Supplementary Materials

Content

Methods

Data engineering strategy

We developed a de novo data engineering pipeline for extracting outcome data from the UK Biobank called “PhenotypeConstructor”. Its core functionality revolves around processing a range of disease definitions to extract the earliest diagnosis dates for various conditions. This includes interpreting ICD diagnosis codes, self-reported diagnoses, doctor-confirmed conditions, as well as medication details, and family health history. The phenotypes, corresponding UK Biobank field names, and codes considered in this study are described in **Supplementary Table S2**.

Figure legends

Figure S1. Loadings of the eight principal components explaining 90% of the variance in the CMR measurements.

Abbreviations: EF = ejection fraction, EDV = end-diastolic volume, ESV = end-systolic volume, i = indexed, LA = left atrial, LV = left ventricular, MAPSE = mitral annular plane systolic excursion, PC = principal component, RA = right atrial, RV = right ventricular, SV = stroke volume, TAPSE = tricuspid annular plane systolic excursion, V = volume, 2Ch = in 2-chamber view.

Figure S2. Cumulative variance explained by the eight principal components explaining 90% of the CMR measurements.

Figure S3. Distribution of UK biobank participants carrying pathogenic and likely pathogenic variants in cardiomyopathy-associated genes.

Figure S4. Survival of incident atrial fibrillation based on CMR measurements.

The curves estimate cumulative incidence for atrial fibrillation categorising the CMR measurements into two groups: an 85% 'reference' group and a 15% 'risk increasing' group, based on either the 15^{th} or 85^{th} percentile of CMR measurements as the cut-off point. Each plot is annotated with the hazard ratio derived from univariable Cox regression, along with the corresponding confidence interval and p-value.

Abbreviations: EF = ejection fraction, EDV = end-diastolic volume, ESV = end-systolic volume, i = indexed, LA = left atrial, LV = left ventricular, RA = right atrial, RV = right ventricular, SV = stroke volume, TAPSE = tricuspid annular plane systolic excursion, V = volume, 4Ch = in 4-chamber view.

Figure S5. Survival of incident heart failure based on CMR measurements.

The curves estimate cumulative incidence for heart failure categorising the CMR measurements into two groups: an 85% 'reference' group and a 15% 'risk increasing' group, based on either the 15^{th} or 85^{th} percentile of CMR measurements as the cut-off point. Each plot is annotated with the hazard ratio derived from univariable Cox regression, along with the corresponding confidence interval and p-value.

Abbreviations: EF = ejection fraction, EDV = end-diastolic volume, ESV = end-systolic volume, i = indexed, LA = left atrial, LV = left ventricular, RA = right atrial, RV = right ventricular, SV = stroke volume, TAPSE = tricuspid annular plane systolic excursion, V = volume, 4Ch = in 4-chamber view.

Figure S6. Spearman correlation between the effect estimates of the analyses on complete-case and imputed data.

Figure S7. Association of CMR measurements with HCM G+ and the three most common HCM genes.

Associations are presented as $-\log_{10}$(p-value) multiplied by the effect direction. Results with a p-value smaller than 6.25×10^{-3} are indicated by a star and smaller than 0.05 are indicated with a diamond. Heterogeneity p-values did not reach statistical significance for any of the CMR measurements.

Abbreviations: CMR = cardiac magnetic resonance imaging, EF = ejection fraction, ESV = end-systolic volume, HCM = hypertrophic cardiomyopathy, i = indexed, RA = right atrial, RV = right ventricular, TAPSE = tricuspid annular plane systolic excursion, V = volume, 4Ch = in 4-chamber view.

Figure S8. Association of CMR measurements with DCM G+ and the three most common DCM genes.

Associations are presented as $-\log_{10}$(p-value) multiplied by the effect direction. Results with a p-value smaller than 6.25×10^{-3} are indicated by a star and smaller than 0.05 are indicated with a diamond. Heterogeneity p-values reached statistical significance for all of the CMR measurements.

Abbreviations: CMR = cardiac magnetic resonance imaging, DCM = dilated cardiomyopathy, EF = ejection fraction, ESV = end-systolic volume, i = indexed, LV = left ventricular.

Figure S9. Association of CMR measurements with the most common HCM genes.

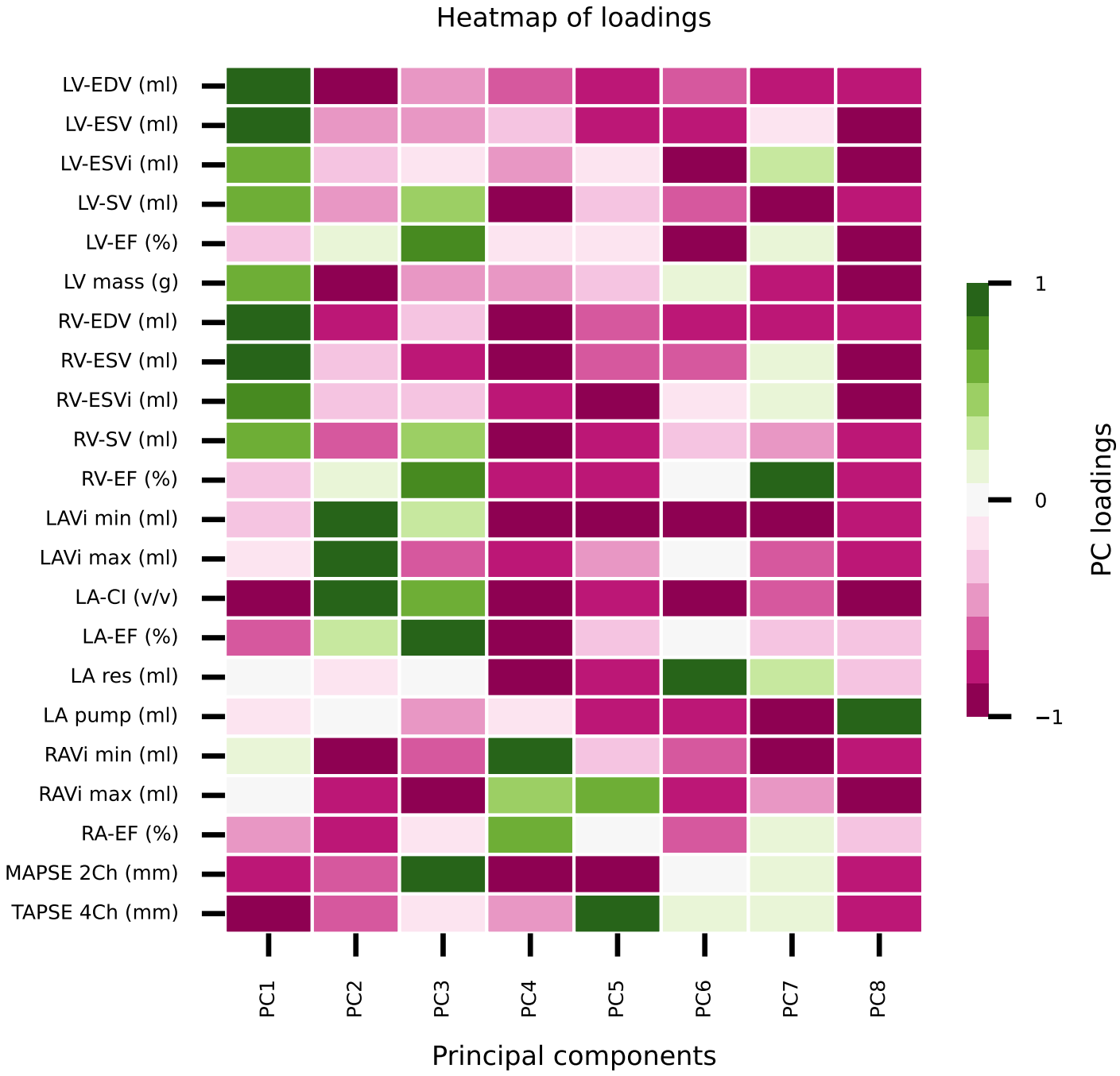
None of the associations of CMR measurements with *MYH7* reached statistical significance.

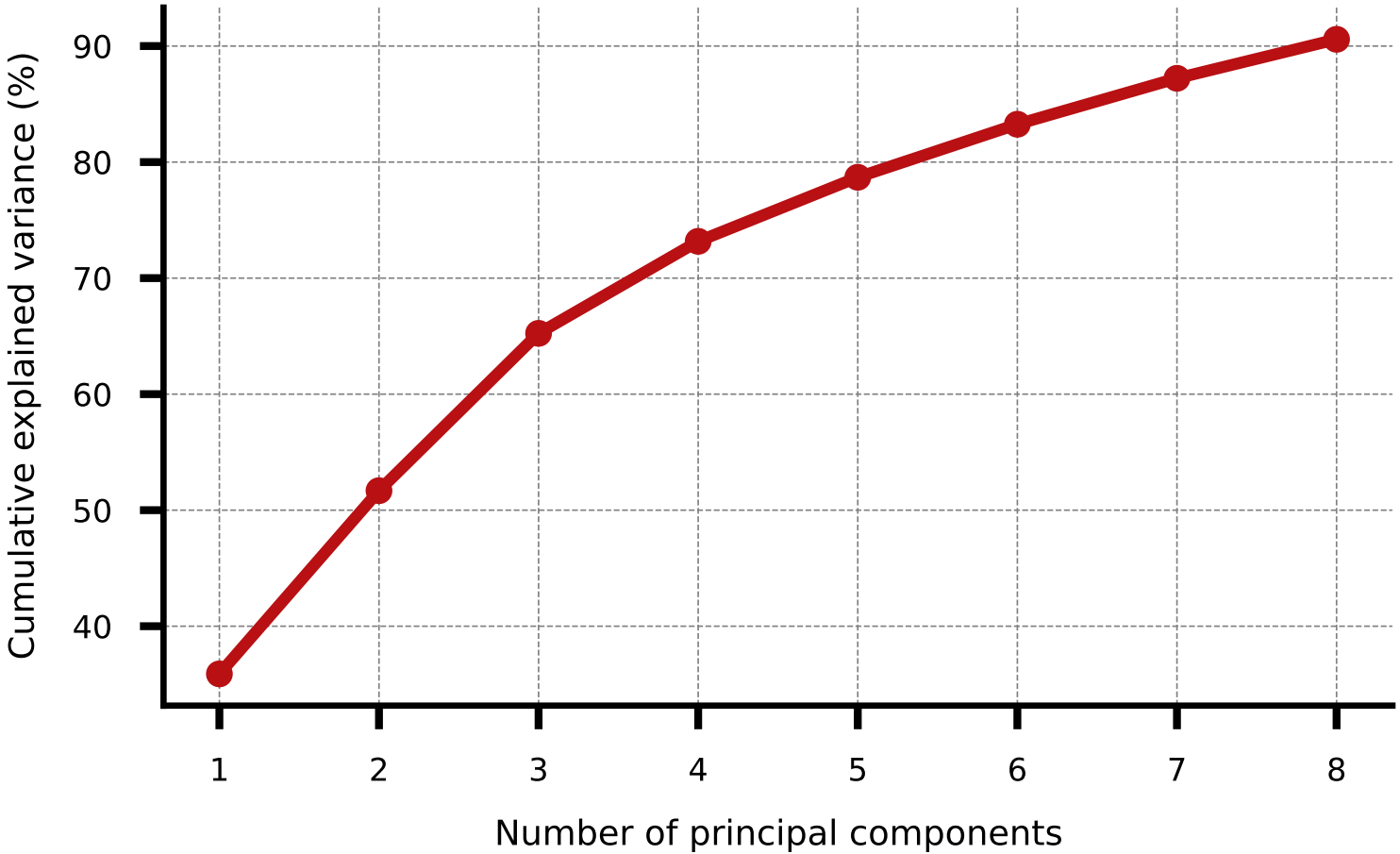
Abbreviations: CMR = cardiac magnetic resonance imaging, EF = ejection fraction, EDV = end-diastolic volume, ESV = end-systolic volume, HCM = hypertrophic cardiomyopathy, i = indexed, LV = left ventricular, MAPSE = mitral annular plane systolic excursion, OR = odds ratio, RV = right ventricular, TAPSE = tricuspid annular plane systolic excursion, 4Ch = in 4-chamber view, 95%CI = 95% confidence interval.

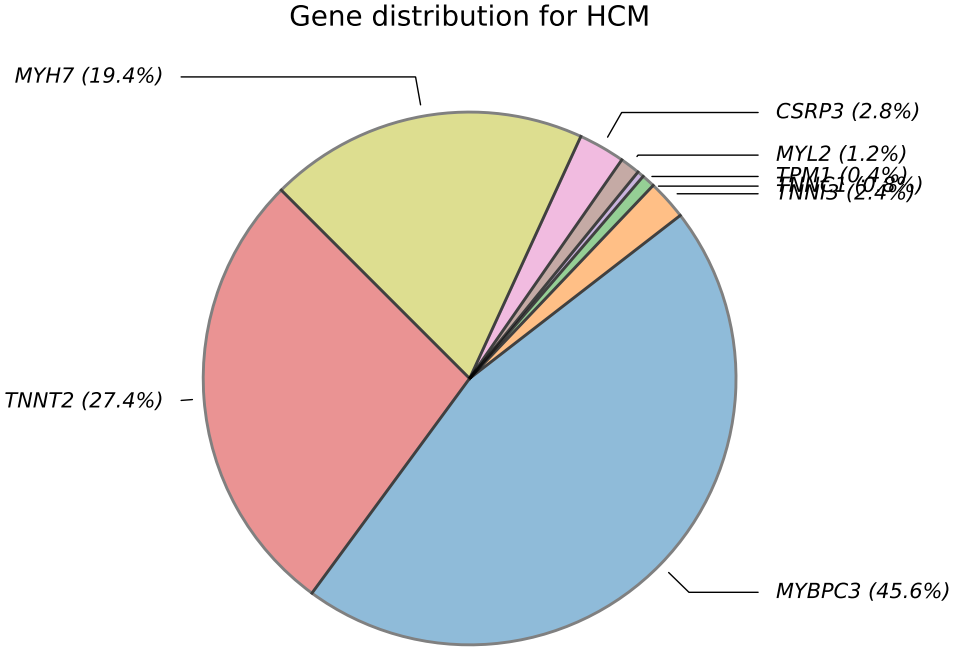
Figure S10. Association of CMR measurements with the most common DCM genes.

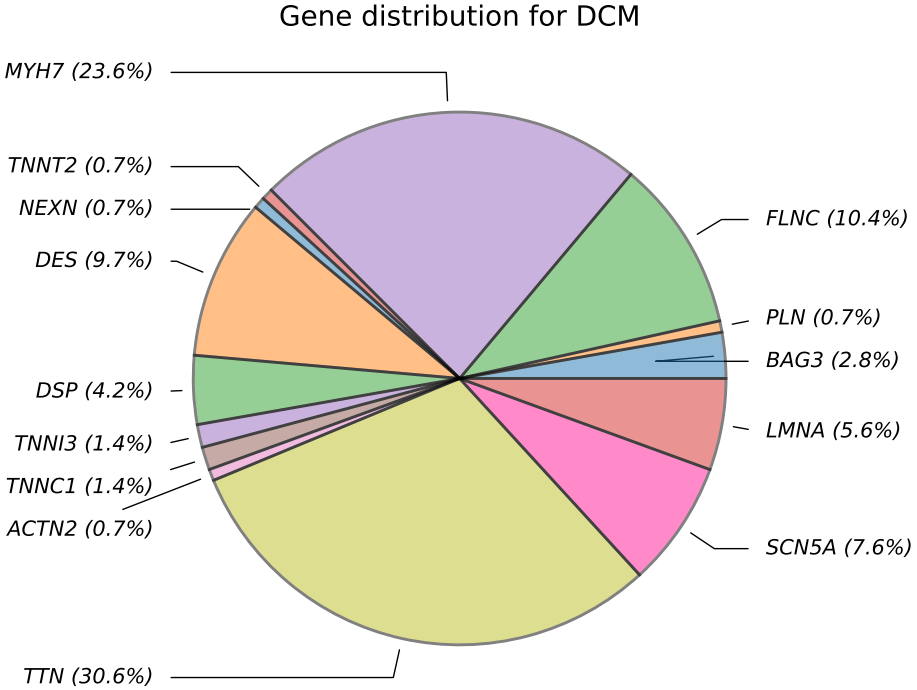
None of the associations of CMR measurements with *FLNC* reached statistical significance.

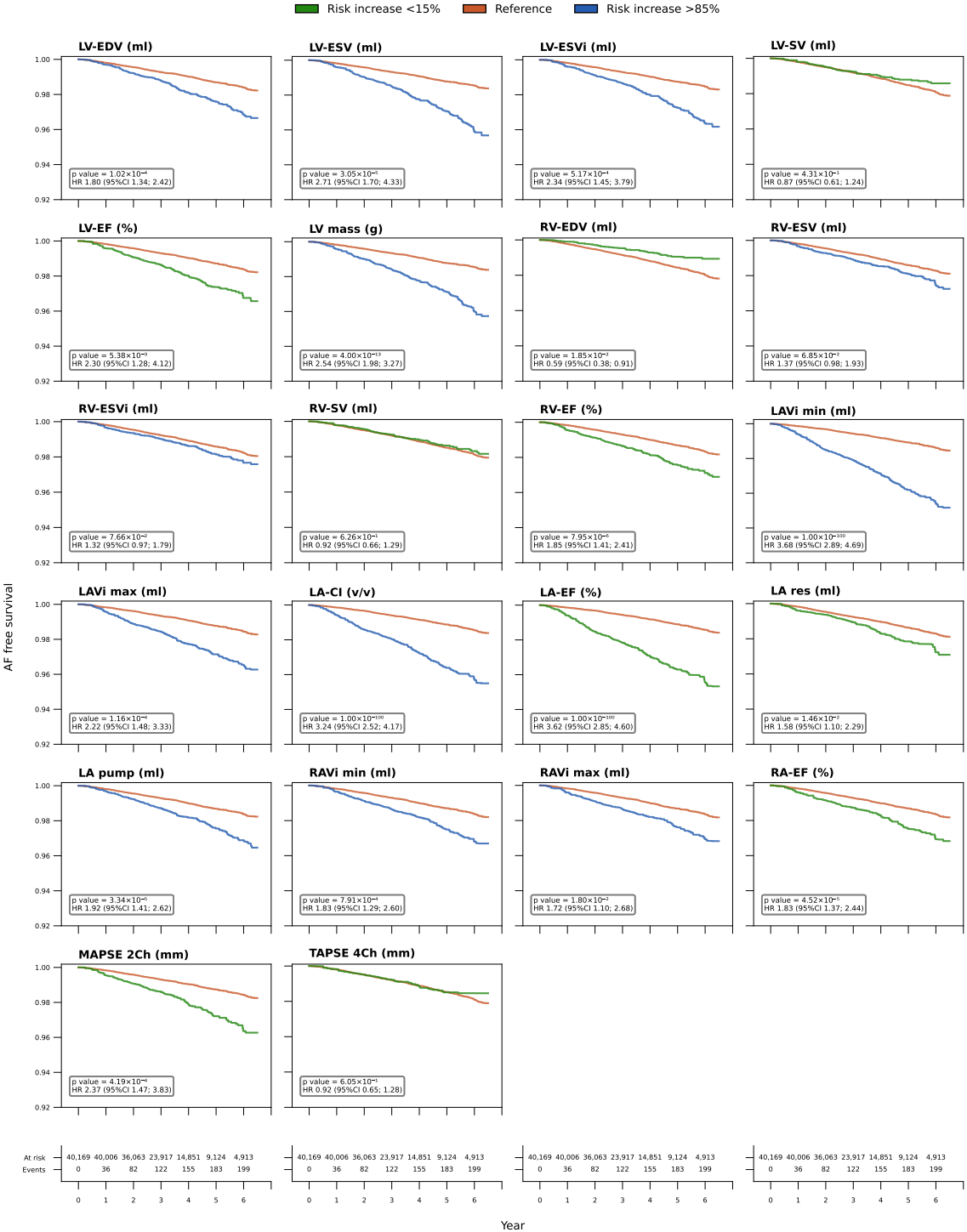
Abbreviations: CMR = cardiac magnetic resonance imaging, DCM = dilated cardiomyopathy, EF = ejection fraction, ESV = end-systolic volume, i = indexed, LV = left ventricular, MAPSE = mitral annular plane systolic excursion, OR = odds ratio, pump = pump volume, 2Ch = in 2-chamber view, 95%CI = 95% confidence interval.

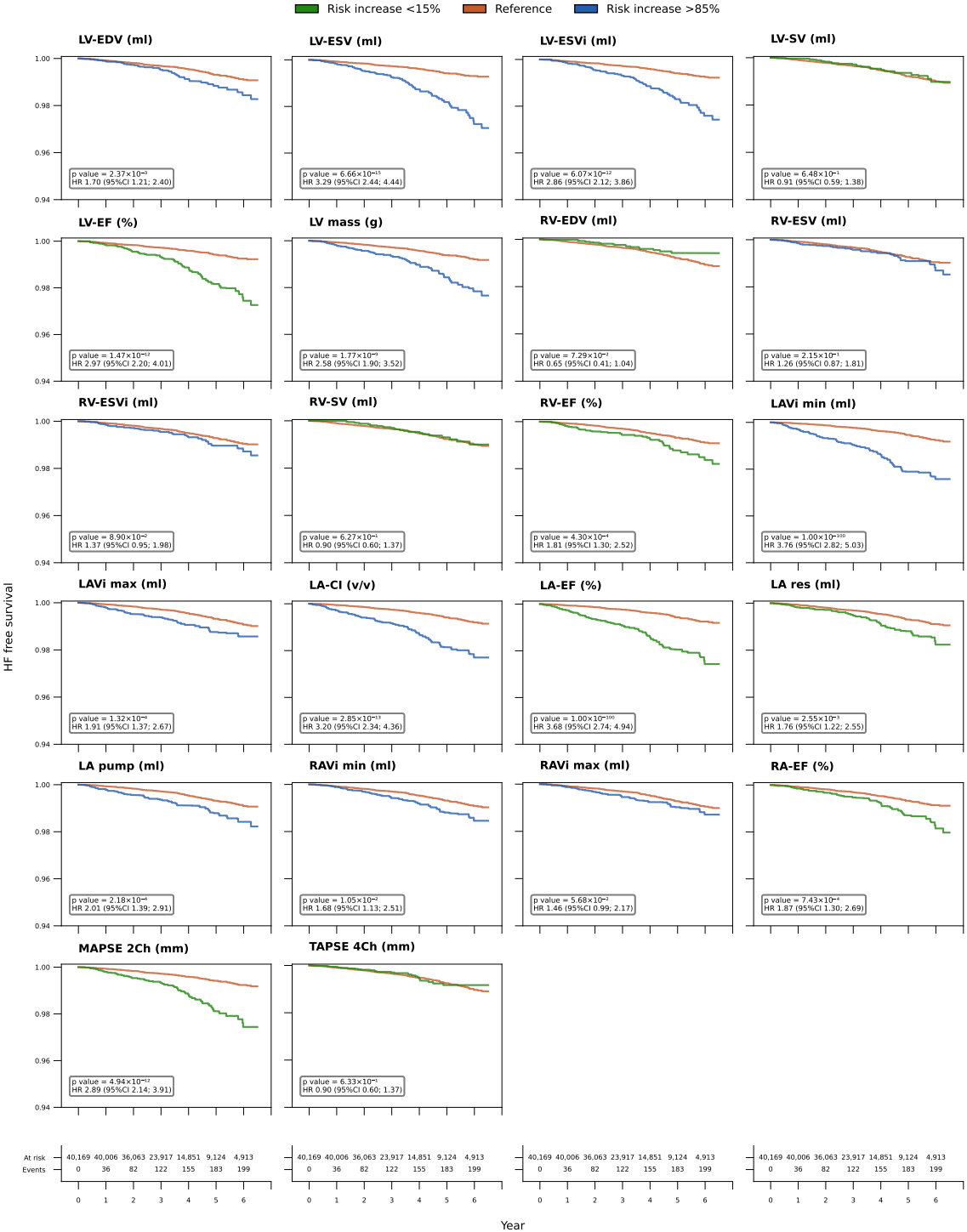

Heatmap of loadings
LV-EDV (ml)
LV-ESV (ml)
LV-ESVi (ml)
LV-SV (ml)
LV-EF (%)
LV mass (g)
RV-EDV (ml)
RV-ESV (ml)
RV-ESVi (ml)
RV-SV (ml)
RV-EF (%)
LAVi min (ml)
LAVi max (ml)
LA-CI (v/v)
LA-EF (%)
LA res (ml)
LA pump (ml)
RAVi min (ml)
RAVi max (ml)
RA-EF (%)
MAPSE 2Ch (mm)
TAPSE 4Ch (mm)
PC1
PC2
PC3
PC4
PC5
PC6
PC7
PC8
Principal components
1
0
−1
PC loadings

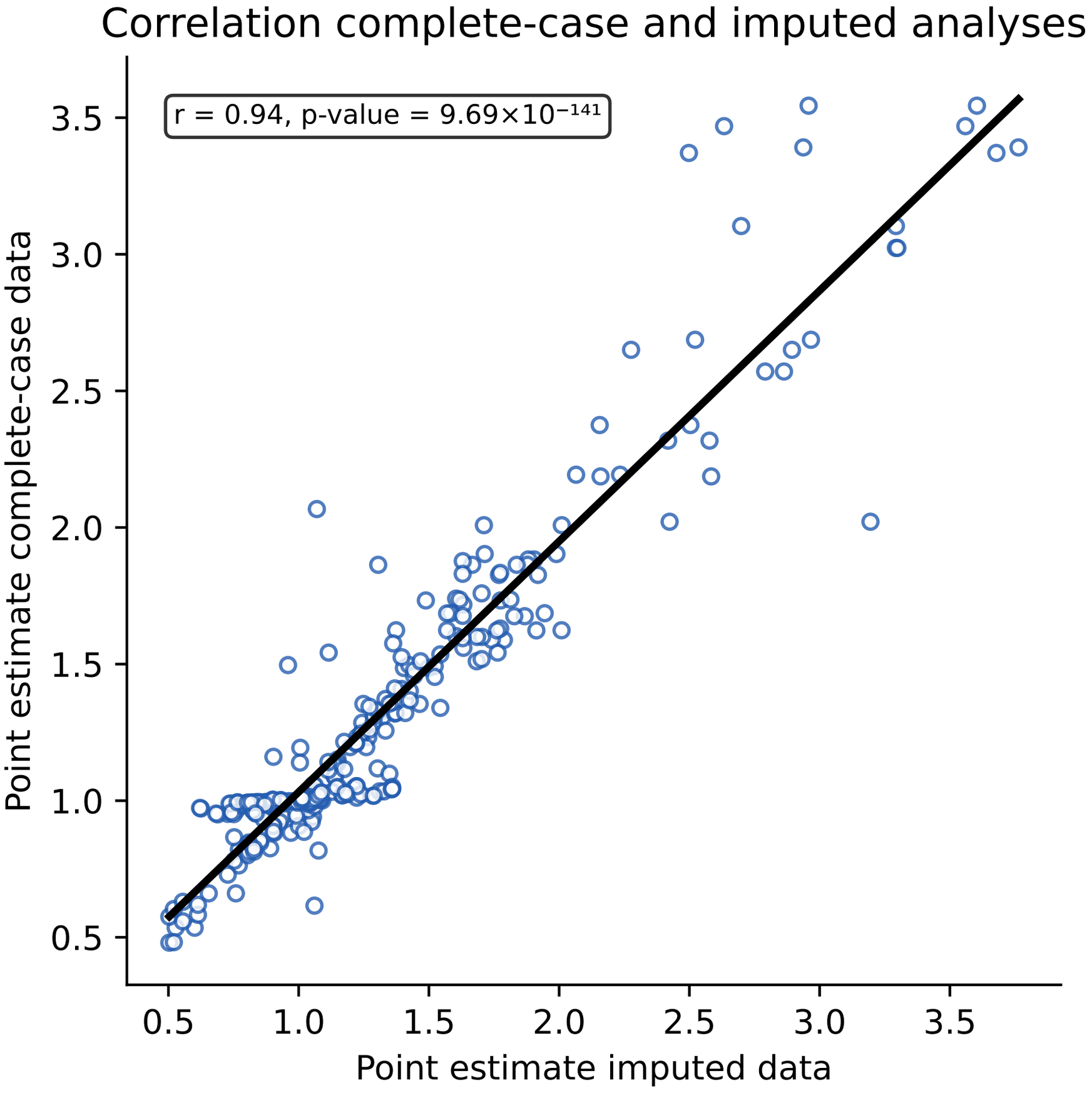

Cumulative explained variance (%)
90
80
70
60
50
40
1
2
3
4
5
6
7
8
Number of principal components

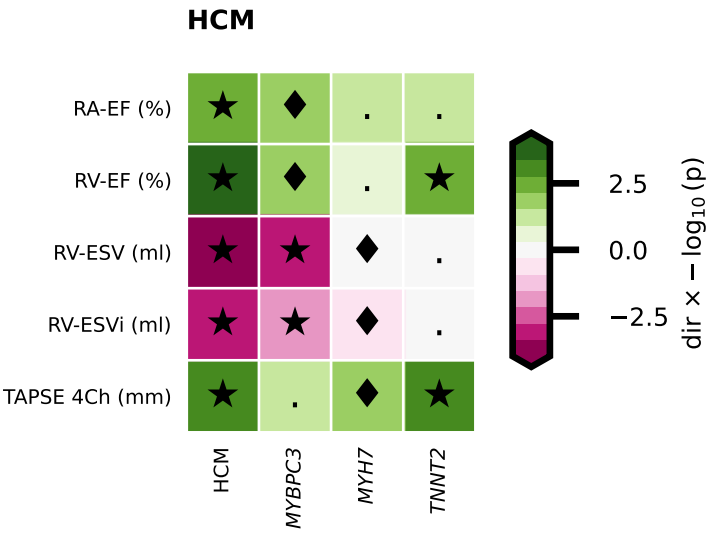

Gene distribution for HCM
MYH7 (19.4%)
CSRP3 (2.8%)
MYL2 (1.2%)
TPM1 (0.4%)
TNNC1 (0.4%)
TNNI3 (2.4%)
TNNT2 (27.4%)
MYBPC3 (45.6%)

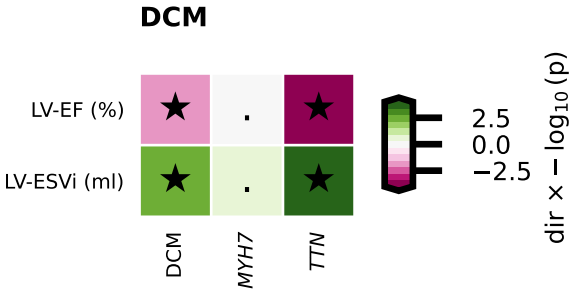

Gene distribution for DCM
MYH7 (23.6%)
TNNT2 (0.7%)
NEXN (0.7%)
DES (9.7%)
DSP (4.2%)
TNNI3 (1.4%)
TNNC1 (1.4%)
ACTN2 (0.7%)
TTN (30.6%)
FLNC (10.4%)
PLN (0.7%)
BAG3 (2.8%)
LMNA (5.6%)
SCN5A (7.6%)

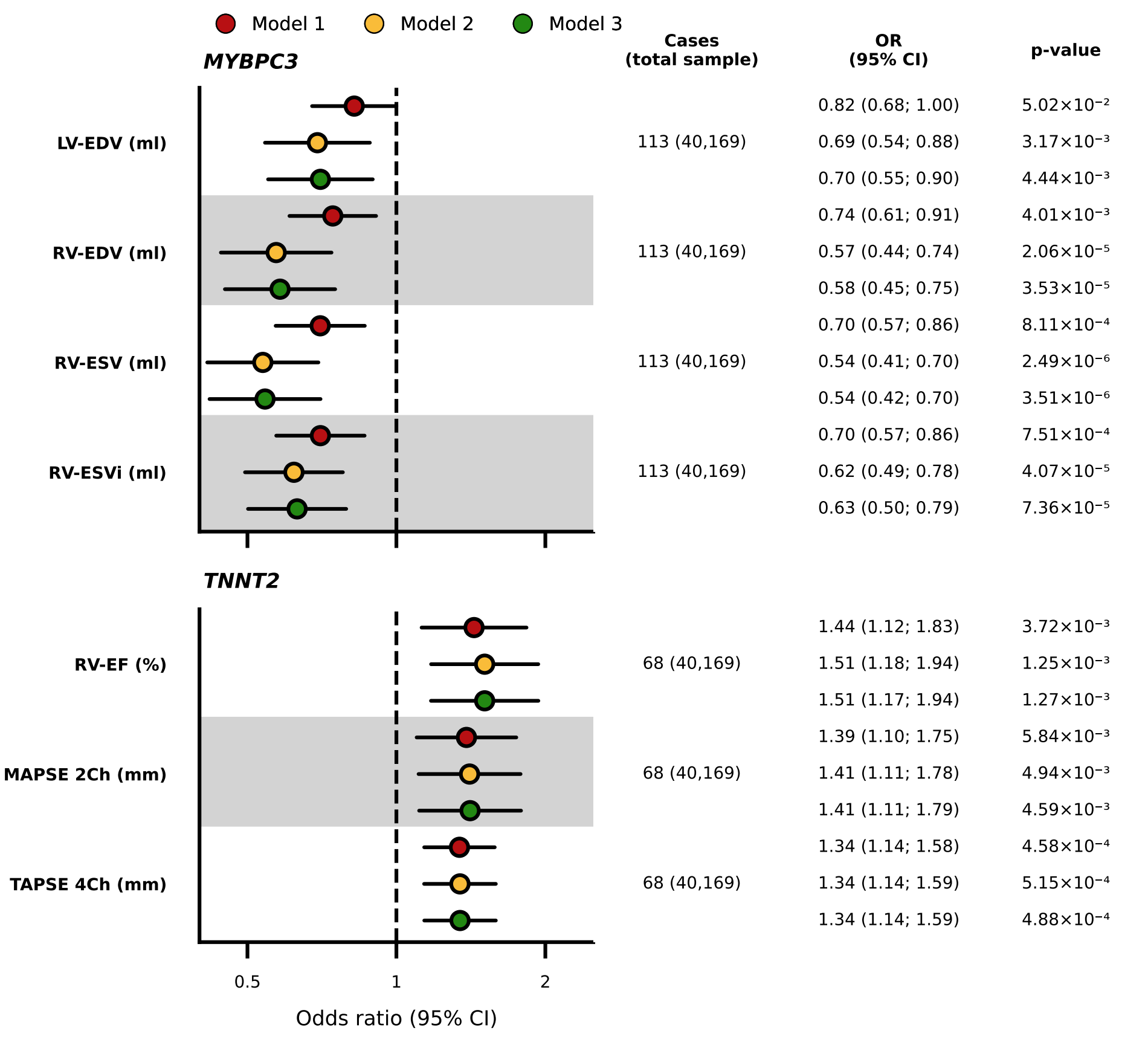

Risk increase <15%
Reference
Risk increase >85%
LV-EDV (ml)
p value = 1.02×10⁻⁴
HR 1.80 (95%CI 1.34; 2.42)
LV-ESV (ml)
p value = 3.05×10⁻⁵
HR 2.71 (95%CI 1.70; 4.33)
LV-ESVi (ml)
p value = 5.17×10⁻⁴
HR 2.34 (95%CI 1.45; 3.79)
LV-SV (ml)
p value = 4.31×10⁻¹
HR 0.87 (95%CI 0.61; 1.24)
LV-EF (%)
p value = 5.38×10⁻³
HR 2.30 (95%CI 1.28; 4.12)
LV mass (g)
p value = 4.00×10⁻¹³
HR 2.54 (95%CI 1.98; 3.27)
RV-EDV (ml)
p value = 1.85×10⁻²
HR 0.59 (95%CI 0.38; 0.91)
RV-ESV (ml)
p value = 6.85×10⁻²
HR 1.37 (95%CI 0.98; 1.93)
RV-ESVi (ml)
p value = 7.66×10⁻²
HR 1.32 (95%CI 0.97; 1.79)
RV-SV (ml)
p value = 6.26×10⁻¹
HR 0.92 (95%CI 0.66; 1.29)
RV-EF (%)
p value = 7.95×10⁻⁶
HR 1.85 (95%CI 1.41; 2.41)
LAVi min (ml)
p value = 1.00×10⁻¹⁰⁰
HR 3.68 (95%CI 2.89; 4.69)
LAVi max (ml)
p value = 1.16×10⁻⁴
HR 2.22 (95%CI 1.48; 3.33)
LA-CI (v/v)
p value = 1.00×10⁻¹⁰⁰
HR 3.24 (95%CI 2.52; 4.17)
LA-EF (%)
p value = 1.00×10⁻¹⁰⁰
HR 3.62 (95%CI 2.85; 4.60)
LA res (ml)
p value = 1.46×10⁻²
HR 1.58 (95%CI 1.10; 2.29)
LA pump (ml)
p value = 3.34×10⁻⁵
HR 1.92 (95%CI 1.41; 2.62)
RAVi min (ml)
p value = 7.91×10⁻⁴
HR 1.83 (95%CI 1.29; 2.60)
RAVi max (ml)
p value = 1.80×10⁻²
HR 1.72 (95%CI 1.10; 2.68)
RA-EF (%)
p value = 4.52×10⁻⁵
HR 1.83 (95%CI 1.37; 2.44)
MAPSE 2Ch (mm)
p value = 4.19×10⁻⁴
HR 2.37 (95%CI 1.47; 3.83)
TAPSE 4Ch (mm)
p value = 6.05×10⁻³
HR 0.92 (95%CI 0.65; 1.28)
AF free survival
1.00
0.98
0.96
0.94
0.92
At risk
Events
40,169 40,006 36,063 23,917 14,851 9,124 4,913
0 36 82 122 155 183 199
0 1 2 3 4 5 6
Year


Risk increase <15%
Reference
Risk increase >85%
LV-EDV (ml)
p value = 2.37×10⁻³
HR 1.70 (95%CI 1.21; 2.40)
LV-ESV (ml)
p value = 6.66×10⁻¹⁵
HR 3.29 (95%CI 2.44; 4.44)
LV-ESVi (ml)
p value = 6.07×10⁻¹²
HR 2.86 (95%CI 2.12; 3.86)
LV-SV (ml)
p value = 6.48×10⁻¹
HR 0.91 (95%CI 0.59; 1.38)
LV-EF (%)
p value = 1.47×10⁻¹²
HR 2.97 (95%CI 2.20; 4.01)
LV mass (g)
p value = 1.77×10⁻⁹
HR 2.58 (95%CI 1.90; 3.52)
RV-EDV (ml)
p value = 7.29×10⁻²
HR 0.65 (95%CI 0.41; 1.04)
RV-ESV (ml)
p value = 2.15×10⁻¹
HR 1.26 (95%CI 0.87; 1.81)
RV-ESVi (ml)
p value = 8.90×10⁻²
HR 1.37 (95%CI 0.95; 1.98)
RV-SV (ml)
p value = 6.27×10⁻¹
HR 0.90 (95%CI 0.60; 1.37)
RV-EF (%)
p value = 4.30×10⁻⁴
HR 1.81 (95%CI 1.30; 2.52)
LAVi min (ml)
p value = 1.00×10⁻¹⁰⁰
HR 3.76 (95%CI 2.82; 5.03)
LAVi max (ml)
p value = 1.32×10⁻⁶
HR 1.91 (95%CI 1.37; 2.67)
LA-CI (v/v)
p value = 2.85×10⁻¹³
HR 3.20 (95%CI 2.34; 4.36)
LA-EF (%)
p value = 1.00×10⁻¹⁰⁰
HR 3.68 (95%CI 2.74; 4.94)
LA res (ml)
p value = 2.55×10⁻³
HR 1.76 (95%CI 1.22; 2.55)
LA pump (ml)
p value = 2.18×10⁻⁴
HR 2.01 (95%CI 1.39; 2.91)
RAVi min (ml)
p value = 1.05×10⁻²
HR 1.68 (95%CI 1.13; 2.51)
RAVi max (ml)
p value = 5.68×10⁻²
HR 1.46 (95%CI 0.99; 2.17)
RA-EF (%)
p value = 7.43×10⁻⁴
HR 1.87 (95%CI 1.30; 2.69)
MAPSE 2Ch (mm)
p value = 4.94×10⁻¹²
HR 2.89 (95%CI 2.14; 3.91)
TAPSE 4Ch (mm)
p value = 6.33×10⁻¹
HR 0.90 (95%CI 0.60; 1.37)
HF free survival
1.00
0.98
0.96
0.94
At risk 40,169 40,006 36,063 23,917 14,851 9,124 4,913
Events 0 36 82 122 155 183 199
0 1 2 3 4 5 6
Year

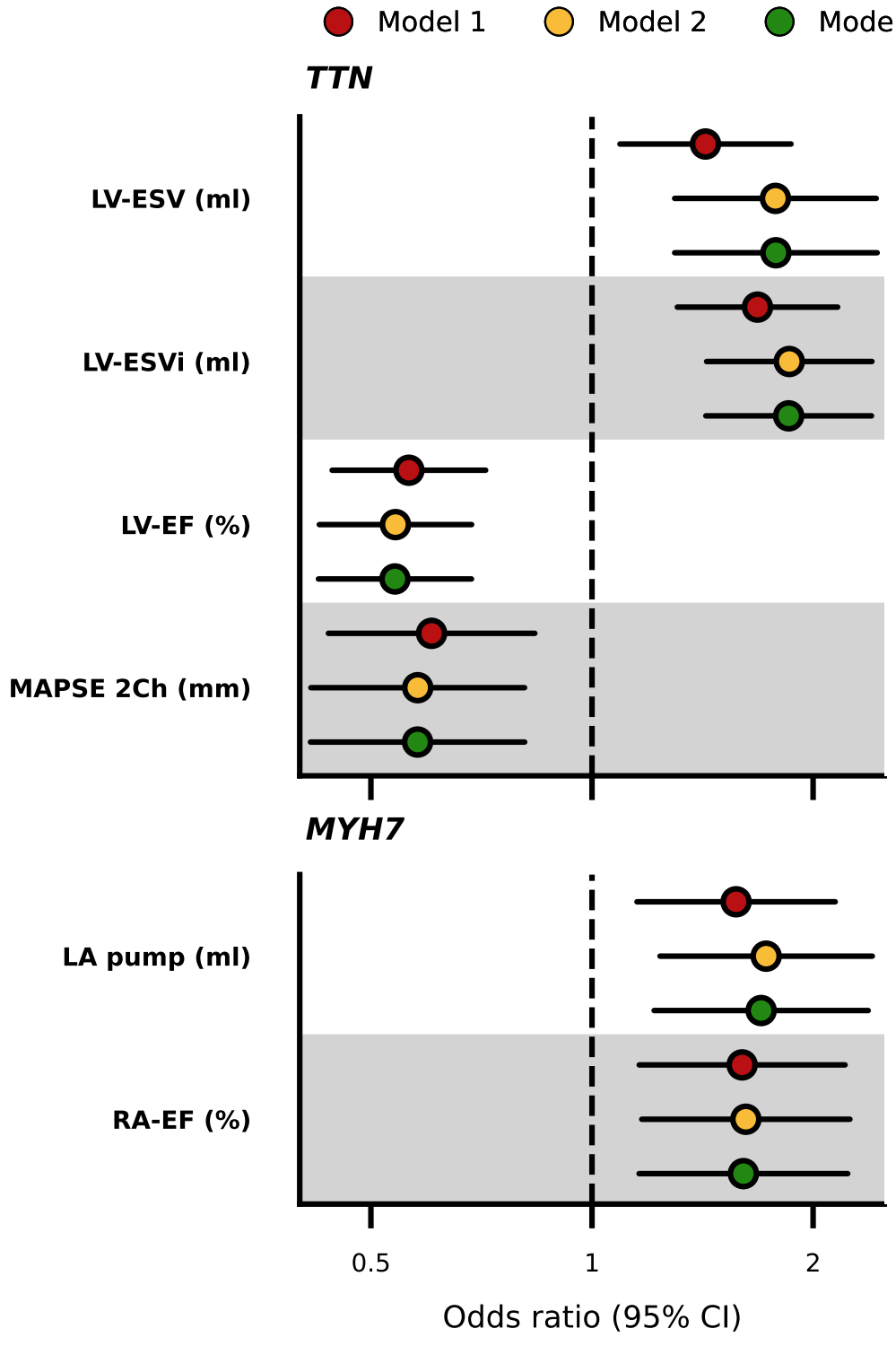

Correlation complete-case and imputed analyses
r = 0.94, p-value = 9.69×10⁻¹⁴¹
Point estimate complete-case data
Point estimate imputed data
0.5
1.0
1.5
2.0
2.5
3.0
3.5


HCM
RA-EF (%)
RV-EF (%)
RV-ESV (ml)
RV-ESVi (ml)
TAPSE 4Ch (mm)
HCM
MYBPC3
MYH7
TNNT2
2.5
0.0
−2.5
dir × −log10 (p)


DCM
LV-EF (%)
LV-ESVi (ml)
DCM
MYH7
TTN
2.5
0.0
−2.5
dir x − log10(p)



	Cases (total sample)	OR (95% CI)	p-value
LV-EDV (ml)	113 (40,169)	0.82 (0.68; 1.00)	5.02×10^{-2}
		0.69 (0.54; 0.88)	3.17×10^{-3}
		0.70 (0.55; 0.90)	4.44×10^{-3}
RV-EDV (ml)	113 (40,169)	0.74 (0.61; 0.91)	4.01×10^{-3}
		0.57 (0.44; 0.74)	2.06×10^{-5}
		0.58 (0.45; 0.75)	3.53×10^{-5}
RV-ESV (ml)	113 (40,169)	0.70 (0.57; 0.86)	8.11×10^{-4}
		0.54 (0.41; 0.70)	2.49×10^{-6}
		0.54 (0.42; 0.70)	3.51×10^{-6}
RV-ESVi (ml)	113 (40,169)	0.70 (0.57; 0.86)	7.51×10^{-4}
		0.62 (0.49; 0.78)	4.07×10^{-5}
		0.63 (0.50; 0.79)	7.36×10^{-5}
RV-EF (%)	68 (40,169)	1.44 (1.12; 1.83)	3.72×10^{-3}
		1.51 (1.18; 1.94)	1.25×10^{-3}
		1.51 (1.17; 1.94)	1.27×10^{-3}
MAPSE 2Ch (mm)	68 (40,169)	1.39 (1.10; 1.75)	5.84×10^{-3}
		1.41 (1.11; 1.78)	4.94×10^{-3}
		1.41 (1.11; 1.79)	4.59×10^{-3}
TAPSE 4Ch (mm)	68 (40,169)	1.34 (1.14; 1.58)	4.58×10^{-4}
		1.34 (1.14; 1.59)	5.15×10^{-4}
		1.34 (1.14; 1.59)	4.88×10^{-4}



	Cases (total sample)	OR (95% CI)	p-value
TTN			
LV-ESV (ml)	44 (40,169)	1.43 (1.09; 1.87)	9.35×10^{-3}
		1.78 (1.30; 2.44)	3.62×10^{-4}
		1.78 (1.30; 2.45)	3.72×10^{-4}
LV-ESVi (ml)	44 (40,169)	1.68 (1.31; 2.16)	5.23×10^{-5}
		1.86 (1.43; 2.41)	2.94×10^{-6}
		1.85 (1.43; 2.40)	3.30×10^{-6}
LV-EF (%)	44 (40,169)	0.56 (0.44; 0.72)	2.96×10^{-6}
		0.54 (0.43; 0.69)	4.28×10^{-7}
		0.54 (0.42; 0.69)	4.54×10^{-7}
MAPSE 2Ch (mm)	44 (40,169)	0.60 (0.44; 0.84)	2.32×10^{-3}
		0.58 (0.41; 0.81)	1.39×10^{-3}
		0.58 (0.41; 0.81)	1.42×10^{-3}
MYH7			
LA pump (ml)	34 (40,169)	1.57 (1.15; 2.14)	4.39×10^{-3}
		1.73 (1.24; 2.41)	1.30×10^{-3}
		1.70 (1.21; 2.38)	1.96×10^{-3}
RA-EF (%)	34 (40,169)	1.60 (1.16; 2.21)	4.27×10^{-3}
		1.62 (1.17; 2.24)	3.77×10^{-3}
		1.61 (1.16; 2.23)	4.45×10^{-3}