Adjusting Cardiac MRI Measures for Body Size

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Outline

- Cardiac MRI (magnetic resonance imaging) in MESA
- Traditional approach to analyzing cardiac MRI measures
- Problems with existing indices for body size
- Proposed LV mass index

Cardiac MRI in MESA

- MESA is the first large-scale application of cardiac MRI in a multi-center study and in a multi-ethnic population

- 4987 participants obtained cardiac MRI procedures at Exam 1

- 1700 participants scheduled for cardiac MRI at Exam 4

- MRI of the heart provides accurate, reproducible, and non-invasive measures of subclinical cardiovascular disease:
  - Left ventricular (LV) mass
  - LV end-diastolic and end-systolic volumes
  - LV systolic function

LV Mass measured by Cardiac MRI

Does not rely on geometric assumptions about the shape of the ventricle, unlike echocardiography and cineangiocardiography

- Obtain a series of image sequences (slices) of the heart
- Manually trace endocardial and epicardial contour on each image slice during end-diastole
- myocardial area = area between epicardial contour and endocardial contour
- myocardial volume = myocardial area $\times$ (slice + gap thickness)
- LV mass = (sum of myocardial volumes) $\times$ myocardial density

$$\text{myocardial density} = 1.05 \text{ g/ml}$$

Current Questions of Interest in MESA

- MC 004 (Heckbert et al.): What is the association between cardiac MRI measures and traditional cardiovascular risk factors?

- MC 005 (Bluemke et al.): What is the association between cardiac MRI measures and age, ethnicity, and gender?

- MC 015 (Arnett et al.): What is the association between novel cardiovascular risk factors and cardiac MRI measures?

Traditional approaches to analyzing LV measures

- LV measures (by echocardiography) have traditionally been indexed by body size to "adjust for the effect of body size"
  - LV measure/height
  - LV measure/height$^{2.7}$
  - LV measure/BSA, where BSA = body surface area
- Since cardiac MRI is relatively new, there is not yet a standard for analyzing LV measures (determined by cardiac MRI)

If the LV measure indexed by BSA, height or height$^{2.7}$ is a physiological quantity of interest, then analysis of that quantity is fine.

If the purpose is to adjust for body size, problems occur.

Problems with existing indices for body size

- Different indices yield different results
- The indices are not well-defined
- The indices are still associated with body size (in "normals")

Different indices yield different results

- Outcome: Indexed unidimensional cardiac measures (e.g. end-diastolic dimension)
- Sample: 318 normotensive participants from Framingham study offspring cohort
- Results:
  - Indexed to height: men > women
  - Indexed to BSA: men < women
- Salton et al. (2002). J. Am. Coll. Cardiol. 39:1055-60

Different indices yield different results

- Outcome: Indexed LV mass
- Sample: 665 patients from the Hypertension Optimal Treatment study
- Results:
  - Indexed to body surface area: no differences among Caucasians, African-Americans, and Hispanics
  - Indexed to height or height$^{2.7}$: Hispanics > other ethnic groups
- Zabalgoitia et al. (1998). Am. J. Cardiol. 81:412-417.

Different indices yield different results

- Outcome: Indexed LV mass
- Sample: 4987 MESA participants who obtained cardiac MRI exam 1 of adequate quality
- Results:
  - Indexed to BSA: Black > Hispanic > White and Asian
  - Indexed to height: Black > Hispanic > White > Asian
  - Indexed to height$^{2.7}$: Black and Hisp > White and Asian
- Results are based on linear regression of indexed LV mass on ethnic group, gender, age, and study site

LV mass/BSA is not well-defined

- Body surface area (BSA) is not well-defined
- BSA is usually not measured directly
- In MESA, BSA is defined as:

$$\text{BSA} = 0.007184\ \text{Weight}^{0.425}\ \ \text{Height}^{0.725}$$

BSA in m^2
Weight in kg
Height in cm

Formula from DuBois and DuBois (1916). Archives of Internal Medicine 17:863-871.

DuBois and DuBois (1916) Formula for Body Surface Area

- Sample of 10 subjects
  - Anna M: “cadaver of a child 21 months old”
  - Fabian R S: “aged 12 years, 10 months, an unusually well formed boy with no signs of puberty as yet”
  - Gerald S: “18 years old, tall and much emaciated”
  - Emma W: “26 years old, a sculptor’s model”
  - R.H.S: “21 1/2 years old. An unusually tall and thin man...”
  - Robert L: “43 years old. Five years previously he had lost both legs in a railroad accident”
  - Harry J: “34 years old, colored ... As a result of his deformity he had developed a form which reminded one of a hermit crab.”

DuBois and DuBois (1916) Formula for Body Surface Area

- Measure BSA directly by enclosing 10 subjects in paper molds

- Determine BSA formula
  - Exclude 21 month female cadaver from analysis
  - Assume BSA = C Weight^{A} Height^{B}, subject to $3A + B = 2$
  - Estimate: A=0.425, B=0.725, and C=0.007184

- Our estimates and 95% CI for A, B, and C based on nonlinear regression (unconstrained):

  A=0.4088 (0.3682, 0.4493)

  B=0.6500 (0.5362, 0.7637)

  C=0.01125 (0.00526, 0.01724)

BSA= C Weight^A Height^B

- Estimates of A, B, and C:

Study	Sample Size	A	B	C
DuBois and DuBois (1916) Arch. Intern. Med. 17:863-871	9	0.425	0.725	0.007184
Boyd (1935) University of Minnesota Press	197	0.5000	0.4838	0.017827
Gehan and George (1970) Cancer Chemother. Rep. 54:225-235	401	0.4225	0.5146	0.0235

- See also Yu et al. (2003) Applied Ergonomics 34:273-278

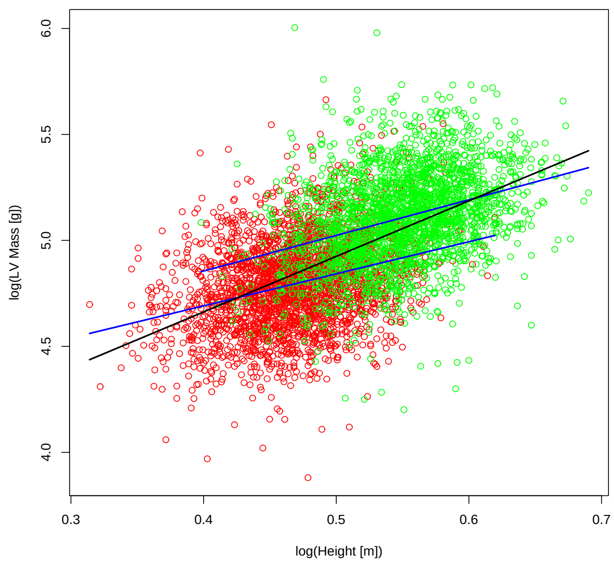
- Large variability in parameter estimates across studies

LV mass/Height$^{2.7}$

- Index derived from a model that ignores confounding by gender
- Sample: 611 non-obese, normotensive adults and children
- De Simone et al. (1992). J. Am. Coll. Cardiol. 20:1251-60
- In MESA:

  Height$^{3.0}$ (similar to Height$^{2.7}$) without gender

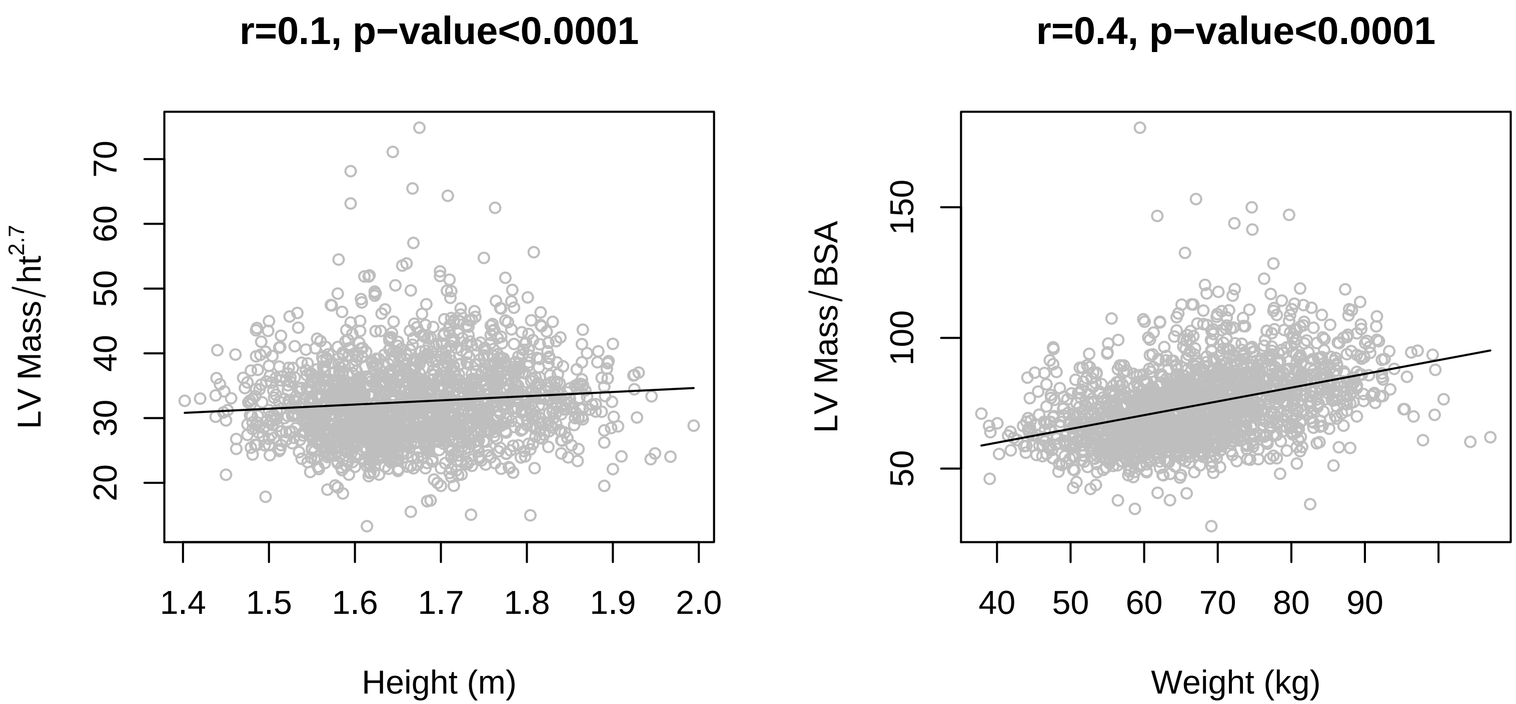
  Height$^{1.8}$ with gender



Existing indices do not remove effect of body size

- Sample: 1746 normotensive, non-obese MESA participants
- Outcome: Indexed LV mass
- Results:
  - LV mass indexed to BSA, height, or height$^{2.7}$: statistically associated with height and weight ($p<0.0001$)
- Results based on linear regression of indexed LV mass on height and weight
- Association remains significant after adjusting for gender, ethnicity, age, and study site

Existing indices are correlated with height and weight



Proposed LV Mass Index

$$\text{LV Mass Index} = \frac{\text{LV Mass}}{c_{mass}\ \text{Height}^{0.54}\ \text{Weight}^{0.61}}$$

- c_{mass}

  Females: $c_{mass} = 6.82$

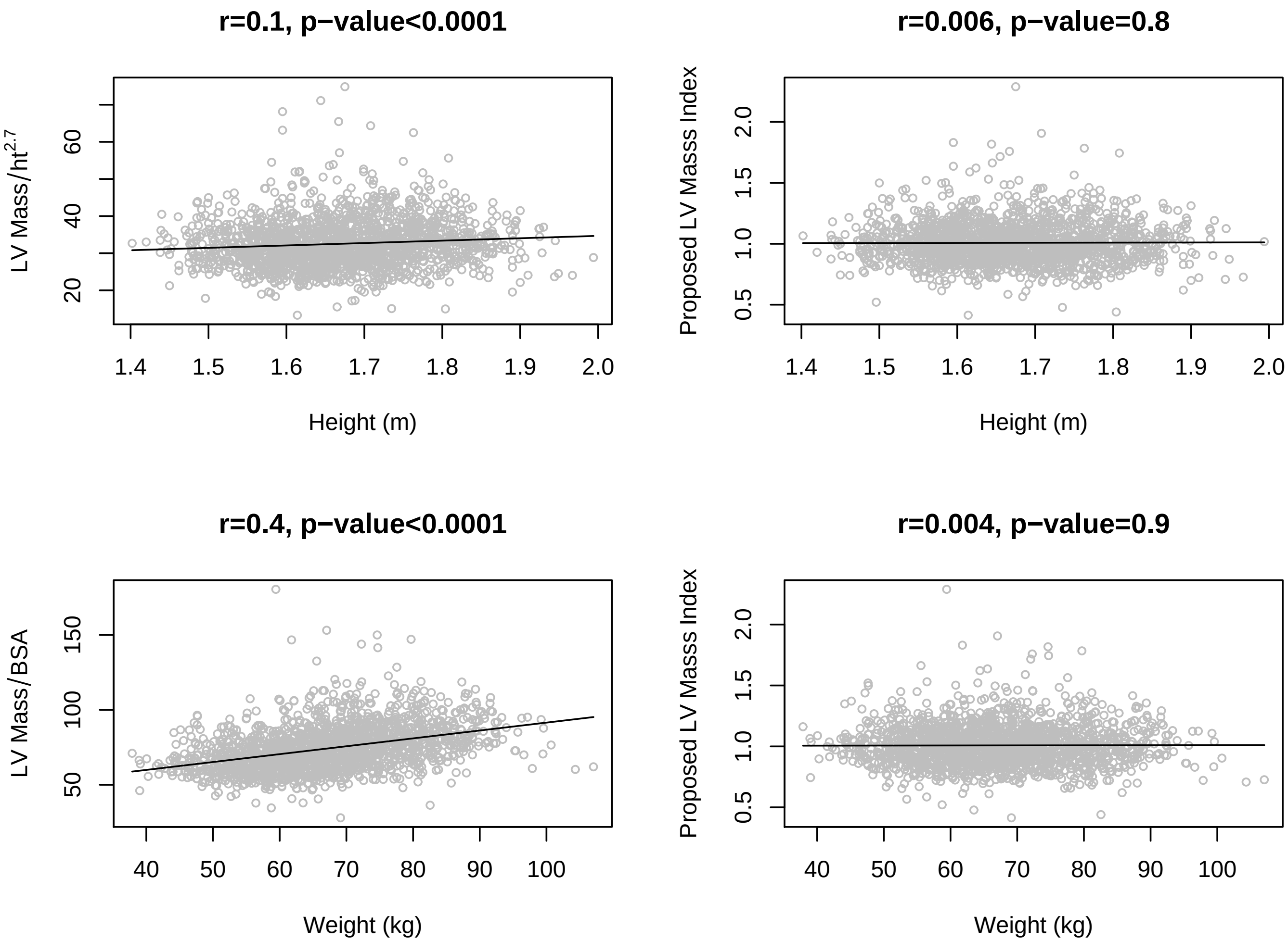
  Males: $c_{mass} = 8.25$

- LV Mass in grams
- Height in meters
- Weight in kilograms
- Derived from:
  - Sample: 1746 normotensive, non-obese MESA participants
  - Multiplicative model, estimated by regressing log(LV mass) on log(height), log(weight), and gender

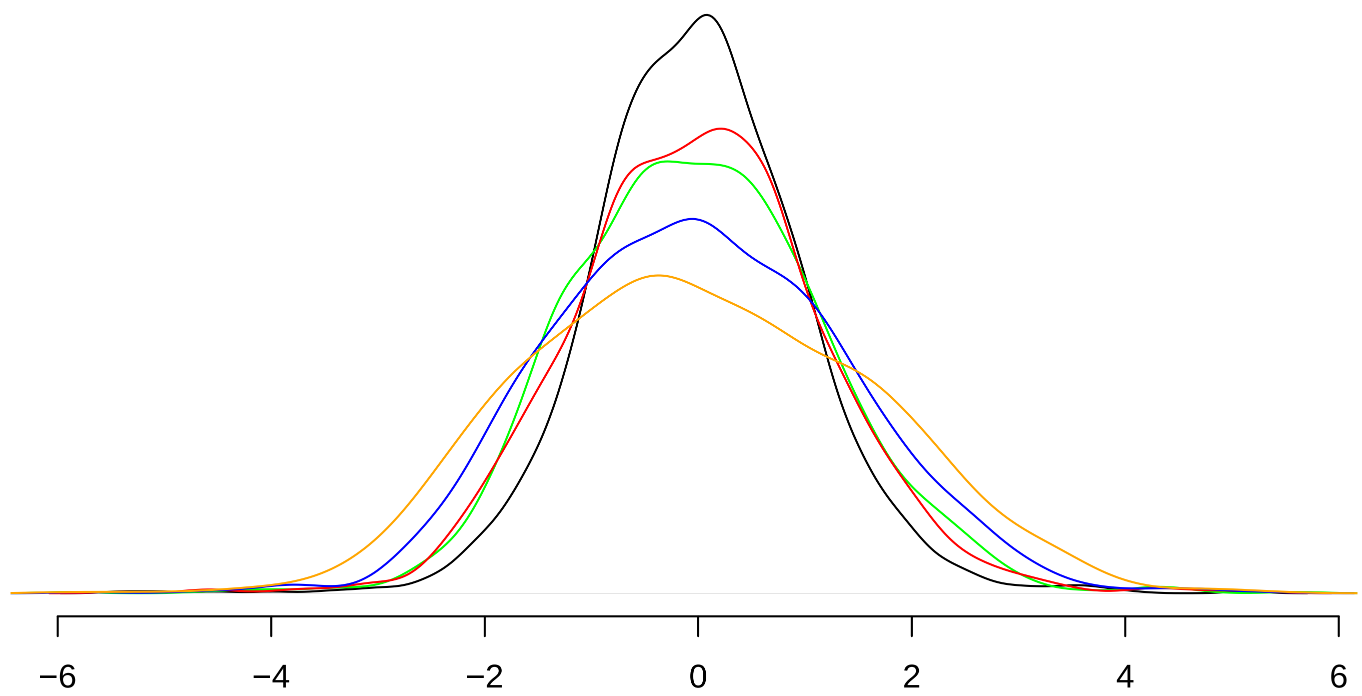
Properties of Proposed LV Mass Index

- Not statistically associated with height and weight in "normals"
  - Based on multiplicative model, by definition
  - Based on linear regression model of LV mass index on height and weight
- Adjusts for gender
- Has smaller variability than existing indices
- Easy to use
  - Cut-offs for defining LV hypertrophy are the same regardless of gender, ethnicity, and age

Proposed Index is not correlated with height or weight



Proposed LV Mass Index Compared to Existing Indices



Proposed index has smaller variability than existing indices

Using the Proposed LV Mass Index

- Clinical purposes (e.g. defining LV hypertrophy)

Transform index to standard normal distribution:

$$Z \equiv \log(\text{LV mass index})/0.1625$$

- $Z = 1.64$: LV mass index is larger than that of 95% of the "normal" population

- $Z = 1.96$: LV mass index is larger than that of 97.5% of the "normal" population

- Clinical purposes

  Use percent predicted measure:

$$\frac{\log(\text{LV mass})}{\log(c_{mass}) + 0.54 \times \log(\text{Height}) + 0.61 \times \log(\text{Weight})}$$

  - If equal to 1: LV mass is same as predicted based on body size and gender
  - If equal to 1.2: LV mass is 20% larger than predicted

- As dependent or independent variable
  - Could model index, z-score, or percent predicted measure

Summary

- LV measures are traditionally indexed by BSA, height, or height$^{2.7}$ to "adjust for the effect of body size"
- Problems with existing indices
  - Different indices yield different conclusions
  - The indices are not well-defined
  - The indices do not remove the effect of body size
- Proposed LV mass index offers several advantages
- Indices for LV volumes can be constructed in a similar manner

- Collaborators: Dick Kronmal, David Bluemke, Susan Heckbert, Greg Hundley, Joao Lima, and Hanyu Ni