifying a patient's clinical profile (Konstam 2003). Furthermore, the
398 seldom appreciated drawbacks of adopting a ratiometric scaling approach may also provide an
399 index of relative systolic function spuriously labile to any variation in preload and afterload
400 (Carabello 2002; Kalogeropoulos & Butler 2017). When SV is appropriately scaled to EDV using
401 allometric methods, the confounding effects of EDV differences can be therefore removed and
402 allow clinically meaningful inter-individual and group comparisons.

403

404 **Limitations**

405 Notwithstanding the fact that we examined the scaling relationship between SV and EDV among
406 both preclinical and chronic heart failure patients, missing observations of cardiac structure and
407 function of patients with acute decompensated heart failure limit a general application of the
408 observed outcomes for taxonomic classifications in the ensuing stages of this pathological disorder.
409 Additionally, the adoption of different imaging techniques for the assessment of left ventricular
410 volumes in MESA and TOPCAT could be another limitation of the present study, even though the
411 point estimates of the EDV exponents were not found to be substantially different between the
412 samples (Figure 2 a, b). Finally, the distribution of EF frequencies, and implicitly the relatively
413 small left ventricular volumes, might have influenced the precision of the point estimate for the
414 EDV allometric exponent due to the substantially greater proportion of participants with a EF ratio

415 $\geq 50\%$. These results appear to warrant further research investigating the scaling properties of the
416 EF index using allometric methods in large samples of acute and chronic heart failure patients being
417 *heterogeneous* in left ventricular size, and the related implications from clinical and
418 epidemiological perspectives.

419

420 **Conclusions**

421 Ratio scaling appears to limit the validity of EF as the traditional measure of the human systolic
422 function unless it is adequately normalized for differences in EDV. The residual size correlation of
423 a EF ratio might preclude a clinically meaningful assessment of cardiac function, ultimately
424 yielding substantially biased estimates of EF for some individuals. A comprehensive integration of
425 absolute measures of the heart function (i.e., left ventricular ESV), clinical parameters, and relevant
426 biomarkers might embody a more pragmatic approach for the optimal pre-emptive screening,
427 decision-making, and therapeutics than the limited scrutiny of a ratiometric EF index failing to
428 serve its purpose in an unbiased manner. Further research will be required to examine scaling
429 properties of the EF% index within large, heterogeneous populations of healthy and diseased
430 individuals for determining the construct validity of the index as a clinical biomarker for risk
431 stratification and therapeutic decisions.

432

433 **Disclosures**

434 The authors have no conflict of interest to disclose regarding this publication.

435

436 **Sources of funding**

437 None

438

439

440

441 **References**

442

443 Abudiab MM, Redfield MM, Melenovsky V, et al. Cardiac output response to exercise in relation to
444 metabolic demand in heart failure with preserved ejection fraction. *Eur J Heart Fail* (2013); **15**: 776-
445 785.

446 Albrecht GH, Gelvin BR and Hartman SE. Ratios as a size adjustment in morphometrics. *Am J Phys*
447 *Anthropol* (1993); **91**: 441-468.

448 Atkinson G and Batterham AM. The clinical relevance of the percentage flow-mediated dilation index. *Curr*
449 *Hypertens Rep* (2015); **17**.

450 Aurigemma GP, Silver KH, Priest MA, et al. Geometric changes allow normal ejection fraction despite
451 depressed myocardial shortening in hypertensive left ventricular hypertrophy. *J Am Coll Cardiol*
452 (1995); **26**: 195-202.

453 Batterham AM, George KP and Mullineaux DR. Allometric scaling of left ventricular mass by body
454 dimensions in males and females. *Med Sci Sports Exerc* (1997); **29**: 181-186.

455 Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. *Am J*
456 *Epidemiol* (2002); **156**: 871-881.

457 Bluemke DA, Kronmal RA, Lima JA, et al. The relationship of left ventricular mass and geometry to
458 incident cardiovascular events: the MESA (Multi-Ethnic Study of Atherosclerosis) study. *J Am Coll*
459 *Cardiol* (2008); **52**: 2148-2155.

460 Borlaug BA and Redfield MM. Diastolic and systolic heart failure are distinct phenotypes within the heart
461 failure spectrum. *Circulation* (2011); **123**: 2006-2013.

462 Brouwers FP, de Boer RA, van der Harst P, et al. Incidence and epidemiology of new onset heart failure with
463 preserved vs. reduced ejection fraction in a community-based cohort: 11-year follow-up of
464 PREVEND. *Eur Heart J* (2013); **34**: 1424-1431.

465 Burnham KP, Anderson DR and Huyvaert KP. AIC model selection and multimodel inference in behavioral
466 ecology: some background, observations, and comparisons. *Behav Ecol Sociobiol* (2011); **65**: 23-35.

467 Carabello BA. Evolution of the study of left ventricular function - Everything old is new again. *Circulation*
468 (2002); **105**: 2701-2703.

- 469 Chung AK, Das SR, Leonard D, et al. Women have higher left ventricular ejection fractions than men
470 independent of differences in left ventricular volume - The Dallas Heart Study. *Circulation* (2006);
471 **113**: 1597-1604.
- 472 Cohn JN, Ferrari R and Sharpe N. Cardiac remodeling--concepts and clinical implications: a consensus paper
473 from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac
474 Remodeling. *J Am Coll Cardiol* (2000); **35**: 569-582.
- 475 Cook C, Cole G, Asaria P, et al. The annual global economic burden of heart failure. *Int J Cardiol* (2014);
476 **171**: 368-376.
- 477 Curran-Everett D. Explorations in statistics: the analysis of ratios and normalized data. *Adv Physiol Educ*
478 (2013); **37**: 213-219.
- 479 Davies MK, Hobbs FDR, Davis RC, et al. Prevalence of left-ventricular systolic dysfunction and heart
480 failure in the Echocardiographic Heart of England Screening study: a population based study. *Lancet*
481 (2001); **358**: 439-444.
- 482 Desai AS, Lewis EF, Li R, et al. Rationale and design of the treatment of preserved cardiac function heart
483 failure with an aldosterone antagonist trial: a randomized, controlled study of spironolactone in
484 patients with symptomatic heart failure and preserved ejection fraction. *Am Heart J* (2011); **162**:
485 966-972 e910.
- 486 Dewey FE, Rosenthal D, Murphy DJ, Jr., et al. Does size matter? Clinical applications of scaling cardiac size
487 and function for body size. *Circulation* (2008); **117**: 2279-2287.
- 488 Dunlay SM, Roger VL and Redfield MM. Epidemiology of heart failure with preserved ejection fraction.
489 *Nat Rev Cardiol* (2017); **14**: 591-602.
- 490 Friedewald WT, Levy RI and Fredrickson DS. Estimation of the concentration of low-density lipoprotein
491 cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* (1972); **18**: 499-502.
- 492 George K, Sharma S, Batterham A, et al. Allometric analysis of the association between cardiac dimensions
493 and body size variables in 464 junior athletes. *Clin Sci* (2001); **100**: 47-54.
- 494 Goldberg LR and Jessup M. Stage B heart failure: management of asymptomatic left ventricular systolic
495 dysfunction. *Circulation* (2006); **113**: 2851-2860.

- 496 Gori M, Lam CS, Gupta DK, et al. Sex-specific cardiovascular structure and function in heart failure with
497 preserved ejection fraction. *Eur J Heart Fail* (2014); **16**: 535-542.
- 498 Habibi M, Chahal H, Opdahl A, et al. Association of CMR-measured LA function with heart failure
499 development: results from the MESA study. *JACC Cardiovasc Imaging* (2014); **7**: 570-579.
- 500 Kalogeropoulos AP and Butler J. Left ventricular ejection fraction in patients with acute heart failure: a
501 limited tool? *Rev Esp Cardiol (Engl Ed)* (2017); **70**: 318-319.
- 502 Kitzman DW, Little WC, Brubaker PH, et al. Pathophysiological characterization of isolated diastolic heart
503 failure in comparison to systolic heart failure. *JAMA* (2002); **288**: 2144-2150.
- 504 Konstam MA. "Systolic and diastolic dysfunction" in heart failure? Time for a new paradigm. *J Card Fail*
505 (2003); **9**: 1-3.
- 506 Laird N. Further comparative analyses of pretest-posttest research designs. *Am Stat* (1983); **37**: 329-330.
- 507 Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by
508 echocardiography in adults: an update from the American Society of Echocardiography and the
509 European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* (2015); **28**: 1-39 e14.
- 510 Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from
511 serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group.
512 *Ann Intern Med* (1999); **130**: 461-470.
- 513 Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern*
514 *Med* (2009); **150**: 604-612.
- 515 Li JK-J. *Comparative Cardiovascular Dynamics of Mammals* (1996). Boca Raton, FL: CRC Press; 59-73.
- 516 Liu CY, Liu YC, Wu C, et al. Evaluation of age-related interstitial myocardial fibrosis with cardiac magnetic
517 resonance contrast-enhanced T1 mapping: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am*
518 *Coll Cardiol* (2013); **62**: 1280-1287.
- 519 Martinez-Selles M, Doughty RN, Poppe K, et al. Gender and survival in patients with heart failure:
520 interactions with diabetes and aetiology. Results from the MAGGIC individual patient meta-
521 analysis. *Eur J Heart Fail* (2012); **14**: 473-479.

- 522 Meta-analysis Global Group in Chronic Heart F. The survival of patients with heart failure with preserved or
523 reduced left ventricular ejection fraction: an individual patient data meta-analysis. *Eur Heart J*
524 (2012); **33**: 1750-1757.
- 525 Natori S, Lai S, Finn JP, et al. Cardiovascular function in multi-ethnic study of atherosclerosis: normal
526 values by age, sex, and ethnicity. *AJR Am J Roentgenol* (2006); **186**: S357-365.
- 527 Packard GC. The essential role for graphs in allometric analysis. *Biol J Linn Soc* (2017); **120**: 468-473.
- 528 Packard GC. Is complex allometry in field metabolic rates of mammals a statistical artifact? *Comp Biochem*
529 *Physiol Part A Mol Integr Physiol* (2017); **203**: 322-327.
- 530 Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. *N*
531 *Engl J Med* (2014); **370**: 1383-1392.
- 532 Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute
533 and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart
534 failure of the European Society of Cardiology (ESC) developed with the special contribution of the
535 Heart Failure Association (HFA) of the ESC. *Eur Heart J* (2016); **37**: 2129-2200.
- 536 Salton CJ, Chuang ML, O'Donnell CJ, et al. Gender differences and normal left ventricular anatomy in an
537 adult population free of hypertension. A cardiovascular magnetic resonance study of the
538 Framingham Heart Study Offspring cohort. *J Am Coll Cardiol* (2002); **39**: 1055-1060.
- 539 Shah AM, Claggett B, Sweitzer NK, et al. Cardiac structure and function and prognosis in heart failure with
540 preserved ejection fraction: findings from the echocardiographic study of the Treatment of Preserved
541 Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) Trial. *Circ Heart Fail*
542 (2014); **7**: 740-751.
- 543 Solomon SD, Claggett B, Lewis EF, et al. Influence of ejection fraction on outcomes and efficacy of
544 spironolactone in patients with heart failure with preserved ejection fraction. *Eur Heart J* (2016); **37**:
545 455-462.
- 546 Stokke TM, Hasselberg NE, Smedsrud MK, et al. Geometry as a confounder when assessing ventricular
547 systolic function: comparison between ejection fraction and strain. *J Am Coll Cardiol* (2017); **70**:
548 942-954.

- 549 Tanner JM. Fallacy of per-weight and per-surface area standards, and their relation to spurious correlation. *J*
550 *Appl Physiol* (1949); **2**: 1-15.
- 551 Townsend N, Bhatnagar P, Wilkins E, et al. Cardiovascular disease statistics, 2015. *British Heart*
552 *Foundation: London* (2015).
- 553 Vanderburgh PM. Two important cautions in the use of allometric scaling: the common exponent and group
554 difference principles. *Meas Phys Educ Exerc Sci* (1998); **2**: 153-163.
- 555 Yeboah J, Rodriguez CJ, Stacey B, et al. Prognosis of individuals with asymptomatic left ventricular systolic
556 dysfunction in the multi-ethnic study of atherosclerosis (MESA). *Circulation* (2012); **126**: 2713-
557 2719.
- 558 Yeon SB, Salton CJ, Gona P, et al. Impact of age, sex, and indexation method on MR left ventricular
559 reference values in the Framingham Heart Study offspring cohort. *J Magn Reson Imaging* (2015);
560 **41**: 1038-1045.
- 561 Ziaieian B and Fonarow GC. Epidemiology and aetiology of heart failure. *Nat Rev Cardiol* (2016); **13**: 368-
562 378.
- 563
- 564
- 565
- 566
- 567
- 568
- 569
- 570
- 571
- 572
- 573
- 574
- 575
- 576
- 577

578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603

Table Legends

Table 1. Summary data for the study participants in MESA and TOPCAT stratified by sex.

Figure Legends

Figure 1. Scatterplots showing the inverse relationship between the ratioetric EF and EDV in MESA (a), $r = -0.67$ (95%CI: -0.76 to -0.55) and TOPCAT (b), $r = -0.41$ (95%CI: -0.46 to -0.35), and linear bivariate relationship between SV and EDV in MESA (c), $r = 0.68$ (95%CI: 0.57 to 0.77), Y-intercept = 44 mL (95%CI: 34 mL to 54 mL) and TOPCAT (d), $r = 0.88$ (95%CI: 0.86 to 0.89), Y-intercept = 13 mL (95%CI: 11 mL to 14 mL).

Figure 2. Scatterplots showing the allometric relationship SV and EDV from the multivariable model, $SV = 1.75 \cdot EDV^{0.78}$ in MESA (a), and $SV = 1.22 \cdot EDV^{0.86}$ in TOPCAT (b), and raw residuals against the predicted values from the 2-parameter power function with normal, heteroscedastic error in MESA (c) and TOPCAT (d) samples.

Supplemental Material Legends

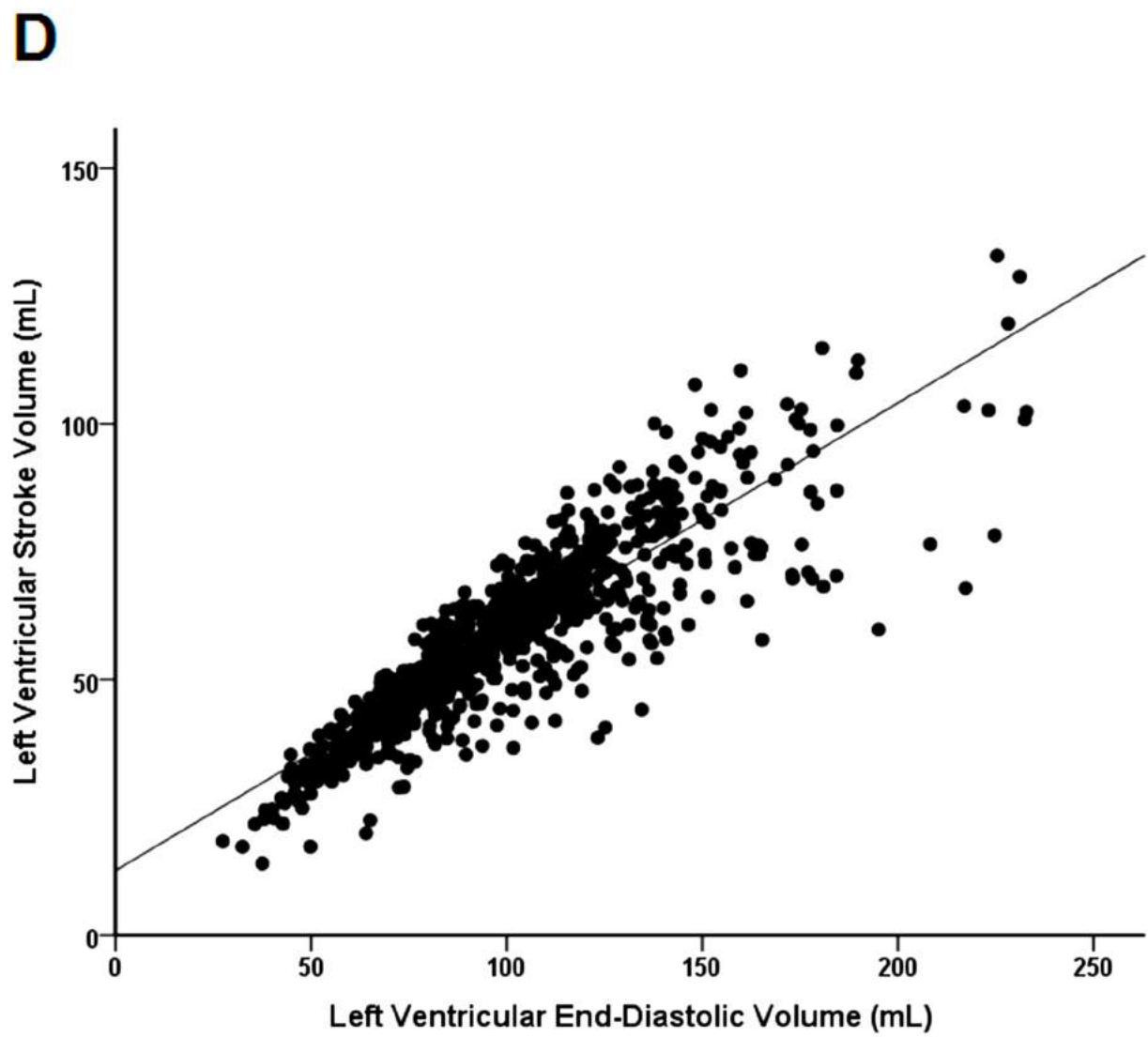
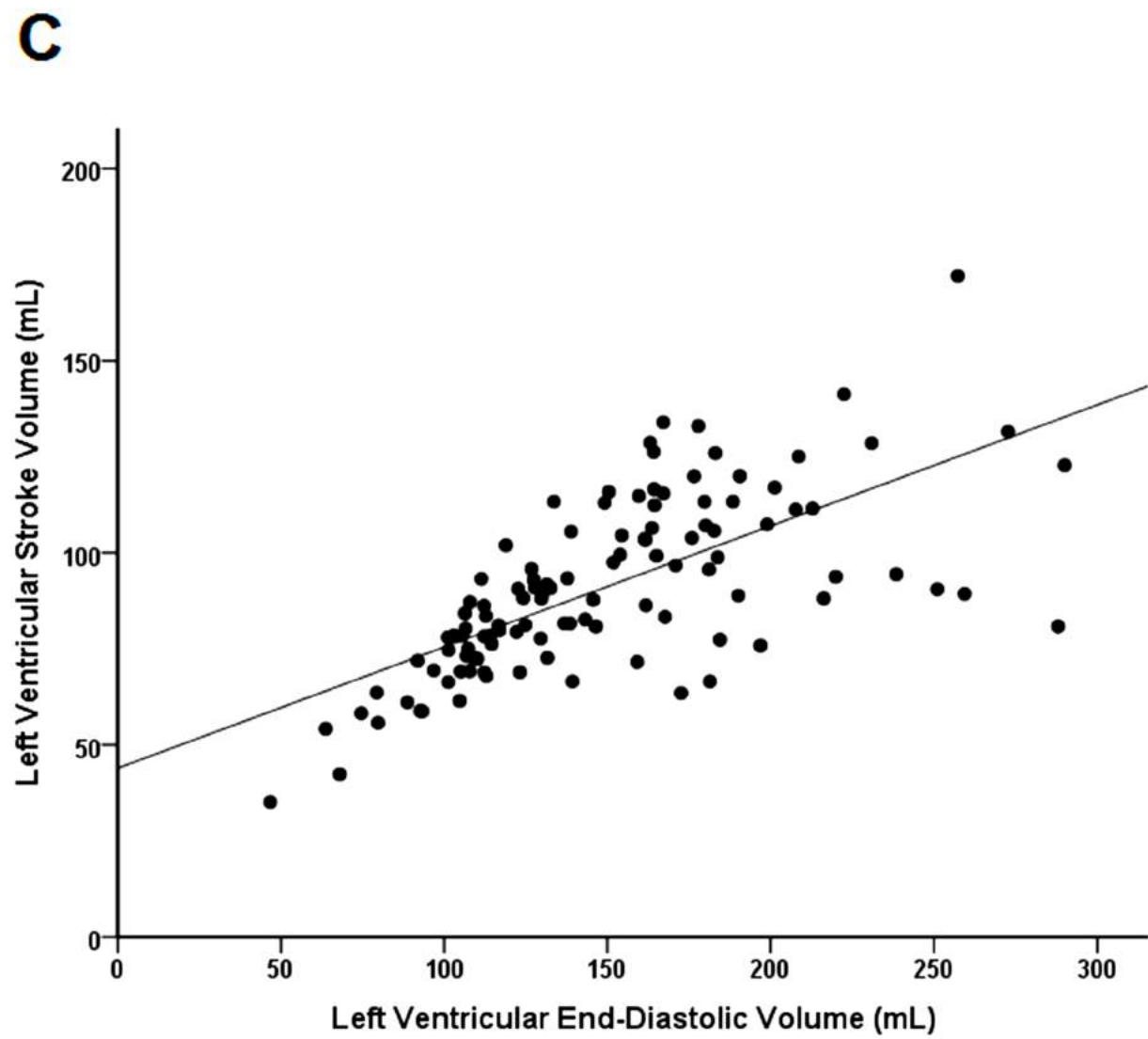
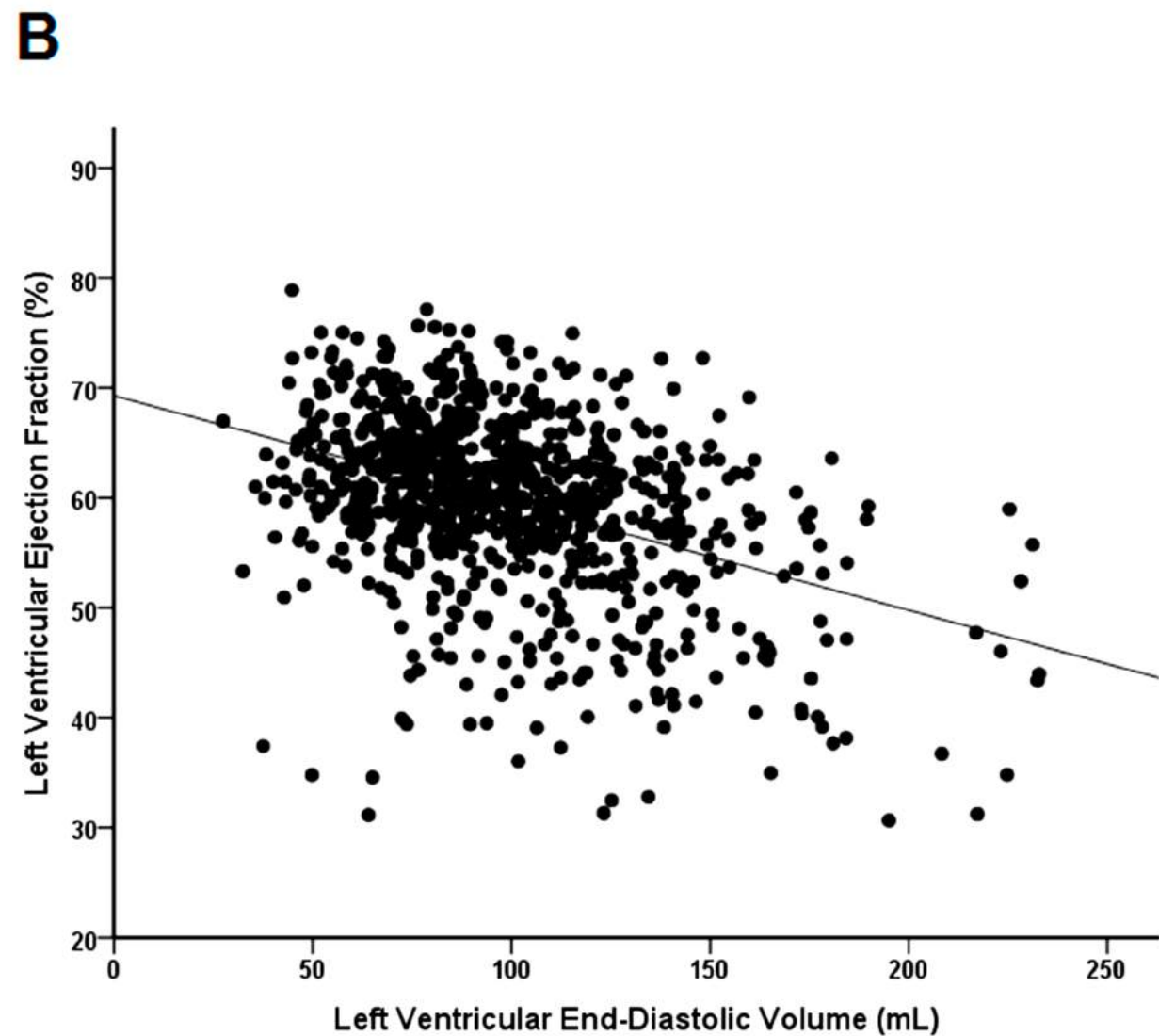
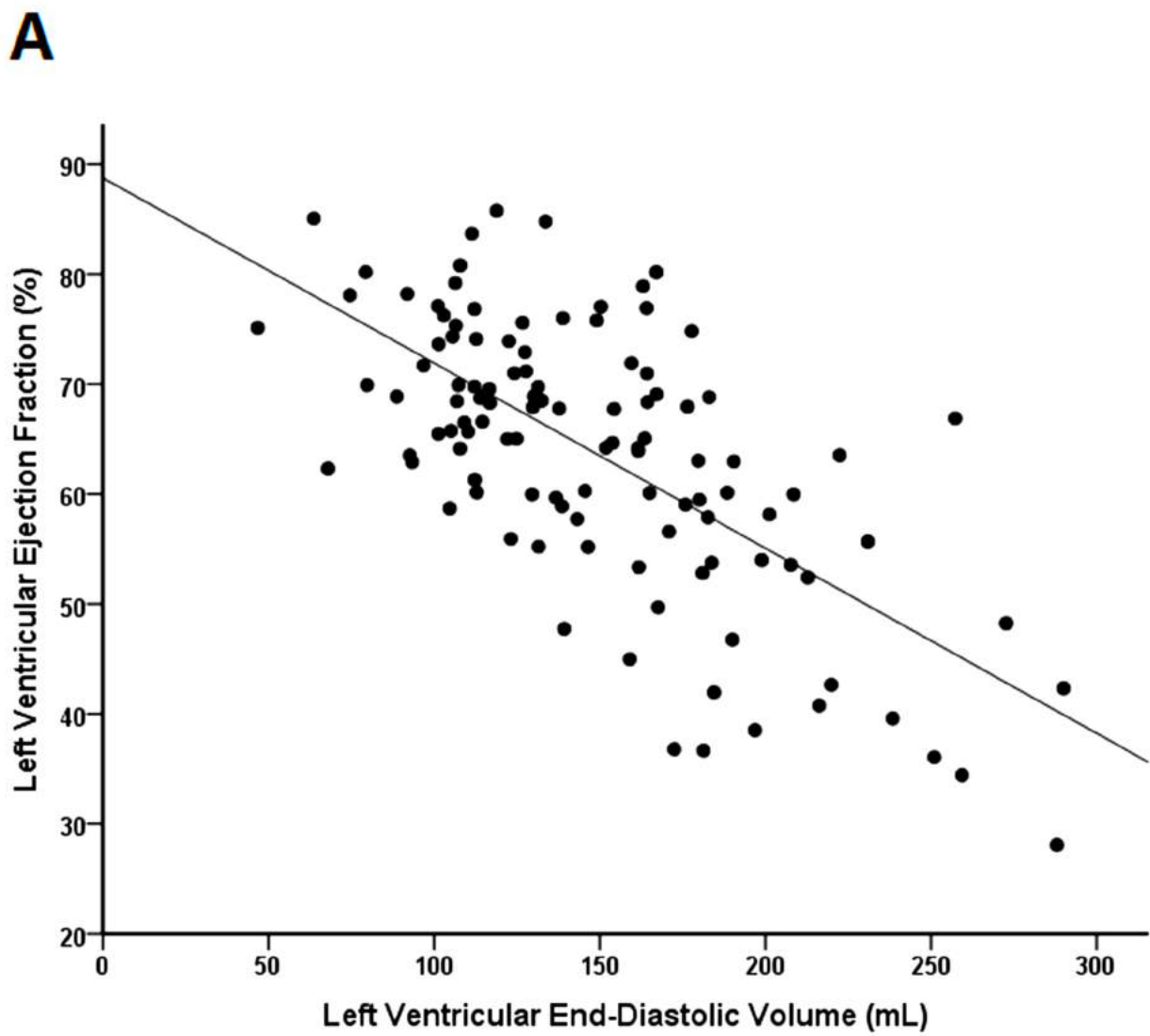
Supplemental Table 1. Statistical models fitted to untransformed data for left ventricular stroke volume and end-diastolic volume in the MESA.

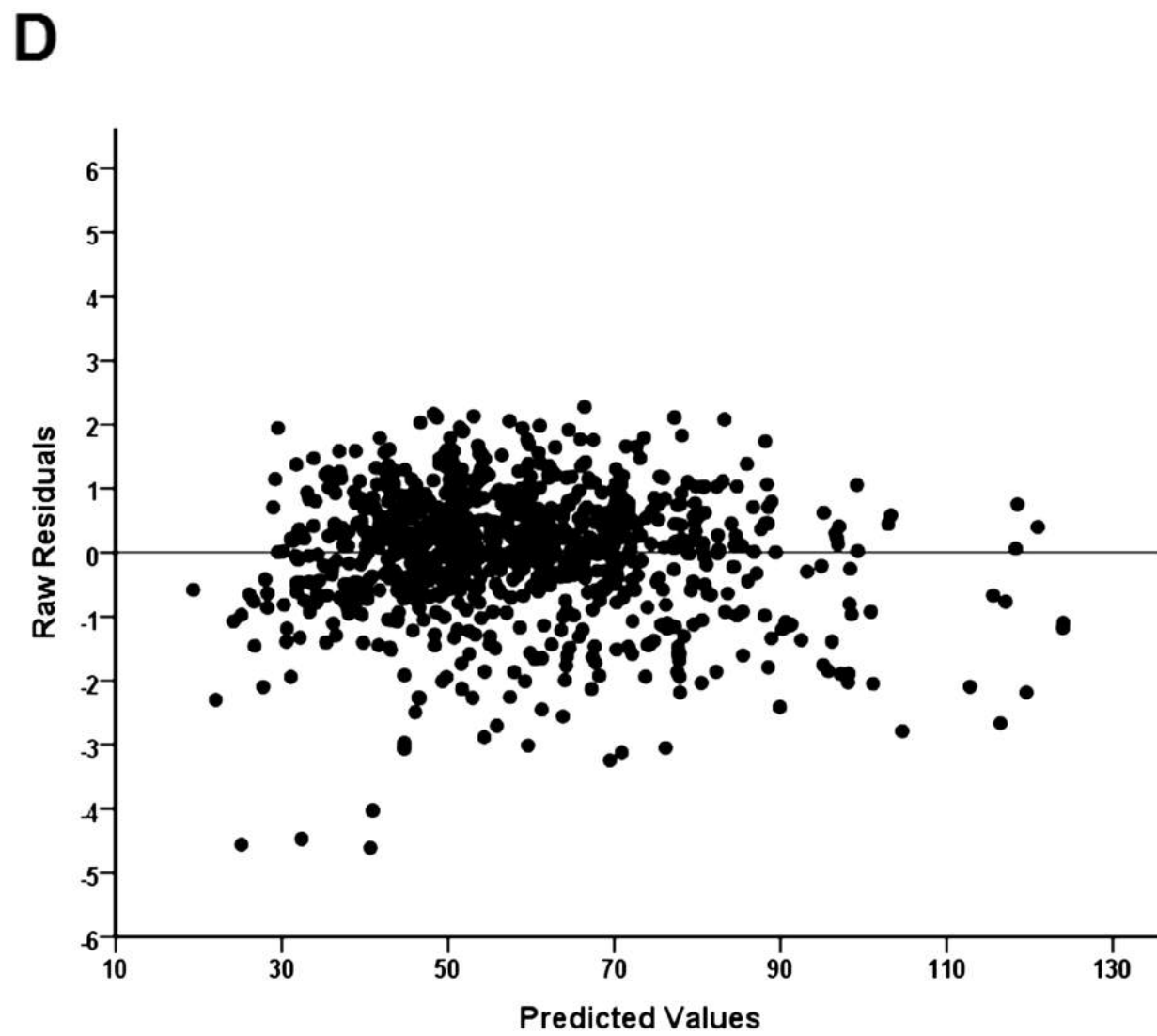
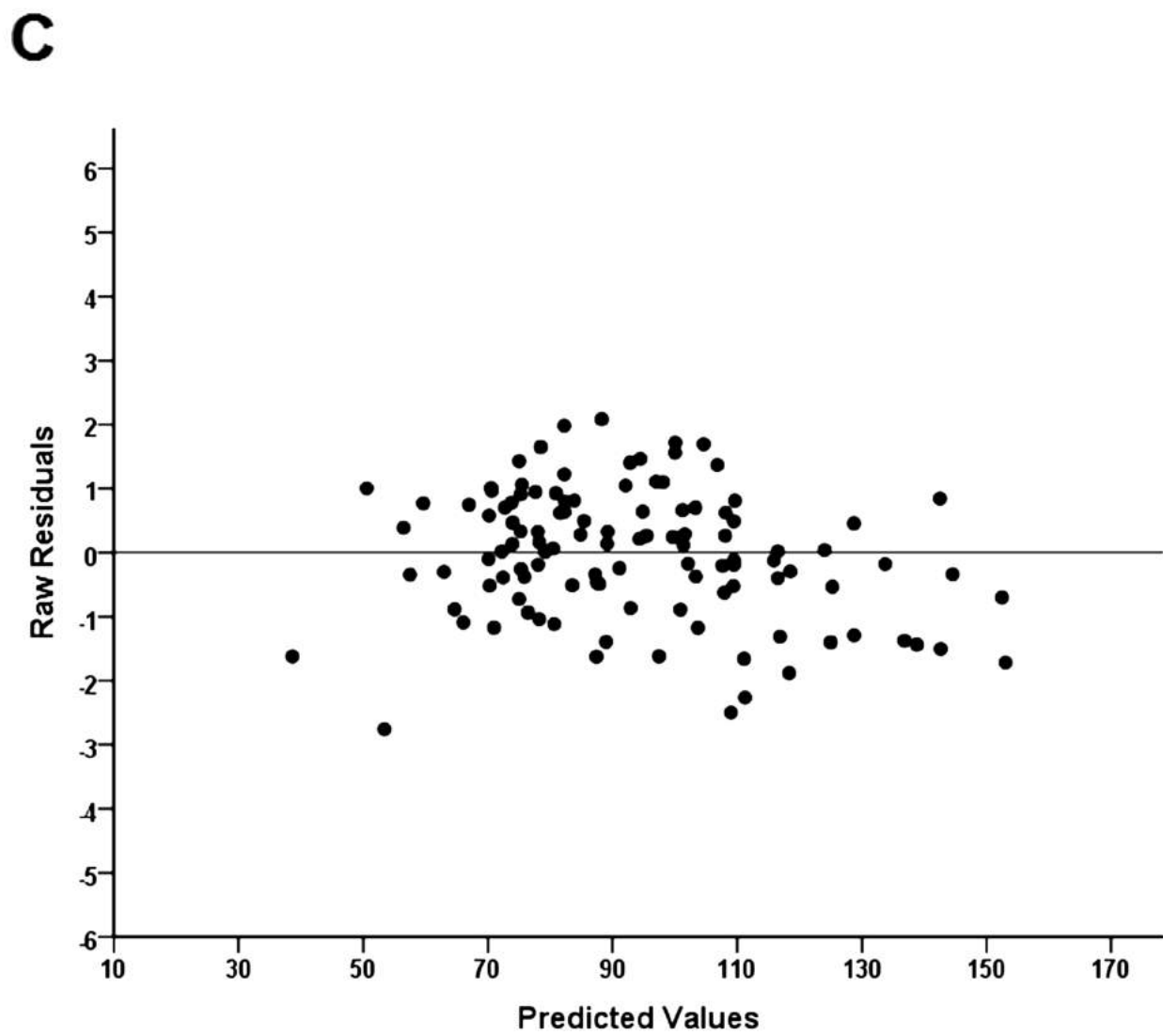
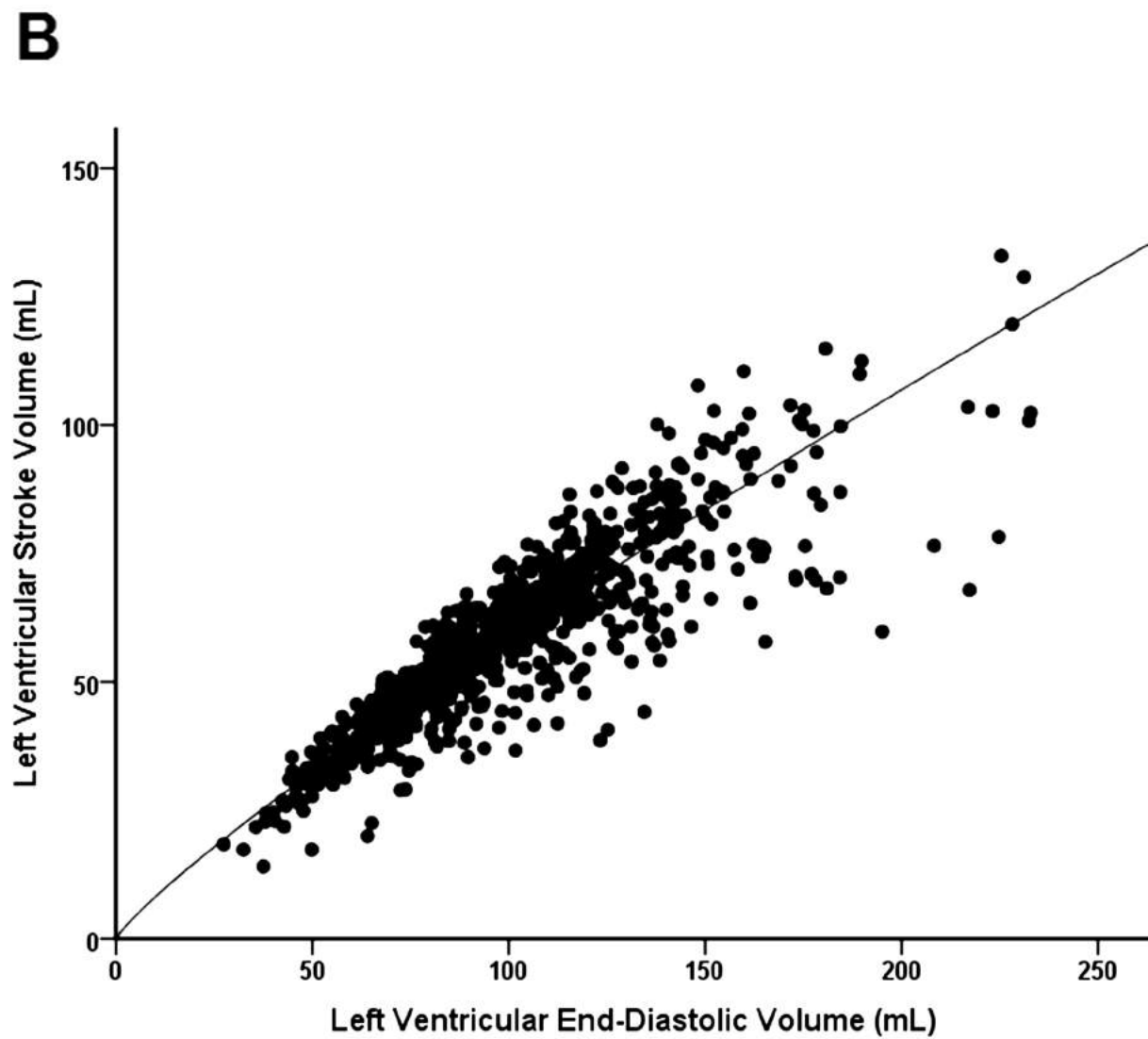
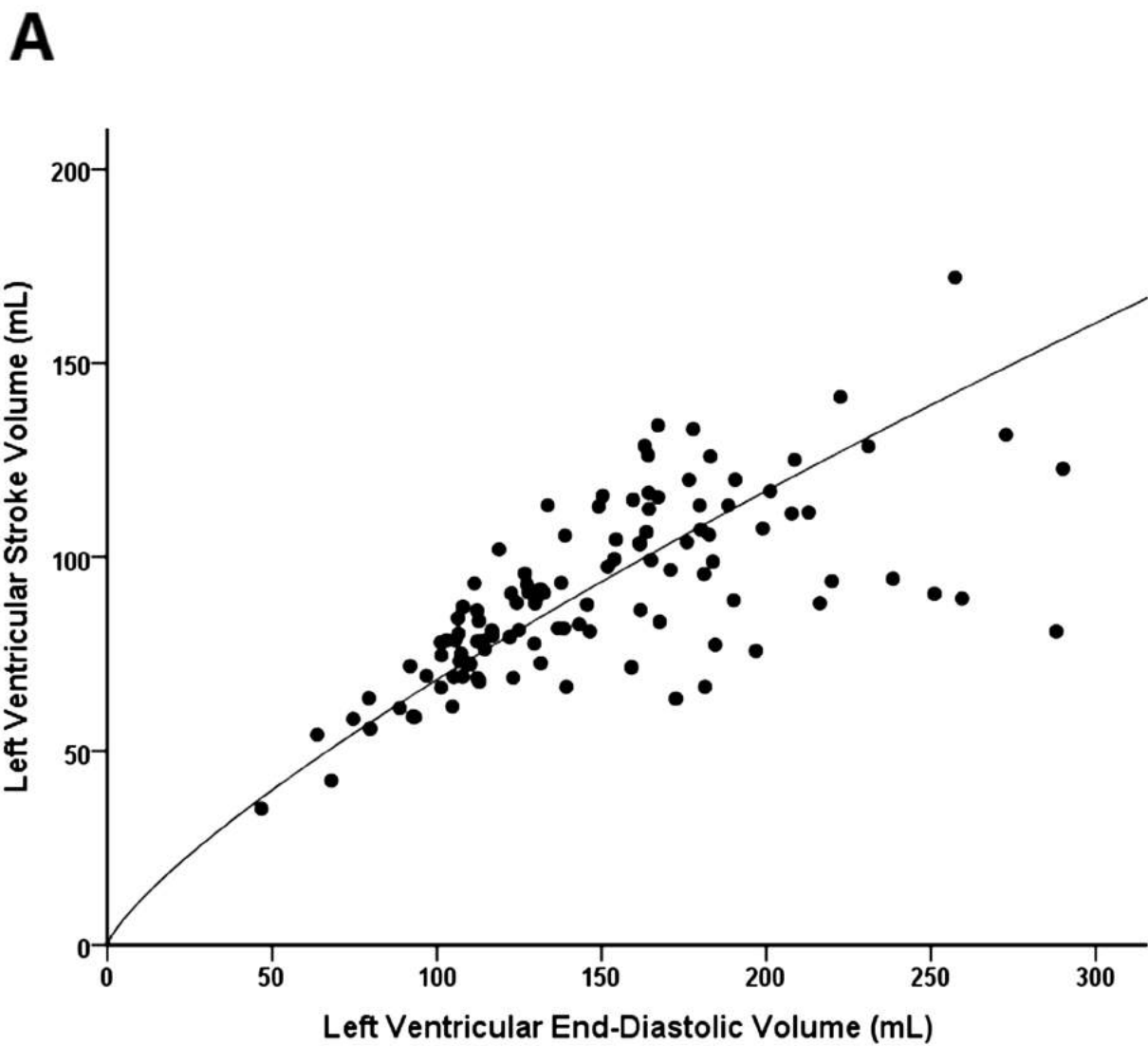
Supplemental Table 2. Statistical models fitted to untransformed data for left ventricular stroke volume and end-diastolic volume in the TOPCAT echocardiographic sub-study.

Table 1. Summary data for the study participants in MESA and TOPCAT stratified by sex.

Variable	MESA		TOPCAT	
	Men (n = 75)	Women (n = 37)	Men (n = 433)	Women (n = 431)
Age, y	68.3 ± 8.0	68.5 ± 8.5	69.5 ± 9.5	70.5 ± 9.8
Weight, kg	85.6 ± 15.6	75.3 ± 15.6	95.8 ± 21.8	84.7 ± 21.5
Height, cm	173.4 ± 7.6	159.6 ± 7.0	174.2 ± 8.2	159.8 ± 7.6 ‡
Waist circumference, cm	102.2 ± 11.8	99.7 ± 15.9	107.3 ± 16.2	102.6 ± 15.2 ‡
BMI, kg/m ²	28.4 ± 4.4	29.6 ± 6.0	31.4 ± 6.2	33.1 ± 7.8 ‡
Diabetes mellitus, n (%)	18 (24)	11 (30)	176 (41)	157 (36)
eGFR, mL/min/1.73m ²	72.2 ± 20.6	69.1 ± 18.4	69.1 ± 20.6	63.3 ± 19.7
Systolic blood pressure, mmHg	135 ± 20	143 ± 22	127 ± 14 ‡	130 ± 15
Diastolic blood pressure, mmHg	74 ± 11	72 ± 11	73 ± 11 ‡	74 ± 11
Heart rate, beats/min	64 ± 11	70 ± 12	68 ± 12	69 ± 11
LV mass, g	206 ± 54	149 ± 45	244 ± 68 ‡	193 ± 59 ‡
LV end-diastolic volume, mL	163 ± 49	121 ± 34	112 ± 34	86 ± 28
LV end-systolic volume, mL	66 ± 39	42 ± 29	48 ± 22	34 ± 16
LV stroke volume, mL	97 ± 23	79 ± 17	64 ± 17	52 ± 15
Adjusted LV stroke volume, mL *	90 ± 15	92 ± 16	58 ± 8	58 ± 7
Ratiometric EF, (%)	61.8 ± 11.5	67.5 ± 12.8	58.3 ± 8.4	61.0 ± 7.3
Normalized EF, (%) *	63.1 ± 10.3	64.8 ± 10.9	59.4 ± 8.1	59.9 ± 7.0
Normalized EF, mL/mL (%) †	186.4 ± 30.4	191.4 ± 32.2	111.8 ± 15.2	112.7 ± 13.2

Data are presented as mean ± SD for continuous variables, and frequency or percentages for categorical variables. *: 2-parameter power function with normal, heteroscedastic error; †: power function ratio; ‡: indicates missing observations; EF: left ventricular ejection fraction; BMI: body-mass index; eGFR: estimated glomerular filtration rate; LV: left ventricular. The normalized parameters of systolic function (footnote *) were derived directly from the model residuals working in the raw arithmetic data space, with the ratiometric EF or LV stroke volume as the dependent variable and LV end-diastolic volume, chronological age, and sex as predictors. Each participant's residual was added to the predicted mean ratio at the mean LV end-diastolic volume in the whole sample, to obtain an adjusted EF or LV stroke volume free from the influence of LV end-diastolic volume (Albrecht *et al.*, 1993; Laird 1983). The normalized index (footnote †) was directly derived from the ratio of LV stroke volume to end-diastolic volume raised to the power of 0.78 and 0.86 in the MESA and TOPCAT samples, respectively.





Supplemental Table 1. Statistical models fitted to untransformed data for left ventricular stroke volume and end-diastolic volume in the MESA

Model	AIC	Δ AIC	Inference
Straight line, no intercept, with normal, homoscedastic error	959.9	50.4	no empirical support
Straight line, intercept, with normal, homoscedastic error	956.6	47.2	no empirical support
Three-parameter power function with normal, homoscedastic error Failed to converge. Re-arranged, convergence criterion changed to 0.18	949.4	40.0	no empirical support
Two-parameter power function with normal, homoscedastic error	948.3	38.8	no empirical support
Straight line, no intercept, with lognormal heteroscedastic error	945.0	35.6	no empirical support
Straight line, intercept, with lognormal heteroscedastic error	942.1	32.6	no empirical support
Two-parameter power function with lognormal, heteroscedastic error	930.9	21.4	no empirical support
Three-parameter power function with lognormal, heteroscedastic error Failed to converge. Re-arranged, convergence criterion changed to 0.16	922.8	13.3	weak support
Straight line, intercept, with normal, heteroscedastic error	918.8	9.4	weak support
Straight line, no intercept, with normal, heteroscedastic error	917.6	8.2	weak support
Three-parameter power function with normal, heteroscedastic error Failed to converge. Re-arranged, convergence criterion changed to 0.17	915.1	5.7	plausible alternative
Two-parameter power function with normal, heteroscedastic error	909.4	0	best

AIC = Akaike's information criterion; Δ AIC = Akaike difference

Supplemental Table 2. Statistical models fitted to untransformed data for left ventricular stroke volume and end-diastolic volume in the TOPCAT echocardiographic sub-study

Model	AIC	Δ AIC	Inference
Three-parameter power function with normal, homoscedastic error Failed to converge. Convergence criterion changed to 0.31	6236.8	422.8	no empirical support
Straight line, no intercept, with normal, homoscedastic error	6183.8	369.7	no empirical support
Straight line, intercept, with normal, homoscedastic error	6129.7	315.6	no empirical support
Two-parameter power function with normal, homoscedastic error	6093.7	279.6	no empirical support
Straight line, no intercept, with lognormal heteroscedastic error	6024.0	210.0	no empirical support
Three-parameter power function with normal, heteroscedastic error Failed to converge. Convergence criterion changed to 0.15	6008.2	194.2	no empirical support
Straight line, intercept, with lognormal heteroscedastic error	5989.8	175.8	no empirical support
Two-parameter power function with lognormal, heteroscedastic error	5958.3	144.2	no empirical support
Three-parameter power function with lognormal, heteroscedastic error	5917.5	103.4	no empirical support
Straight line, no intercept, with normal, heteroscedastic error	5871.5	57.4	no empirical support
Straight line, intercept, with normal, heteroscedastic error	5842.5	28.5	no empirical support
Two-parameter power function with normal, heteroscedastic error	5814.1	0	best

AIC = Akaike's information criterion; Δ AIC = Akaike difference