

HeartShare Baseline Characteristics

Deep Phenotyping Study and Registry Analytic Cohorts

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Table of contents

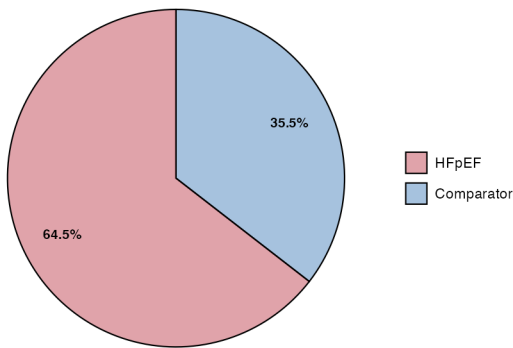
1 Cohort Composition	2
1.1 Deep Phenotyping Participant Distribution	2
1.2 Registry Participant Distribution	3
2 HeartShare Deep Phenotyping Study	4
2.1 Table 1: Demographics & Comorbidities	4
2.2 Table 2: Labs	6
2.3 Table 3: Exercise & Pulmonary Function	6
2.4 Table 4: Physical Function & PROs	7
2.5 Table 5: Medications	7
2.6 Table 6: Echocardiography	8
2.7 Table 7: CMR	9
2.8 Table 8: ECG	9
2.9 Table 9: CT Body Composition	10
2.10 Key Figures	10
2.11 Deep Phenotyping: Stratification by Site	14
3 HeartShare Registry	18
3.1 Registry: HF vs Comparator	18
3.2 Registry: Stratification by Site	21
4 Summary Figures	24
4.1 Radial Bar Plot: Multi-Domain Phenotypic Profile	24
4.2 Forest Plot: Standardized Mean Differences	25
4.3 Ridgeline Density Plots	26
4.4 UpSet Plot: Comorbidity Combinations	27
4.5 Site Heterogeneity Heatmap	29
4.6 Parallel Coordinates Plot	33
4.7 Correlation Network	34

1 Cohort Composition

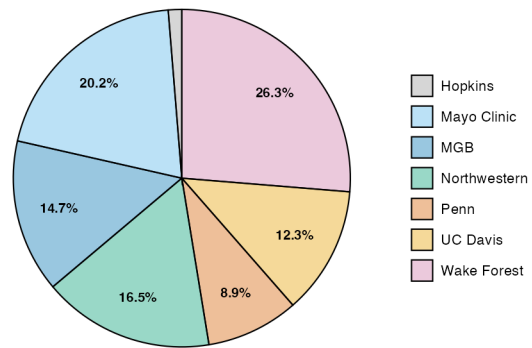
1.1 Deep Phenotyping Participant Distribution

Site	HFpEF	Comparator	Overall
Hopkins	8 (2.0%)	0 (0.0%)	8 (1.3%)
Mayo Clinic	84 (21.0%)	41 (18.6%)	125 (20.2%)
MGB	45 (11.2%)	46 (20.9%)	91 (14.7%)
Northwestern	83 (20.8%)	19 (8.6%)	102 (16.5%)
Penn	41 (10.2%)	14 (6.4%)	55 (8.9%)
UC Davis	48 (12.0%)	28 (12.7%)	76 (12.3%)
Wake Forest	91 (22.8%)	72 (32.7%)	163 (26.3%)
Total	400 (100.0%)	220 (100.0%)	620 (100.0%)

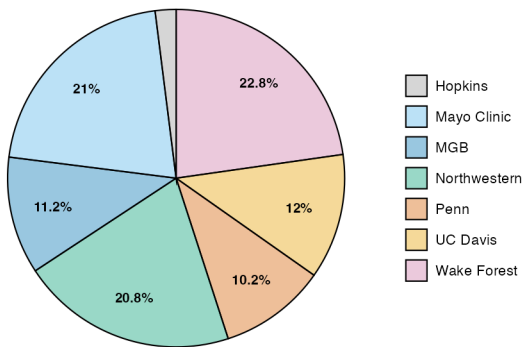
Deep Phenotyping by Group



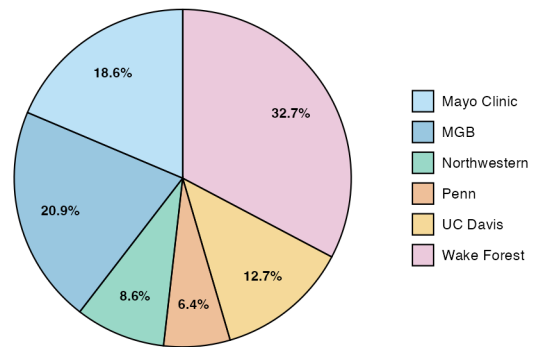
Deep Phenotyping by Site



HFpEF by Site



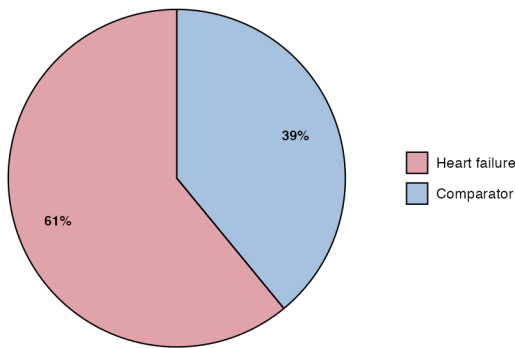
Comparator by Site



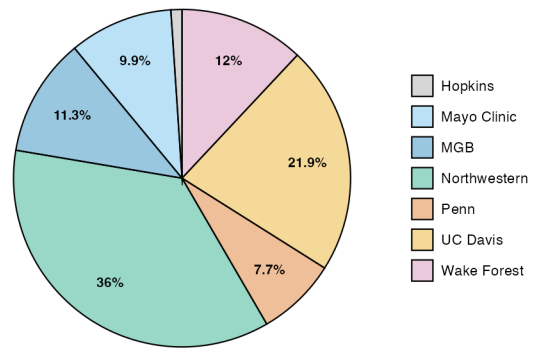
1.2 Registry Participant Distribution

Site	Heart failure	Comparator	Overall
Hopkins	42 (1.7%)	0 (0.0%)	42 (1.1%)
Mayo Clinic	344 (14.3%)	50 (3.2%)	394 (9.9%)
MGB	370 (15.3%)	79 (5.1%)	449 (11.3%)
Northwestern	730 (30.2%)	697 (45.1%)	1427 (36.0%)
Penn	283 (11.7%)	21 (1.4%)	304 (7.7%)
UC Davis	488 (20.2%)	381 (24.6%)	869 (21.9%)
Wake Forest	157 (6.5%)	318 (20.6%)	475 (12.0%)
Total	2414 (100.0%)	1546 (100.0%)	3960 (100.0%)

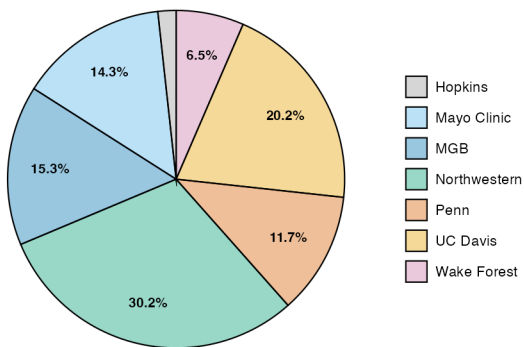
Registry by Group



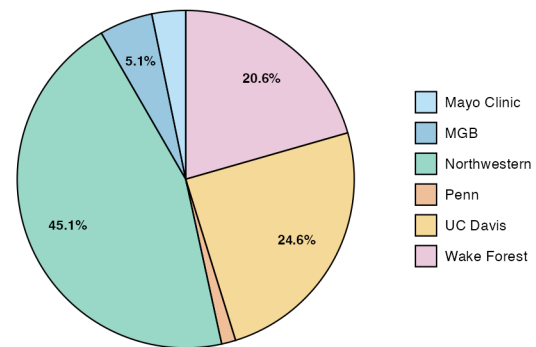
Registry by Site



HF by Site



Comparator by Site



2 HeartShare Deep Phenotyping Study

2.1 Table 1: Demographics & Comorbidities

Characteristic	Overall N = 620	Deep Phenotyping Participant Type		p-value
		HFpEF N = 400	Comparator N = 220	
Age (years)	68.5 (12.4)	71.8 (10.1)	62.4 (13.8)	<0.001
Sex				0.046
Male	244 (39.4%)	147 (36.8%)	97 (44.1%)	
Female	374 (60.4%)	252 (63.2%)	122 (55.5%)	
Other	1 (0.2%)	0 (0.0%)	1 (0.5%)	
Race				<0.001
Asian	22 (3.6%)	7 (1.8%)	15 (7.0%)	
Black or African American	116 (19.1%)	86 (21.9%)	30 (14.0%)	
Native Hawaiian or Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	
White	451 (74.4%)	291 (74.2%)	160 (74.8%)	
More than one race	15 (2.5%)	6 (1.5%)	9 (4.2%)	
Other	1 (0.2%)	1 (0.3%)	0 (0.0%)	
Prefer not to answer	1 (0.2%)	1 (0.3%)	0 (0.0%)	
Ethnicity				<0.001
Not Hispanic or Latino	578 (94.1%)	383 (97.0%)	195 (89.0%)	
Cuban	2 (0.3%)	1 (0.3%)	1 (0.5%)	
Mexican, Mexican American, Chicano	23 (3.7%)	9 (2.3%)	14 (6.4%)	
Puerto Rican	2 (0.3%)	0 (0.0%)	2 (0.9%)	
Other Hispanic or Latino	6 (1.0%)	1 (0.3%)	5 (2.3%)	
Unknown	2 (0.3%)	1 (0.3%)	1 (0.5%)	
Prefer not to answer	1 (0.2%)	0 (0.0%)	1 (0.5%)	
BMI (kg/m²)	31.8 (7.2)	33.8 (7.3)	28.2 (5.3)	<0.001
BMI Classification				
Underweight	4 (0.6%)	2 (0.5%)	2 (0.9%)	
Normal weight	99 (16.0%)	33 (8.3%)	66 (30.0%)	
Overweight	177 (28.5%)	95 (23.8%)	82 (37.3%)	
Class I obesity	160 (25.8%)	115 (28.8%)	45 (20.5%)	
Class II obesity	101 (16.3%)	84 (21.0%)	17 (7.7%)	
Class III obesity	79 (12.7%)	71 (17.8%)	8 (3.6%)	
Waist circumference (cm)	104.6 (18.0)	109.2 (18.0)	96.1 (14.6)	<0.001
Hip circumference (cm)	112.3 (16.1)	116.7 (16.3)	104.4 (12.2)	<0.001
Neck circumference (cm)	38.6 (4.9)	39.4 (4.9)	37.2 (4.6)	<0.001
Waist-to-hip ratio	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.029
Systolic BP (mmHg)	124.7 (18.5)	124.7 (19.2)	124.5 (17.3)	0.86
Diastolic BP (mmHg)	71.9 (11.9)	70.3 (12.0)	74.8 (11.3)	<0.001
Heart rate (bpm)	68.5 (11.2)	68.8 (11.7)	68.1 (10.5)	0.76
Pulse pressure (mmHg)	52.7 (14.2)	54.4 (14.5)	49.8 (13.1)	<0.001
Central SBP (mmHg)	118.8 (28.9)	119.6 (33.1)	117.4 (19.2)	0.89
Central DBP (mmHg)	72.6 (12.0)	71.4 (11.5)	74.7 (12.4)	<0.001
Augmentation index (%)	90.1 (44.3)	91.9 (46.0)	87.0 (41.0)	0.20
NYHA Class				<0.001
I	234 (40.2%)	51 (13.6%)	183 (88.8%)	
II	249 (42.8%)	228 (60.6%)	21 (10.2%)	
III	97 (16.7%)	95 (25.3%)	2 (1.0%)	

(continued)

Characteristic	Deep Phenotyping Participant Type			p-value
	Overall N = 620	HFpEF N = 400	Comparator N = 220	
IV	2 (0.3%)	2 (0.5%)	0 (0.0%)	
Atrial fibrillation/flutter	203 (33.7%)	187 (48.4%)	16 (7.4%)	<0.001
Hypertension	451 (73.5%)	353 (89.1%)	98 (45.0%)	<0.001
Coronary artery disease	180 (30.8%)	154 (41.7%)	26 (12.1%)	<0.001
Diabetes mellitus	158 (25.8%)	120 (30.5%)	38 (17.4%)	<0.001
CKD (eGFR <60)	103 (19.8%)	89 (27.7%)	14 (7.0%)	<0.001
COPD	71 (11.7%)	65 (16.7%)	6 (2.8%)	<0.001
Obstructive sleep apnea	287 (47.8%)	243 (62.5%)	44 (20.8%)	<0.001
Obesity	340 (54.8%)	270 (67.5%)	70 (31.8%)	<0.001
Comorbidity count	4.5 (2.8)	5.6 (2.5)	2.3 (2.0)	<0.001
Congestion score (0-6)	1.1 (1.1)	1.5 (1.1)	0.3 (0.6)	<0.001
H2FPEF score (0-9)	4.1 (2.6)	5.4 (2.1)	1.7 (1.7)	<0.001

¹ Mean (SD); n (%)
² Wilcoxon rank sum test; Fisher's exact test; NA; Pearson's Chi-squared test

2.2 Table 2: Labs

Characteristic	Overall N = 620	Deep Phenotyping Participant Type		p-value
		HFpEF N = 400	Comparator N = 220	
Hemoglobin (g/dL)	13.7 [12.7, 14.6]	13.6 [12.5, 14.6]	13.8 [13.0, 14.7]	0.085
Hematocrit (%)	41.2 [38.6, 44.1]	41.1 [38.3, 44.3]	41.3 [39.0, 44.0]	0.47
WBC (K/uL)	6.1 [5.1, 7.4]	6.4 [5.3, 7.5]	5.6 [4.6, 6.7]	<0.001
Platelets (K/uL)	240.0 [199.0, 278.0]	239.0 [195.0, 282.0]	240.0 [206.0, 271.0]	0.77
Creatinine (mg/dL)	0.9 [0.8, 1.1]	1.0 [0.8, 1.1]	0.8 [0.7, 1.0]	<0.001
eGFR (mL/min/1.73m ²)	77.7 [63.8, 93.2]	70.5 [58.6, 84.9]	91.8 [77.4, 100.9]	<0.001
Sodium (mmol/L)	139.0 [138.0, 141.0]	140.0 [138.0, 141.0]	139.0 [138.0, 141.0]	0.18
Potassium (mmol/L)	4.3 [4.0, 4.5]	4.3 [4.0, 4.5]	4.3 [4.1, 4.5]	0.46
HbA1c (%)	5.7 [5.4, 6.1]	5.7 [5.4, 6.1]	5.6 [5.3, 5.9]	<0.001
Total cholesterol (mg/dL)	162.0 [135.0, 191.0]	154.0 [124.0, 187.0]	173.0 [152.0, 200.0]	<0.001
HDL cholesterol (mg/dL)	53.0 [42.0, 67.0]	51.0 [40.0, 63.0]	57.0 [46.0, 70.0]	<0.001
LDL cholesterol (mg/dL)	80.0 [58.0, 110.0]	71.0 [53.0, 101.0]	89.5 [69.0, 115.0]	<0.001
Triglycerides (mg/dL)	102.0 [74.0, 150.0]	109.0 [79.0, 152.0]	93.0 [69.0, 138.5]	0.004
Troponin I (ng/mL)	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.28
hs-CRP (mg/L)	1.7 [0.7, 4.2]	2.6 [1.1, 6.0]	0.9 [0.5, 2.5]	<0.001
Albumin (g/dL)	4.2 [4.0, 4.4]	4.1 [3.9, 4.4]	4.3 [4.1, 4.5]	<0.001
Prealbumin (mg/dL)	24.0 [21.0, 27.0]	24.0 [21.0, 27.0]	25.0 [22.0, 27.0]	0.22
Urine ACR (ug/mg)	7.0 [0.0, 21.5]	11.0 [0.0, 31.0]	3.5 [0.0, 12.0]	<0.001

¹ Median [Q1, Q3]
² Wilcoxon rank sum test

2.3 Table 3: Exercise & Pulmonary Function

Characteristic	Overall N = 620	Deep Phenotyping Participant Type		p-value
		HFpEF N = 400	Comparator N = 220	
Peak VO ₂ (mL/kg/min)	16.5 (6.7)	13.5 (4.5)	21.0 (6.9)	<0.001
% Predicted peak VO ₂	54.9 (18.6)	46.6 (13.9)	67.0 (17.9)	<0.001
Peak RER	1.1 (0.1)	1.1 (0.1)	1.2 (0.1)	<0.001
Peak heart rate (bpm)	127.2 (24.7)	117.0 (22.1)	142.2 (20.4)	<0.001
VE/VC0 ₂ slope	30.4 (5.6)	31.4 (6.2)	28.9 (4.2)	<0.001
Peak O ₂ pulse (mL/beat)	11.1 (3.6)	10.6 (3.3)	11.7 (3.9)	0.010
VO ₂ at VAT (mL/kg/min)	839.7 (293.0)	781.8 (263.3)	922.6 (313.3)	<0.001
Peak exercise SBP (mmHg)	172.7 (25.9)	168.3 (24.9)	179.4 (26.0)	<0.001
Peak exercise DBP (mmHg)	74.4 (13.8)	74.1 (13.4)	75.0 (14.5)	0.51
FEV ₁ (% predicted)	101.9 (44.8)	97.8 (50.5)	110.3 (28.2)	<0.001
FVC (% predicted)	107.3 (48.4)	103.6 (55.3)	114.6 (28.6)	<0.001
FEV ₁ /FVC (% predicted)	91.3 (20.5)	90.7 (21.0)	92.6 (19.6)	0.022
DLC0 corrected (% predicted)	NA (NA)	NA (NA)	NA (NA)	
6MWT distance (m)	406.8 (124.7)	358.3 (112.3)	487.7 (100.1)	<0.001
Post-6MWT Borg dyspnea (0-10)	2.0 (2.0)	2.7 (2.1)	0.7 (1.0)	<0.001
Post-6MWT Borg fatigue (0-10)	1.8 (2.2)	2.6 (2.3)	0.5 (0.9)	<0.001
6MWT SpO ₂ change (%)	-0.4 (4.1)	-0.8 (4.3)	0.3 (3.7)	0.001

¹ Mean (SD)
² Wilcoxon rank sum test; NA

2.4 Table 4: Physical Function & PROs

Characteristic	Overall N = 620	Deep Phenotyping Participant Type		p-value
		HFpEF N = 400	Comparator N = 220	
Gait speed (m/s)	1.0 (0.3)	0.9 (0.3)	1.1 (0.3)	<0.001
Repeated chair stand time (sec)	13.8 (5.5)	15.0 (5.4)	11.7 (5.1)	<0.001
MoCA total score (0-30)	25.4 (3.2)	24.8 (3.3)	26.3 (2.9)	<0.001
KCCQ-12 Overall Summary	74.8 (24.3)	64.2 (22.9)	94.1 (11.2)	<0.001
KCCQ-12 Clinical Summary	75.5 (23.8)	64.7 (22.5)	94.9 (9.4)	<0.001
KCCQ-12 Physical Limitation	74.7 (25.7)	63.5 (24.6)	94.6 (11.7)	<0.001
KCCQ-12 Symptom Frequency	76.1 (24.6)	65.6 (24.1)	95.2 (9.4)	<0.001
KCCQ-12 Quality of Life	70.2 (29.6)	58.9 (28.2)	90.5 (19.7)	<0.001
KCCQ-12 Social Limitation	76.7 (27.0)	67.8 (27.0)	95.9 (13.7)	<0.001
CES-D-10 depression score (0-30)	8.5 (3.7)	9.2 (3.9)	7.3 (3.1)	<0.001
Epworth Sleepiness Scale (0-24)	6.4 (4.4)	7.1 (4.7)	5.0 (3.4)	<0.001
STOP-BANG score (0-8)	2.5 (1.3)	2.7 (1.2)	2.2 (1.4)	<0.001

¹ Mean (SD)
² Wilcoxon rank sum test

2.5 Table 5: Medications

Characteristic	Overall N = 620	Deep Phenotyping Participant Type		p-value
		HFpEF N = 400	Comparator N = 220	
ACE inhibitor	66 (12.1%)	37 (10.0%)	29 (16.4%)	0.032
ARB	129 (23.6%)	100 (27.0%)	29 (16.4%)	0.006
ARNI	35 (6.4%)	35 (9.5%)	0 (0.0%)	<0.001
Beta-blocker	200 (36.6%)	173 (46.8%)	27 (15.3%)	<0.001
MRA	120 (21.9%)	116 (31.4%)	4 (2.3%)	<0.001
SGLT2 inhibitor	144 (26.3%)	139 (37.6%)	5 (2.8%)	<0.001
GLP-1 receptor agonist	41 (7.5%)	33 (8.9%)	8 (4.5%)	0.068
Any diuretic	296 (54.1%)	276 (74.6%)	20 (11.3%)	<0.001
Loop diuretic	166 (30.3%)	166 (44.9%)	0 (0.0%)	<0.001
Thiazide diuretic	63 (11.5%)	50 (13.5%)	13 (7.3%)	0.034
Calcium channel blocker	127 (23.2%)	98 (26.5%)	29 (16.4%)	0.009
Statin	294 (53.7%)	216 (58.4%)	78 (44.1%)	0.002
Anticoagulant	140 (25.6%)	131 (35.4%)	9 (5.1%)	<0.001
Antiplatelet	120 (21.9%)	95 (25.7%)	25 (14.1%)	0.002
Antiarrhythmic	39 (7.1%)	37 (10.0%)	2 (1.1%)	<0.001
Digoxin	1 (0.2%)	0 (0.0%)	1 (0.6%)	0.32
Nitrate	32 (5.9%)	29 (7.8%)	3 (1.7%)	0.004
Proton pump inhibitor	126 (23.0%)	103 (27.8%)	23 (13.0%)	<0.001
Total medications	6.0 [3.0, 10.0]	8.0 [5.0, 13.0]	4.0 [1.0, 6.0]	<0.001
Diuretic classes				<0.001
0	253 (46.3%)	96 (25.9%)	157 (88.7%)	
1	147 (26.9%)	129 (34.9%)	18 (10.2%)	
2	98 (17.9%)	96 (25.9%)	2 (1.1%)	
3	46 (8.4%)	46 (12.4%)	0 (0.0%)	

(continued)

Characteristic	Deep Phenotyping Participant Type			p-value
	Overall N = 620	HFpEF N = 400	Comparator N = 220	
4	3 (0.5%)	3 (0.8%)	0 (0.0%)	

¹ n (%); Median [Q1, Q3]
² Pearson's Chi-squared test; Fisher's exact test; Wilcoxon rank sum test

2.6 Table 6: Echocardiography

Characteristic	Deep Phenotyping Participant Type			p-value
	Overall N = 620	HFpEF N = 400	Comparator N = 220	
LVEF biplane (%)	62.2 (6.0)	62.0 (6.3)	62.4 (5.4)	0.66
LVEDD (mm)	43.7 (5.7)	43.6 (5.9)	43.8 (5.3)	0.61
LVEDV (mL)	79.6 (25.8)	78.1 (26.3)	82.1 (24.9)	0.046
LVESV (mL)	30.5 (12.1)	30.0 (12.3)	31.2 (11.7)	0.12
LV mass (g)	144.4 (47.2)	152.7 (50.7)	131.1 (37.7)	<0.001
Relative wall thickness	0.4 (0.1)	0.5 (0.1)	0.4 (0.1)	<0.001
Septal wall thickness (mm)	9.9 (2.0)	10.4 (2.1)	9.2 (1.6)	<0.001
Posterior wall thickness (mm)	9.6 (1.9)	10.0 (2.0)	9.0 (1.5)	<0.001
LA volume index (mL/m²)	29.8 (11.1)	32.4 (12.0)	25.7 (8.0)	<0.001
LA reservoir strain (%)	26.2 (10.5)	22.7 (10.4)	31.5 (8.1)	<0.001
Mitral E velocity (cm/s)	76.5 (23.8)	81.0 (26.5)	69.6 (16.7)	<0.001
E/A ratio	1.1 (0.4)	1.1 (0.5)	1.1 (0.4)	0.72
Average E/e'	9.7 (4.5)	11.0 (5.0)	7.7 (2.6)	<0.001
Lateral E/e'	8.6 (4.2)	9.8 (4.7)	7.0 (2.7)	<0.001
Septal E/e'	11.2 (5.4)	12.6 (6.1)	8.8 (2.9)	<0.001
Lateral e' (cm/s)	9.8 (3.1)	9.2 (3.0)	10.8 (3.1)	<0.001
Septal e' (cm/s)	7.5 (2.3)	7.0 (2.0)	8.4 (2.4)	<0.001
Lateral s' (cm/s)	9.6 (2.8)	9.1 (2.8)	10.3 (2.7)	<0.001
Global longitudinal strain (%)	18.5 (3.2)	18.0 (3.4)	19.3 (2.7)	<0.001
LV apex-to-base ratio	1.3 (0.4)	1.3 (0.5)	1.3 (0.4)	0.27
RVEF (%)	52.6 (17.2)	52.7 (15.7)	52.4 (19.4)	0.75
RV free wall strain (%)	21.2 (6.6)	20.4 (7.0)	22.6 (5.7)	<0.001
RV 4C longitudinal strain (%)	18.3 (5.7)	17.6 (5.9)	19.4 (5.2)	<0.001
TAPSE (mm)	21.8 (5.0)	21.4 (4.9)	22.5 (5.0)	0.018
PA systolic pressure (mmHg)	27.0 (13.1)	29.6 (14.4)	22.4 (8.8)	<0.001
RA pressure (mmHg)	4.4 (2.6)	4.5 (2.6)	4.3 (2.5)	0.29
Fractional area change (%)	40.3 (10.4)	40.1 (10.6)	40.6 (10.2)	0.69
IVC max diameter (mm)	16.0 (4.1)	16.2 (4.2)	15.5 (3.9)	0.10
TR peak velocity (m/s)	2.3 (0.6)	2.4 (0.6)	2.1 (0.4)	<0.001

¹ Mean (SD)
² Wilcoxon rank sum test

2.7 Table 7: CMR

Characteristic	Overall N = 620	Deep Phenotyping Participant Type		p-value
		HFpEF N = 400	Comparator N = 220	
CMR LVEF (%)	57.9 (6.6)	58.1 (7.1)	57.7 (6.1)	0.64
CMR LVEDVi (mL/m ²)	64.0 (16.0)	62.0 (16.4)	66.2 (15.3)	0.001
CMR LVESVi (mL/m ²)	27.3 (9.4)	26.4 (10.4)	28.1 (8.2)	0.005
CMR LV mass index (g/m ²)	44.4 (9.7)	45.5 (10.4)	43.2 (8.7)	0.069
CMR LV stroke volume (mL)	72.0 (19.4)	71.7 (18.5)	72.4 (20.4)	0.94
CMR RVEF (%)	54.3 (8.4)	53.8 (8.8)	54.8 (8.0)	0.35
CMR RVEDVi (mL/m ²)	66.3 (19.2)	65.7 (18.7)	66.9 (19.7)	0.34
CMR RVESVi (mL/m ²)	32.0 (12.0)	31.3 (12.9)	32.7 (11.0)	0.045
CMR RV stroke volume (mL)	70.1 (19.8)	70.4 (18.6)	69.9 (21.1)	0.66
Native T1 (ms)	1,024.0 (38.0)	1,029.7 (40.6)	1,017.8 (34.1)	0.003
ECV (%)	27.9 (3.6)	28.7 (3.8)	27.1 (3.3)	<0.001
Indexed ECV (mL/m ²)	11.5 (2.8)	12.1 (3.4)	10.9 (2.0)	0.008

¹ Mean (SD)
² Wilcoxon rank sum test

2.8 Table 8: ECG

Characteristic	Overall N = 620	Deep Phenotyping Participant Type		p-value
		HFpEF N = 400	Comparator N = 220	
Atrial fibrillation	27 (5.1%)	26 (7.9%)	1 (0.5%)	<0.001
Atrial flutter	0 (0.0%)	0 (0.0%)	0 (0.0%)	>0.99
Ventricular rate (bpm)	66.9 (11.6)	68.0 (12.4)	65.2 (9.9)	0.038
PR interval (ms)	172.6 (34.4)	177.0 (38.0)	166.4 (27.6)	<0.001
QRS duration (ms)	97.8 (25.3)	101.9 (27.8)	91.0 (18.6)	<0.001
QT interval (ms)	419.4 (36.9)	424.2 (39.2)	411.4 (31.2)	<0.001
QTc Bazett (ms)	438.6 (29.3)	446.7 (30.1)	425.4 (22.4)	<0.001
QTc Fredericia (ms)	431.6 (27.6)	438.6 (28.9)	420.3 (21.0)	<0.001
P axis (degrees)	48.0 (25.7)	48.6 (28.0)	47.2 (22.2)	0.57
R axis (degrees)	17.4 (45.0)	12.4 (48.3)	25.6 (37.6)	<0.001
T axis (degrees)	40.0 (39.7)	41.5 (44.9)	37.6 (29.2)	0.47
QRST angle (degrees)	40.4 (44.3)	48.9 (49.9)	26.5 (28.1)	<0.001
Cornell voltage (mV)	1,317.7 (680.8)	1,417.4 (741.6)	1,154.1 (529.7)	<0.001
JT duration (ms)	321.6 (32.7)	322.3 (34.0)	320.4 (30.5)	0.44
JT index (%)	103.1 (7.3)	103.9 (7.5)	101.8 (6.8)	0.002
LVH (Minnesota Code)	7 (1.3%)	6 (1.8%)	1 (0.5%)	0.26
LVH (Sokolow-Lyon)	7 (1.3%)	4 (1.2%)	3 (1.5%)	>0.99

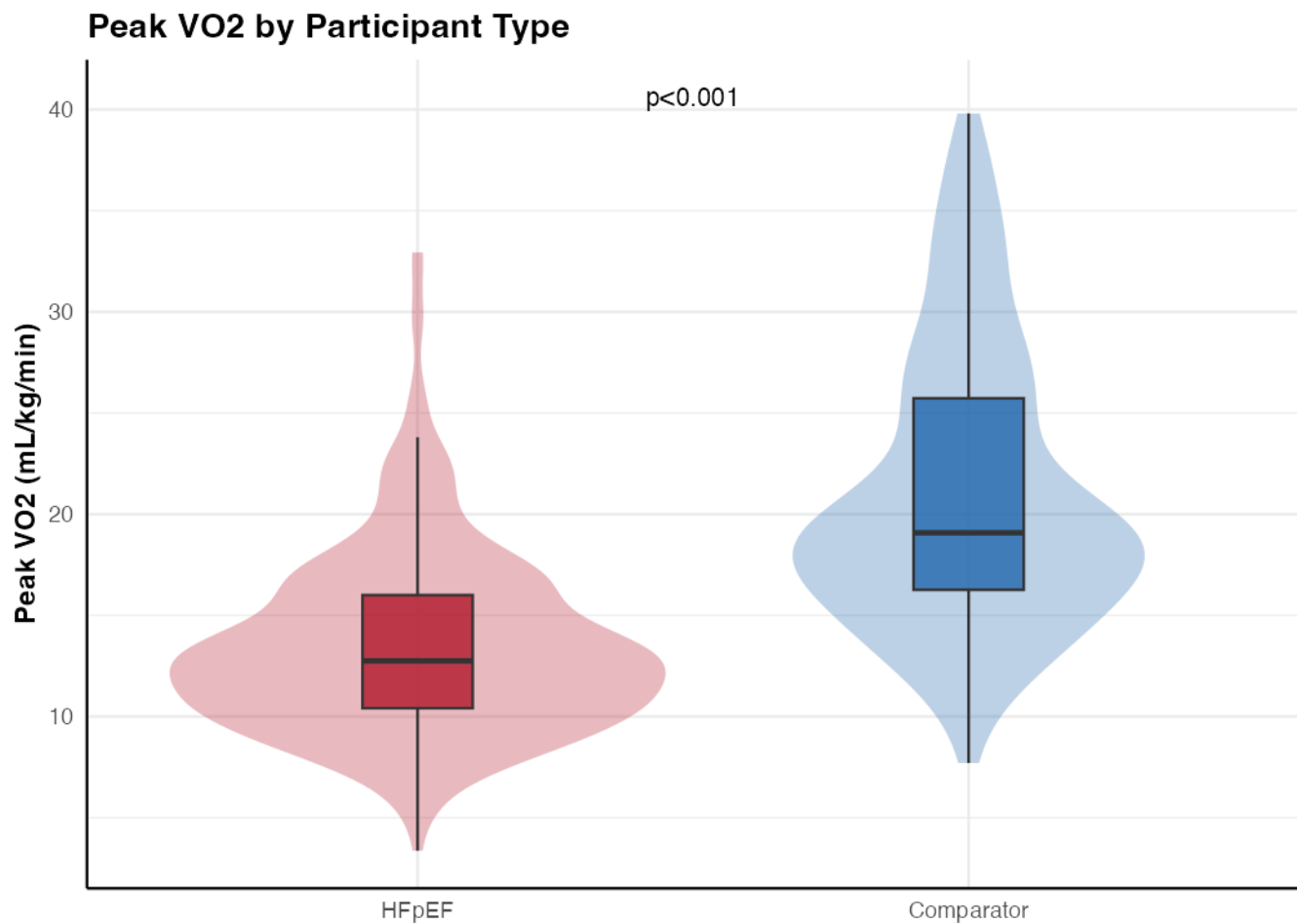
¹ n (%); Mean (SD)
² Pearson's Chi-squared test; Fisher's exact test; Wilcoxon rank sum test

2.9 Table 9: CT Body Composition

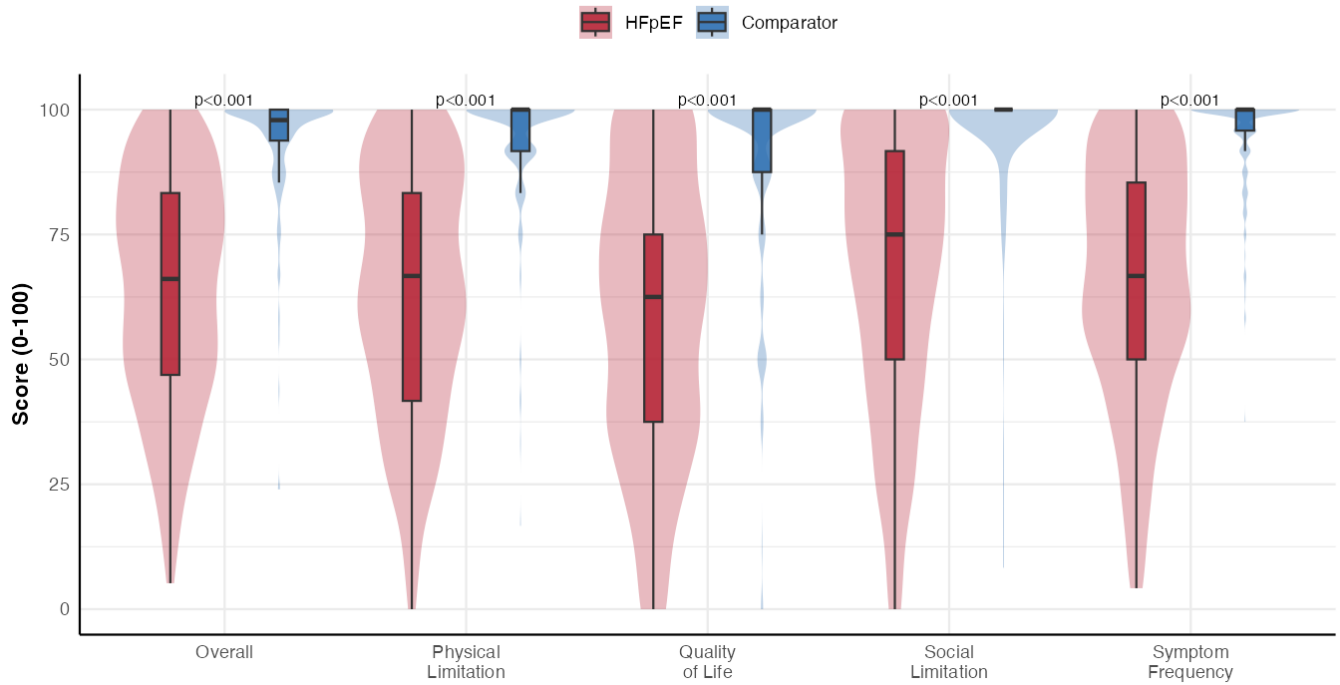
Characteristic	Overall N = 620	Deep Phenotyping Participant Type		p-value
		HFpEF N = 400	Comparator N = 220	
Skeletal muscle area at L3 (cm ²)	134.0 (38.4)	132.5 (37.2)	136.1 (40.1)	0.46
Skeletal muscle density at L3 (HU)	29.0 (10.5)	24.7 (9.4)	34.9 (8.8)	<0.001
Subcutaneous fat area at L3 (cm ²)	275.9 (142.5)	314.4 (149.6)	223.9 (113.6)	<0.001
Subcutaneous fat density at L3 (HU)	-101.8 (8.5)	-101.8 (9.9)	-101.7 (6.2)	0.17
Visceral fat area at L3 (cm ²)	188.2 (121.4)	222.3 (121.1)	140.8 (105.1)	<0.001
Visceral fat density at L3 (HU)	-96.8 (8.0)	-98.2 (7.4)	-95.0 (8.4)	<0.001
Intramuscular fat area at L3 (cm ²)	13.4 (9.3)	16.7 (10.1)	9.0 (5.5)	<0.001
Intramuscular fat density at L3 (HU)	-62.0 (6.2)	-63.2 (5.5)	-60.3 (6.7)	<0.001

¹ Mean (SD)
² Wilcoxon rank sum test

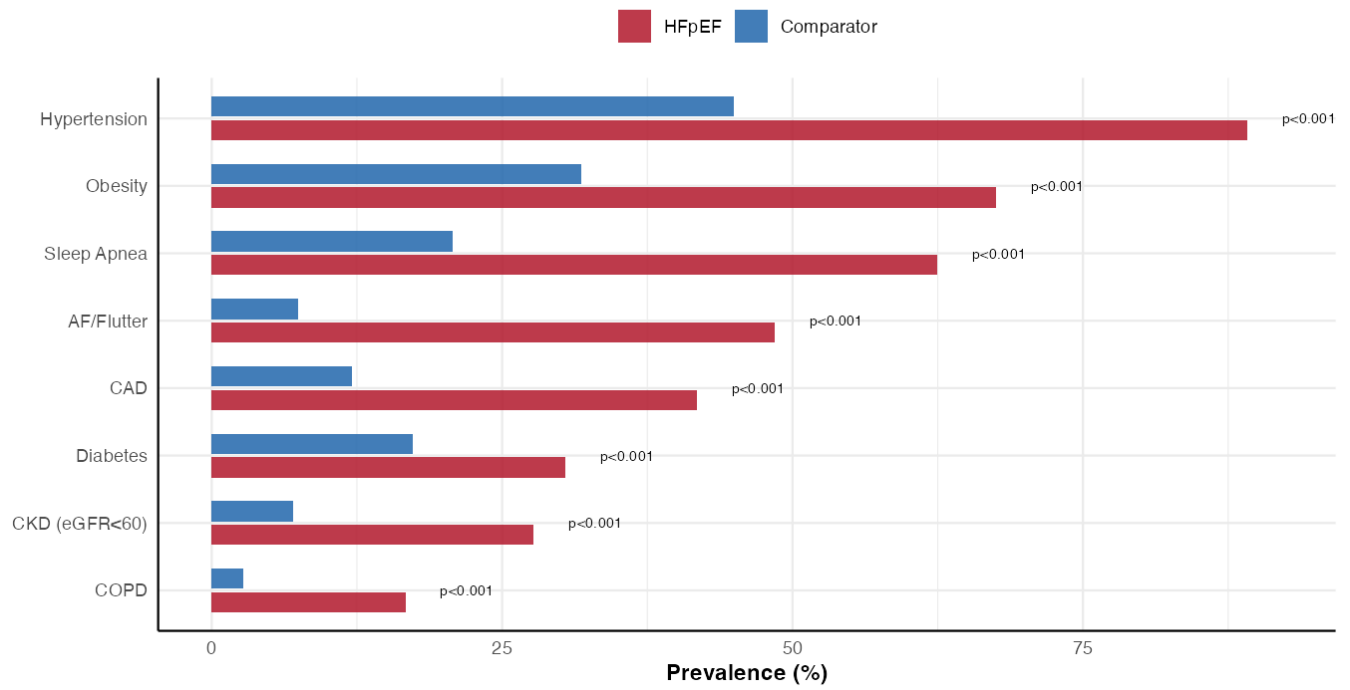
2.10 Key Figures



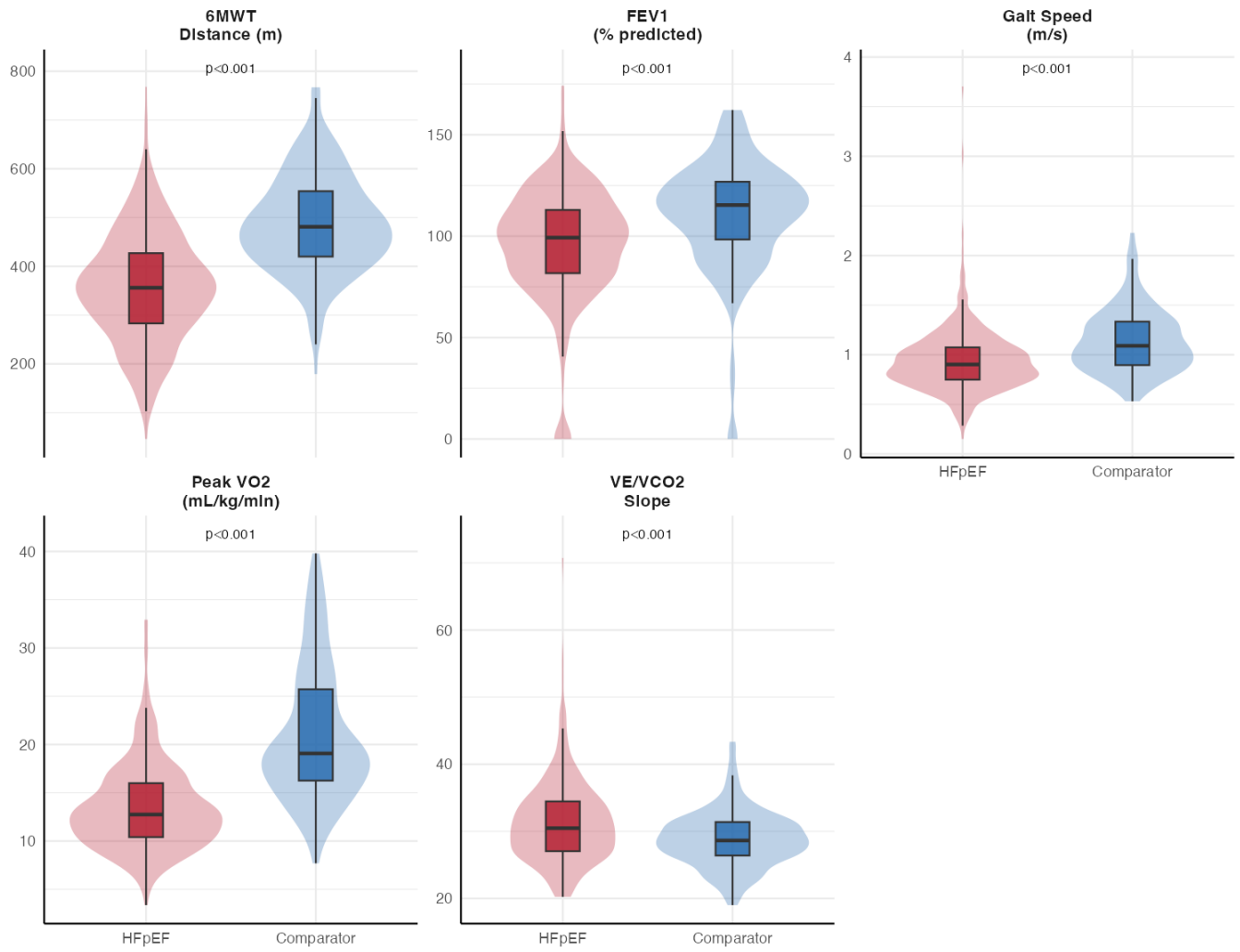
KCCQ-12 Domain Scores by Participant Type



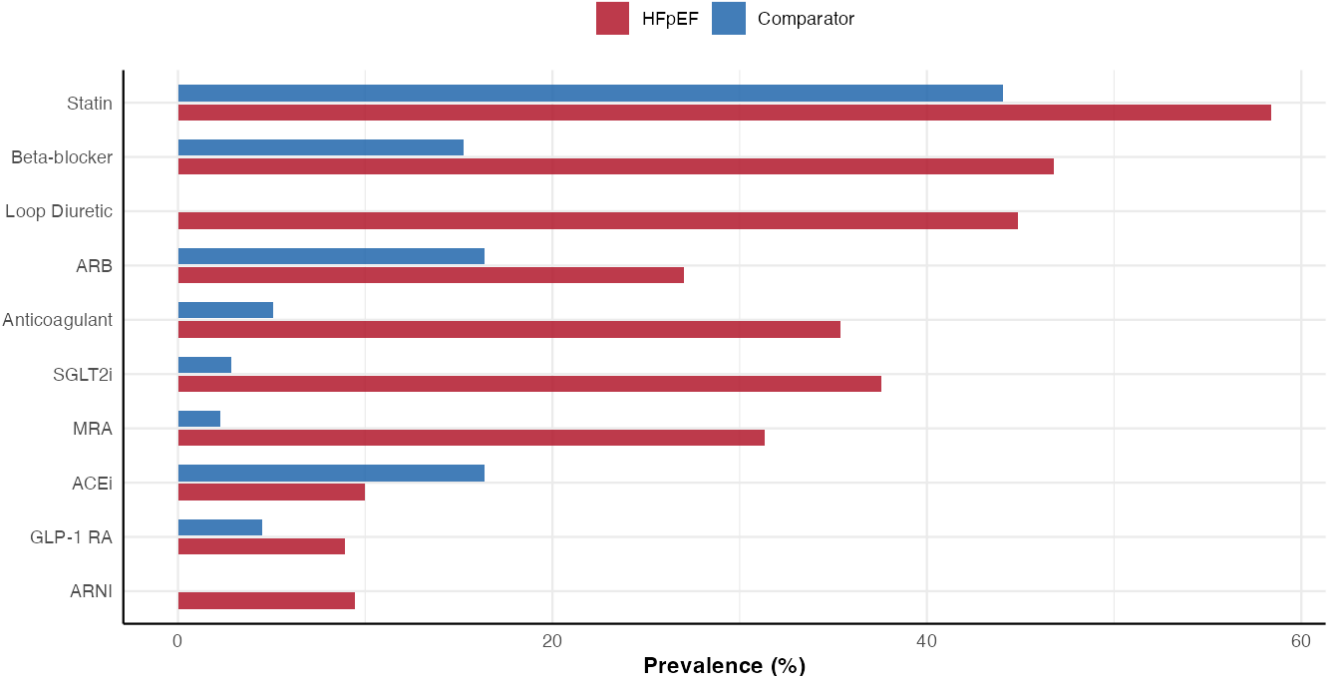
Comorbidity Prevalence by Participant Type



Exercise Capacity, Pulmonary Function, and Physical Performance



Medication Use by Participant Type



2.11 Deep Phenotyping: Stratification by Site

2.11.1 HFpEF

Characteristic	Mayo Clinic N = 84	MGB N = 45	Northwestern N = 83	Penn N = 41	UC Davis N = 48	Wake Forest N = 91	p-value
Age	71.7 (9.3)	70.6 (11.6)	73.6 (11.0)	71.1 (9.2)	72.3 (9.4)	70.7 (10.4)	0.29
Sex							0.79
Male	30 (35.7%)	19 (42.2%)	32 (38.6%)	13 (31.7%)	20 (42.6%)	30 (33.0%)	
Female	54 (64.3%)	26 (57.8%)	51 (61.4%)	28 (68.3%)	27 (57.4%)	61 (67.0%)	
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
BMI	32.7 (6.4)	32.9 (8.3)	32.2 (8.1)	37.7 (8.7)	32.7 (5.7)	35.4 (5.9)	<0.001
NYHA Class							
I	9 (10.7%)	3 (6.8%)	21 (28.8%)	6 (15.4%)	6 (13.0%)	6 (7.1%)	
II	54 (64.3%)	34 (77.3%)	23 (31.5%)	33 (84.6%)	29 (63.0%)	51 (60.7%)	
III	20 (23.8%)	7 (15.9%)	29 (39.7%)	0 (0.0%)	11 (23.9%)	27 (32.1%)	
IV	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
AF/Flutter	46 (56.1%)	21 (46.7%)	47 (56.6%)	17 (44.7%)	28 (65.1%)	25 (28.7%)	<0.001
Hypertension	67 (79.8%)	42 (93.3%)	75 (90.4%)	38 (95.0%)	43 (91.5%)	81 (91.0%)	0.11
Diabetes	24 (28.9%)	11 (24.4%)	31 (37.3%)	13 (33.3%)	18 (38.3%)	21 (23.6%)	0.29
CKD	21 (28.8%)	9 (24.3%)	20 (30.8%)	10 (41.7%)	10 (25.0%)	17 (22.4%)	0.53
Peak VO2	12.2 (3.9)	15.8 (5.2)	14.2 (4.6)	12.4 (5.7)	16.5 (3.8)	12.0 (3.0)	<0.001
6MWT distance	358.8 (115.9)	398.8 (136.1)	340.9 (92.3)	304.5 (92.3)	420.7 (109.1)	340.6 (99.7)	<0.001
KCCQ Overall	58.4 (23.0)	63.2 (22.2)	68.3 (23.3)	62.6 (23.8)	63.0 (24.8)	67.8 (21.2)	0.050
CES-D	9.6 (3.8)	10.1 (4.7)	9.0 (3.3)	8.6 (3.8)	9.7 (4.5)	8.5 (3.6)	0.25
H2FPEF score	5.9 (2.1)	4.5 (2.5)	4.9 (2.2)	5.7 (1.8)	6.0 (1.9)	5.2 (1.6)	0.001
Congestion score							
0	21 (25.0%)	6 (13.6%)	11 (15.1%)	7 (17.1%)	7 (15.2%)	8 (9.4%)	
1	36 (42.9%)	16 (36.4%)	25 (34.2%)	23 (56.1%)	11 (23.9%)	30 (35.3%)	
2	22 (26.2%)	17 (38.6%)	20 (27.4%)	10 (24.4%)	12 (26.1%)	40 (47.1%)	
3	5 (6.0%)	3 (6.8%)	11 (15.1%)	1 (2.4%)	7 (15.2%)	6 (7.1%)	
4	0 (0.0%)	2 (4.5%)	3 (4.1%)	0 (0.0%)	8 (17.4%)	1 (1.2%)	
5	0 (0.0%)	0 (0.0%)	2 (2.7%)	0 (0.0%)	1 (2.2%)	0 (0.0%)	
6	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
eGFR	69.7 (19.3)	73.4 (18.8)	71.7 (22.7)	68.0 (22.7)	68.1 (21.0)	70.7 (15.0)	0.85
Hemoglobin	13.2 (1.5)	13.5 (1.2)	14.1 (1.7)	13.4 (1.5)	13.6 (1.7)	13.6 (1.8)	0.010

¹ Mean (SD); n (%)

² Kruskal-Wallis rank sum test; Fisher's exact test; NA; Pearson's Chi-squared test

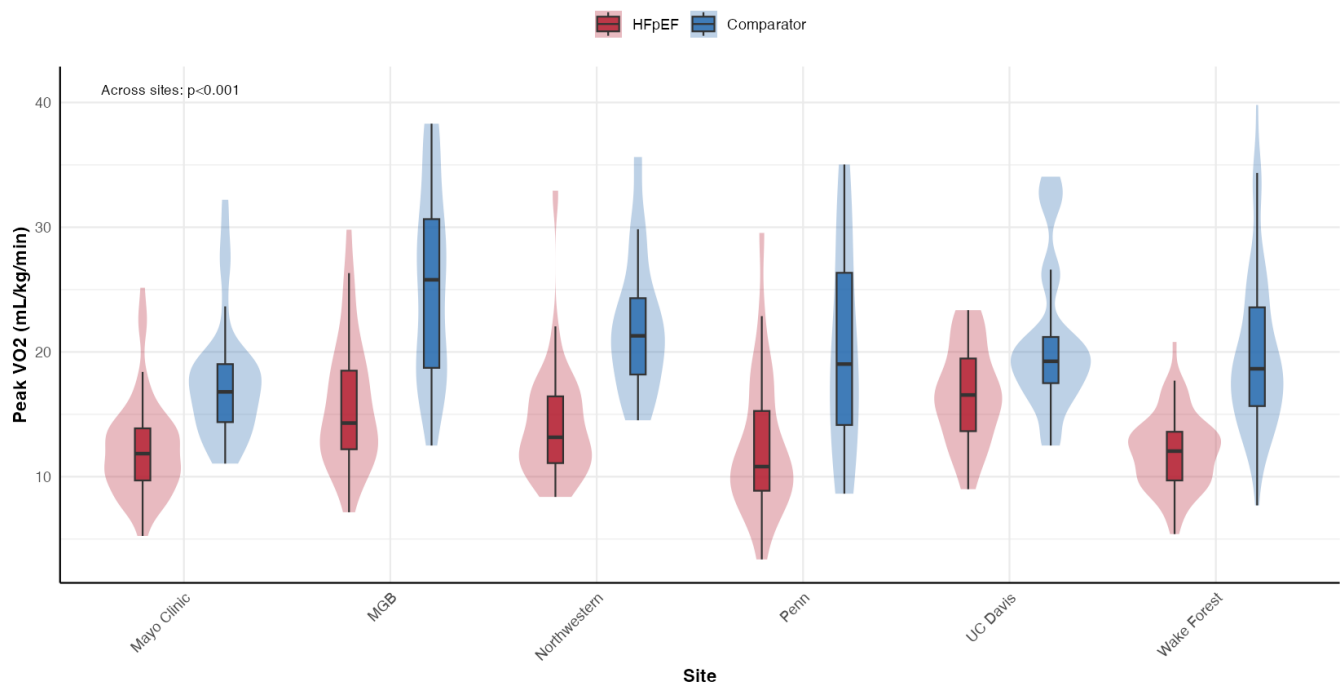
2.11.2 Comparators

Characteristic	Mayo Clinic N = 41	MGB N = 46	Northwestern N = 19	Penn N = 14	UC Davis N = 28	Wake Forest N = 72	p-value
Age	66.7 (12.5)	55.9 (13.0)	63.8 (14.3)	60.4 (6.6)	67.6 (10.1)	62.3 (15.5)	0.001
Sex							0.25
Male	20 (48.8%)	24 (52.2%)	12 (63.2%)	5 (35.7%)	12 (42.9%)	24 (33.3%)	
Female	21 (51.2%)	22 (47.8%)	7 (36.8%)	9 (64.3%)	16 (57.1%)	47 (65.3%)	
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	
BMI	27.5 (5.0)	26.6 (4.6)	27.1 (3.3)	28.5 (6.9)	29.7 (6.2)	29.1 (5.5)	0.12
AF/Flutter	3 (7.7%)	0 (0.0%)	1 (5.3%)	0 (0.0%)	6 (23.1%)	6 (8.3%)	0.016
HTN	19 (46.3%)	15 (32.6%)	10 (52.6%)	5 (35.7%)	19 (70.4%)	30 (42.3%)	0.050
Diabetes	3 (7.3%)	10 (21.7%)	4 (21.1%)	1 (7.1%)	8 (29.6%)	12 (16.7%)	0.17
CKD	1 (2.5%)	2 (4.8%)	2 (11.8%)	0 (0.0%)	3 (10.7%)	6 (9.7%)	0.53
Peak VO2	17.6 (4.8)	25.4 (7.5)	22.1 (5.6)	20.0 (8.6)	20.9 (6.0)	19.9 (6.4)	<0.001
6MWT distance	503.7 (104.0)	528.0 (106.4)	422.6 (73.6)	469.8 (104.3)	492.6 (91.2)	471.3 (92.0)	<0.001
KCCQ Overall	95.6 (8.5)	97.1 (4.8)	94.9 (9.9)	89.5 (11.9)	92.1 (12.3)	92.7 (14.4)	0.067
CES-D	7.0 (2.6)	7.6 (3.8)	6.7 (2.2)	9.4 (4.4)	7.3 (3.5)	7.1 (2.5)	0.22
eGFR	87.9 (15.1)	99.5 (17.9)	85.0 (19.1)	91.3 (13.2)	86.5 (17.7)	83.0 (16.8)	<0.001
Hemoglobin	13.9 (1.3)	13.7 (1.3)	14.2 (1.3)	13.4 (1.1)	13.7 (1.3)	13.9 (1.5)	0.56

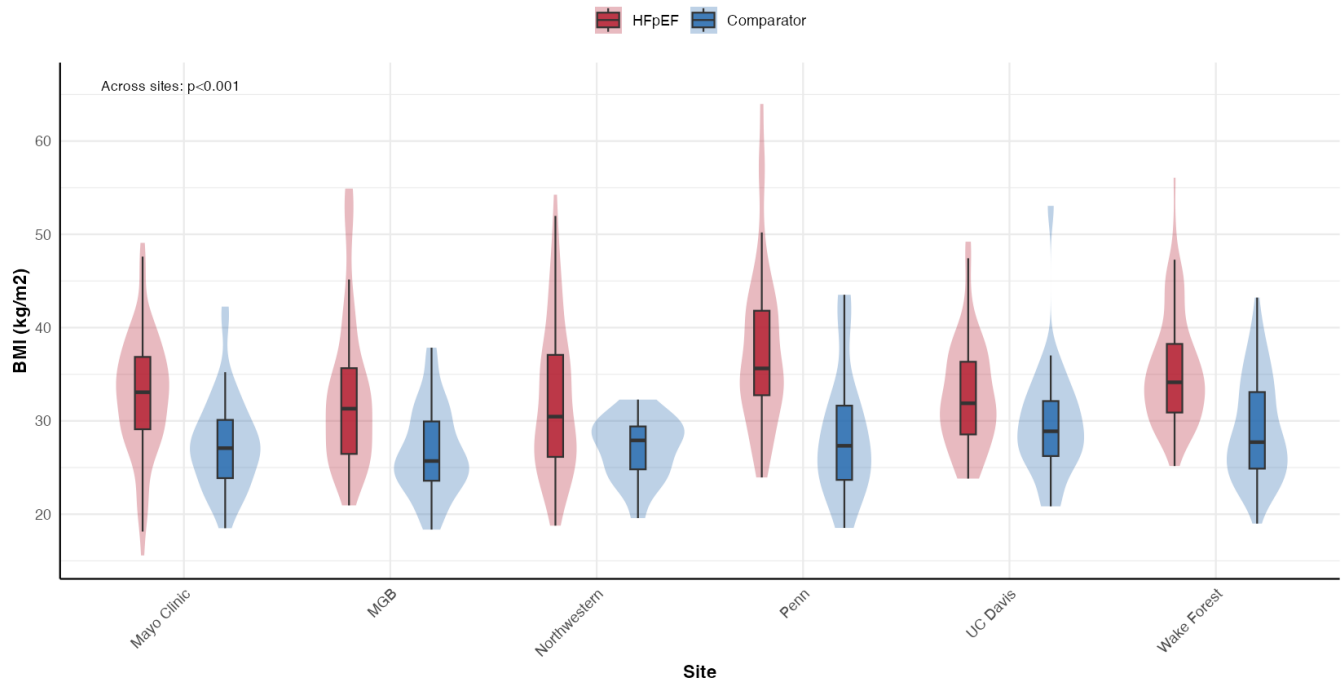
¹ Mean (SD); n (%)

² Kruskal-Wallis rank sum test; Fisher's exact test; Pearson's Chi-squared test

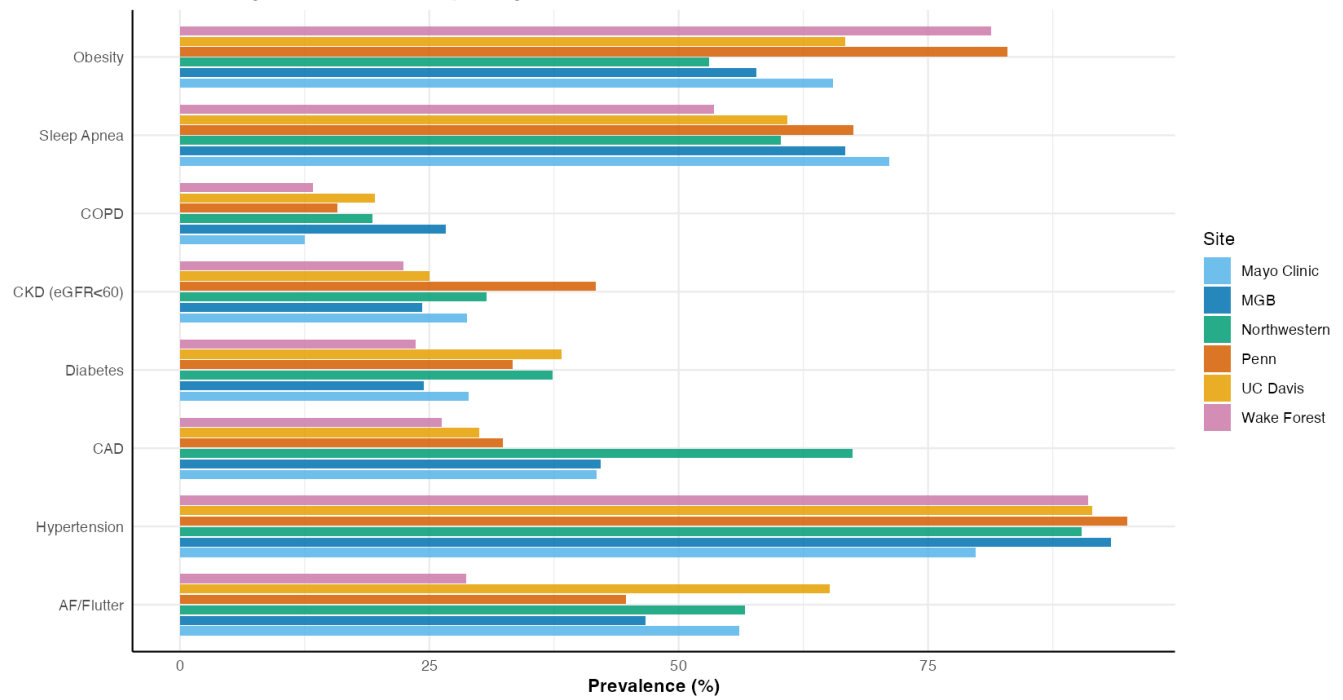
Peak VO2 by Site and Participant Type



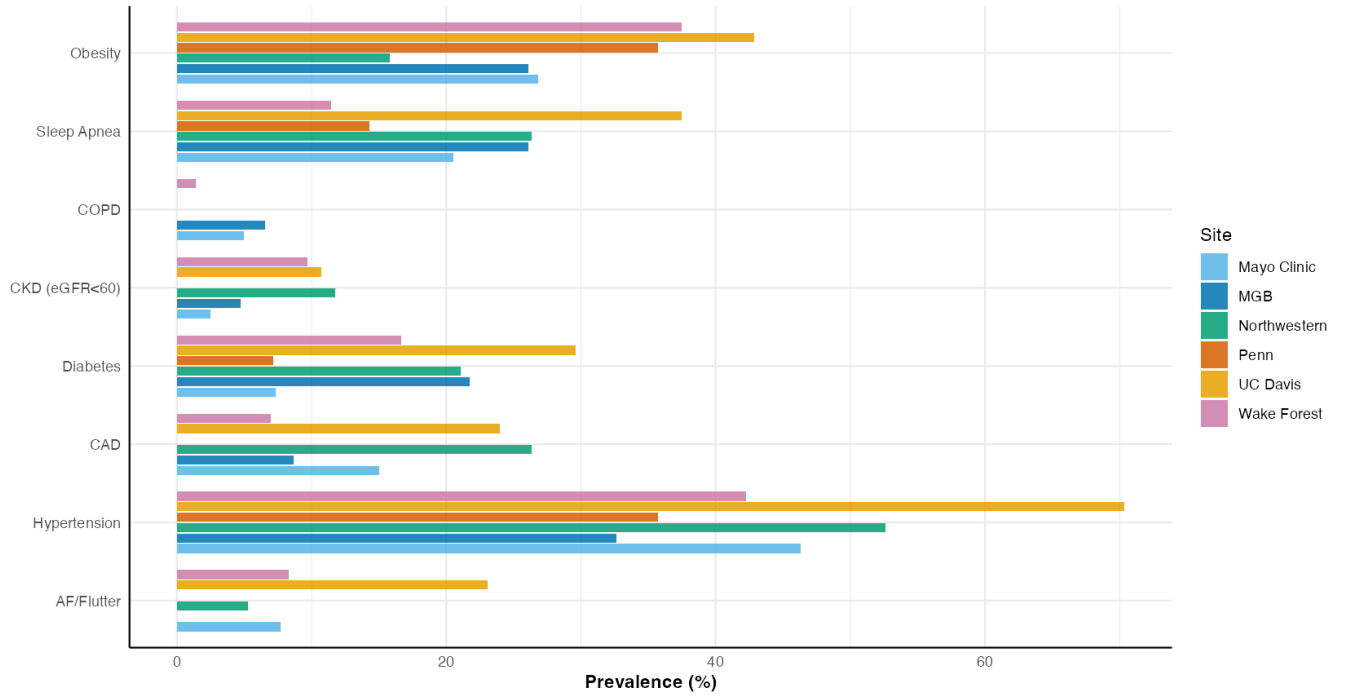
BMI by Site and Participant Type



Comorbidity Prevalence in HFpEF by Site



Comorbidity Prevalence in Comparators by Site



3 HeartShare Registry

3.1 Registry: HF vs Comparator

Registry analytic cohort (registry_complete = Yes): 3960 participants

Group	N
Heart failure	2414
Comparator	1546

Characteristic	Overall N = 3,960	Registry Participant Type		p-value
		Heart failure N = 2,414	Comparator N = 1,546	
Age (years)	66.2 (13.7)	70.3 (11.0)	59.9 (15.0)	<0.001
Sex				<0.001
Male	1,885 (47.6%)	1,265 (52.4%)	620 (40.1%)	
Female	2,070 (52.3%)	1,147 (47.5%)	923 (59.7%)	
Other	5 (0.1%)	2 (0.1%)	3 (0.2%)	
Race				
Asian	180 (4.7%)	50 (2.1%)	130 (8.8%)	
Black or African American	379 (9.8%)	232 (9.8%)	147 (9.9%)	
Native Hawaiian or Pacific Islander	1 (0.0%)	1 (0.0%)	0 (0.0%)	
White	3,184 (82.7%)	2,049 (86.3%)	1,135 (76.8%)	
More than one race	93 (2.4%)	33 (1.4%)	60 (4.1%)	
Other	7 (0.2%)	3 (0.1%)	4 (0.3%)	
Prefer not to answer	8 (0.2%)	6 (0.3%)	2 (0.1%)	
Ethnicity				
Not Hispanic or Latino	3,656 (92.3%)	2,308 (95.6%)	1,348 (87.2%)	
Cuban	8 (0.2%)	6 (0.2%)	2 (0.1%)	
Mexican, Mexican American, Chicano	125 (3.2%)	39 (1.6%)	86 (5.6%)	
Puerto Rican	37 (0.9%)	10 (0.4%)	27 (1.7%)	
Other Hispanic or Latino	96 (2.4%)	27 (1.1%)	69 (4.5%)	
Unknown	26 (0.7%)	16 (0.7%)	10 (0.6%)	
Prefer not to answer	12 (0.3%)	8 (0.3%)	4 (0.3%)	
BMI (kg/m², self-reported)	29.8 (7.2)	30.9 (7.7)	27.9 (5.9)	<0.001
AF/Flutter	1,226 (32.3%)	1,105 (48.0%)	121 (8.1%)	<0.001
Hypertension	2,415 (61.6%)	1,746 (73.2%)	669 (43.6%)	<0.001
CAD	905 (24.3%)	746 (33.3%)	159 (10.8%)	<0.001
Diabetes	726 (18.4%)	579 (24.2%)	147 (9.5%)	<0.001
CKD (eGFR <60)	100 (19.8%)	86 (27.7%)	14 (7.1%)	<0.001
COPD	407 (10.5%)	339 (14.4%)	68 (4.5%)	<0.001
Sleep apnea	1,408 (37.3%)	1,123 (48.8%)	285 (19.3%)	<0.001
Obesity	326 (54.3%)	260 (67.4%)	66 (30.8%)	<0.001
Comorbidity count	3.2 (2.2)	4.0 (2.1)	1.8 (1.6)	<0.001
Self-reported NYHA Class				<0.001
Class I	1,608 (40.6%)	638 (26.4%)	970 (62.7%)	
Class II	1,742 (44.0%)	1,223 (50.7%)	519 (33.6%)	
Class III	543 (13.7%)	497 (20.6%)	46 (3.0%)	
Class IV	67 (1.7%)	56 (2.3%)	11 (0.7%)	

(continued)

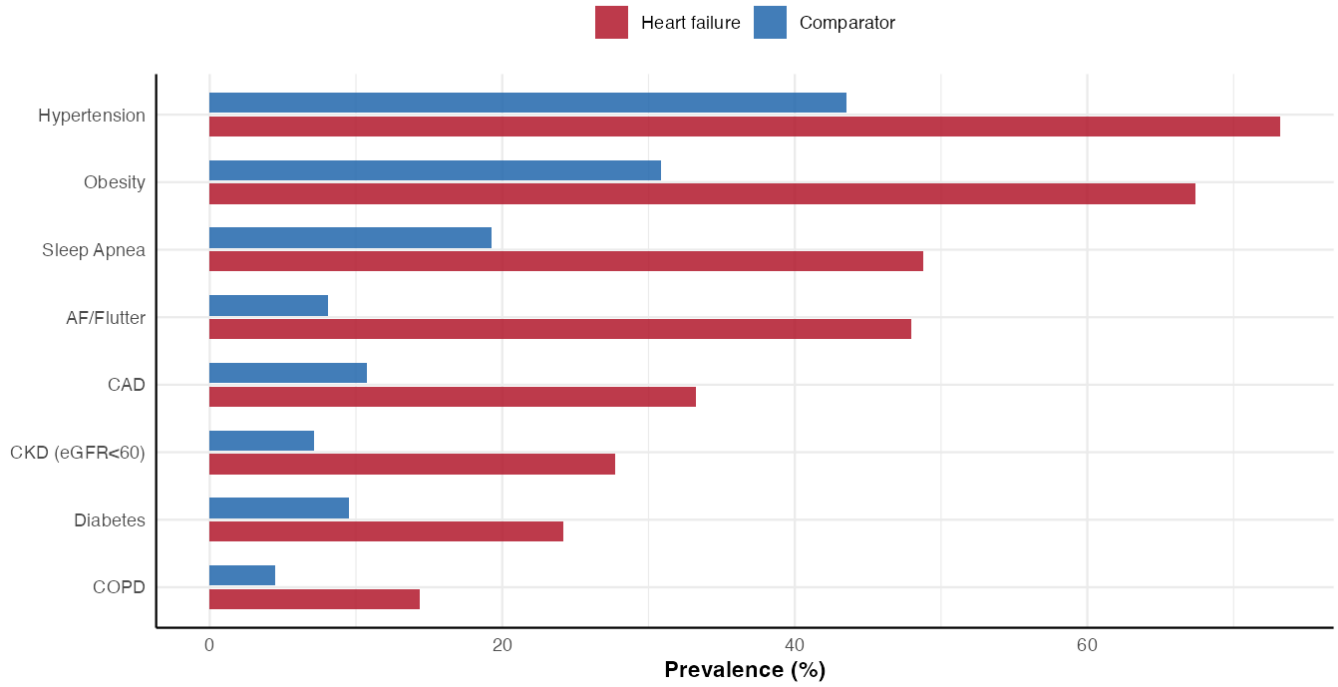
Characteristic	Registry Participant Type			p-value
	Overall N = 3,960	Heart failure N = 2,414	Comparator N = 1,546	
KCCQ-12 Overall Summary	78.2 (23.1)	69.7 (24.0)	91.4 (13.5)	<0.001
KCCQ-12 Clinical Summary	79.7 (22.4)	71.6 (23.4)	92.4 (12.6)	<0.001
KCCQ-12 Physical Limitation	78.3 (25.2)	69.1 (26.5)	92.4 (14.3)	<0.001
KCCQ-12 Quality of Life	73.4 (28.5)	64.1 (29.1)	87.8 (20.4)	<0.001
KCCQ-12 Social Limitation	78.8 (26.6)	71.3 (27.8)	93.1 (16.3)	<0.001
CES-D-10 score	8.3 (3.6)	8.6 (3.8)	7.8 (3.3)	<0.001
Epworth Sleepiness Scale	5.8 (4.1)	6.3 (4.3)	5.1 (3.7)	<0.001
STOP-BANG score	2.9 (1.2)	3.1 (1.1)	2.6 (1.2)	<0.001
Difficulty walking 1 block	1,027 (25.9%)	916 (37.9%)	111 (7.2%)	<0.001
Difficulty climbing 1 flight	763 (19.3%)	679 (28.1%)	84 (5.4%)	<0.001

¹ Mean (SD); n (%)
² Wilcoxon rank sum test; Fisher's exact test; NA; Pearson's Chi-squared test

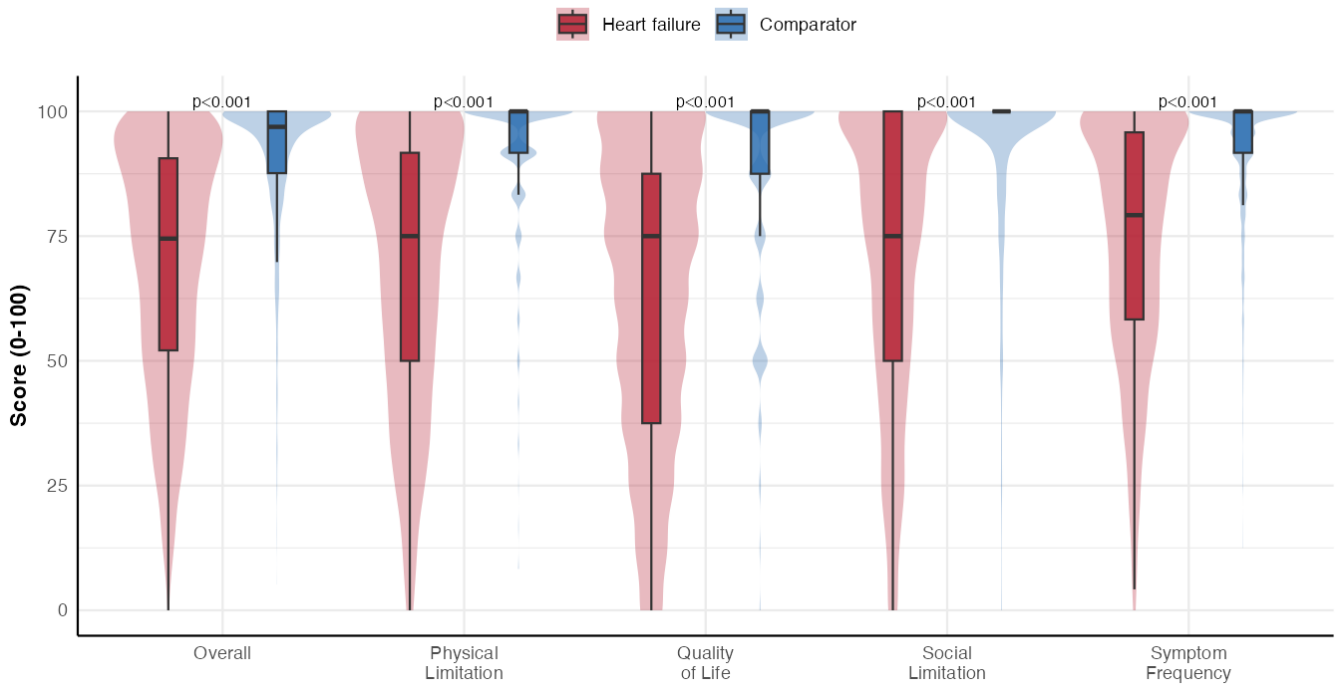
Characteristic	Registry Participant Type			p-value
	Overall N = 3,960	Heart failure N = 2,414	Comparator N = 1,546	
ACEi	412 (12.0%)	249 (11.4%)	163 (12.9%)	0.18
ARB	670 (19.4%)	468 (21.4%)	202 (16.0%)	<0.001
ARNI	541 (15.7%)	537 (24.6%)	4 (0.3%)	<0.001
Beta-blocker	1,601 (46.5%)	1,363 (62.4%)	238 (18.9%)	<0.001
MRA	851 (24.7%)	811 (37.1%)	40 (3.2%)	<0.001
SGLT2i	870 (25.3%)	840 (38.4%)	30 (2.4%)	<0.001
GLP-1 RA	158 (4.6%)	131 (6.0%)	27 (2.1%)	<0.001
Any diuretic	1,682 (48.8%)	1,503 (68.8%)	179 (14.2%)	<0.001
Loop diuretic	843 (24.5%)	826 (37.8%)	17 (1.3%)	<0.001
Thiazide	261 (7.6%)	158 (7.2%)	103 (8.2%)	0.31
CCB	517 (15.0%)	315 (14.4%)	202 (16.0%)	0.20
Statin	1,829 (53.1%)	1,311 (60.0%)	518 (41.1%)	<0.001
Anticoagulant	894 (26.0%)	807 (36.9%)	87 (6.9%)	<0.001
Antiplatelet	796 (23.1%)	651 (29.8%)	145 (11.5%)	<0.001
Total medications	6.0 [3.0, 9.0]	7.0 [5.0, 11.0]	3.0 [2.0, 6.0]	<0.001

¹ n (%); Median [Q1, Q3]
² Pearson's Chi-squared test; Wilcoxon rank sum test

Comorbidity Prevalence — Registry



KCCQ-12 Domain Scores — Registry



3.2 Registry: Stratification by Site

3.2.1 Heart failure

Characteristic	Mayo Clinic N = 344	MGB N = 370	Northwestern N = 730	Penn N = 283	UC Davis N = 488	Wake Forest N = 157	p-value
Age	71.9 (9.5)	68.0 (11.3)	71.2 (11.2)	67.2 (11.0)	71.0 (11.1)	71.7 (10.4)	<0.001
Sex							
Male	177 (51.5%)	212 (57.3%)	391 (53.6%)	157 (55.5%)	256 (52.5%)	60 (38.2%)	
Female	166 (48.3%)	158 (42.7%)	339 (46.4%)	125 (44.2%)	232 (47.5%)	97 (61.8%)	
Other	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	
BMI	30.8 (7.2)	29.8 (7.3)	30.2 (7.6)	32.7 (8.6)	30.5 (7.5)	33.7 (6.7)	<0.001
AF/Flutter	177 (54.0%)	175 (50.1%)	338 (47.9%)	127 (46.0%)	221 (49.1%)	51 (33.3%)	0.002
HTN	235 (68.9%)	232 (63.2%)	533 (73.9%)	206 (73.6%)	372 (77.3%)	131 (84.5%)	<0.001
Diabetes	79 (23.0%)	75 (20.5%)	177 (24.3%)	66 (23.5%)	125 (26.0%)	40 (26.0%)	0.54
CKD	21 (29.2%)	9 (26.5%)	20 (31.3%)	9 (45.0%)	9 (23.1%)	16 (21.6%)	0.38
NYHA Class							
Class I	54 (15.7%)	106 (28.6%)	228 (31.2%)	84 (29.7%)	128 (26.2%)	31 (19.7%)	
Class II	187 (54.4%)	199 (53.8%)	340 (46.6%)	143 (50.5%)	238 (48.8%)	93 (59.2%)	
Class III	97 (28.2%)	57 (15.4%)	144 (19.7%)	47 (16.6%)	109 (22.3%)	31 (19.7%)	
Class IV	6 (1.7%)	8 (2.2%)	18 (2.5%)	9 (3.2%)	13 (2.7%)	2 (1.3%)	
KCCQ Overall	66.5 (23.6)	70.8 (23.7)	71.0 (24.3)	69.6 (24.7)	70.4 (24.1)	69.7 (22.0)	0.035
CES-D	8.8 (3.6)	8.6 (3.7)	8.5 (3.8)	8.7 (4.1)	8.8 (3.9)	8.2 (3.6)	0.24
Comorbidity count	4.4 (2.2)	3.9 (2.1)	4.0 (2.3)	3.9 (1.9)	4.0 (1.9)	3.9 (2.1)	0.014

¹ Mean (SD); n (%)

² Kruskal-Wallis rank sum test; NA; Pearson's Chi-squared test

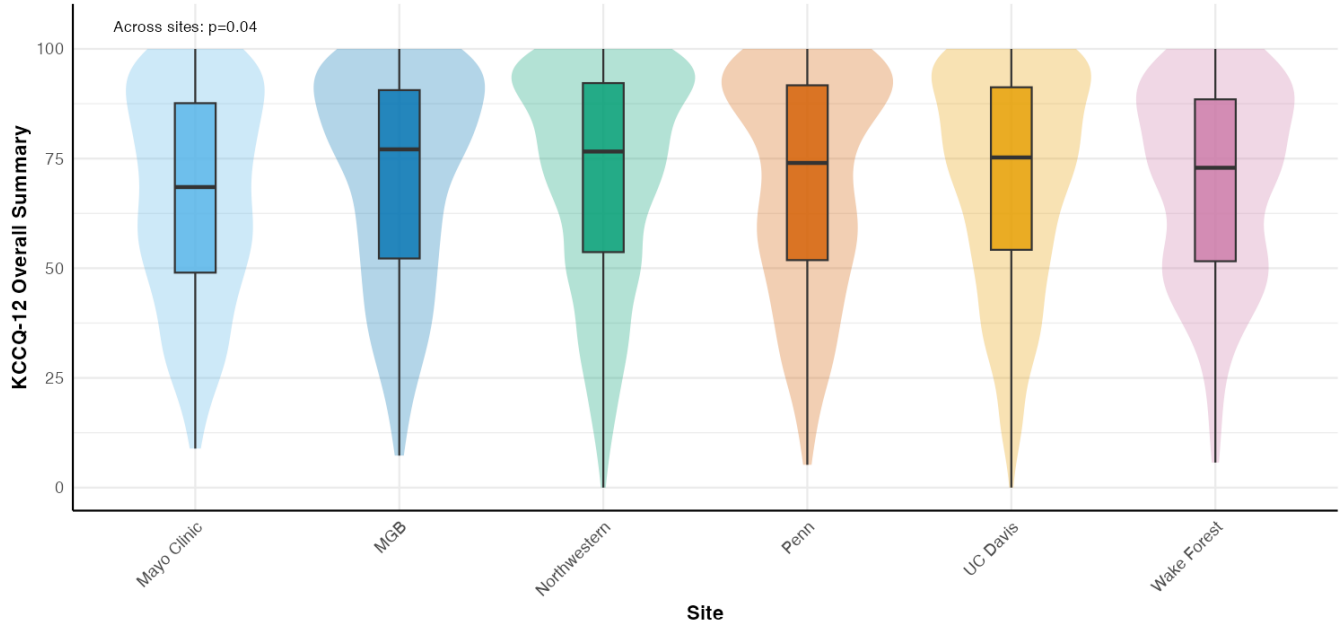
3.2.2 Comparators

Characteristic	Mayo Clinic N = 50	MGB N = 79	Northwestern N = 697	Penn N = 21	UC Davis N = 381	Wake Forest N = 318	p-value
Age	65.7 (13.7)	55.5 (13.7)	54.3 (14.7)	60.0 (7.4)	68.4 (11.2)	62.1 (14.7)	<0.001
Sex							
Male	24 (48.0%)	37 (46.8%)	261 (37.4%)	8 (38.1%)	188 (49.3%)	102 (32.1%)	
Female	26 (52.0%)	42 (53.2%)	434 (62.3%)	13 (61.9%)	193 (50.7%)	215 (67.6%)	
Other	0 (0.0%)	0 (0.0%)	2 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	
BMI	28.4 (6.1)	26.7 (5.6)	27.7 (6.1)	28.4 (6.9)	27.9 (5.2)	28.7 (6.3)	0.069
AF/Flutter	4 (8.2%)	2 (2.5%)	19 (2.8%)	1 (5.0%)	81 (22.7%)	14 (4.5%)	
HTN	22 (44.0%)	27 (34.2%)	241 (34.8%)	10 (47.6%)	242 (64.0%)	127 (40.3%)	<0.001
Diabetes	5 (10.0%)	12 (15.2%)	56 (8.1%)	2 (9.5%)	47 (12.4%)	25 (7.9%)	0.092
CKD	1 (2.6%)	2 (4.8%)	2 (14.3%)	0 (0.0%)	3 (10.3%)	6 (9.7%)	0.48
KCCQ Overall	93.6 (14.1)	95.2 (10.3)	92.5 (12.3)	90.4 (10.7)	88.5 (15.9)	91.5 (13.1)	<0.001
CES-D	7.1 (2.6)	7.2 (3.8)	8.0 (3.5)	9.7 (4.1)	7.8 (3.2)	7.6 (2.8)	0.006
Comorbidity count	2.1 (2.0)	1.8 (2.2)	1.4 (1.4)	2.0 (1.5)	2.8 (1.5)	1.6 (1.4)	<0.001

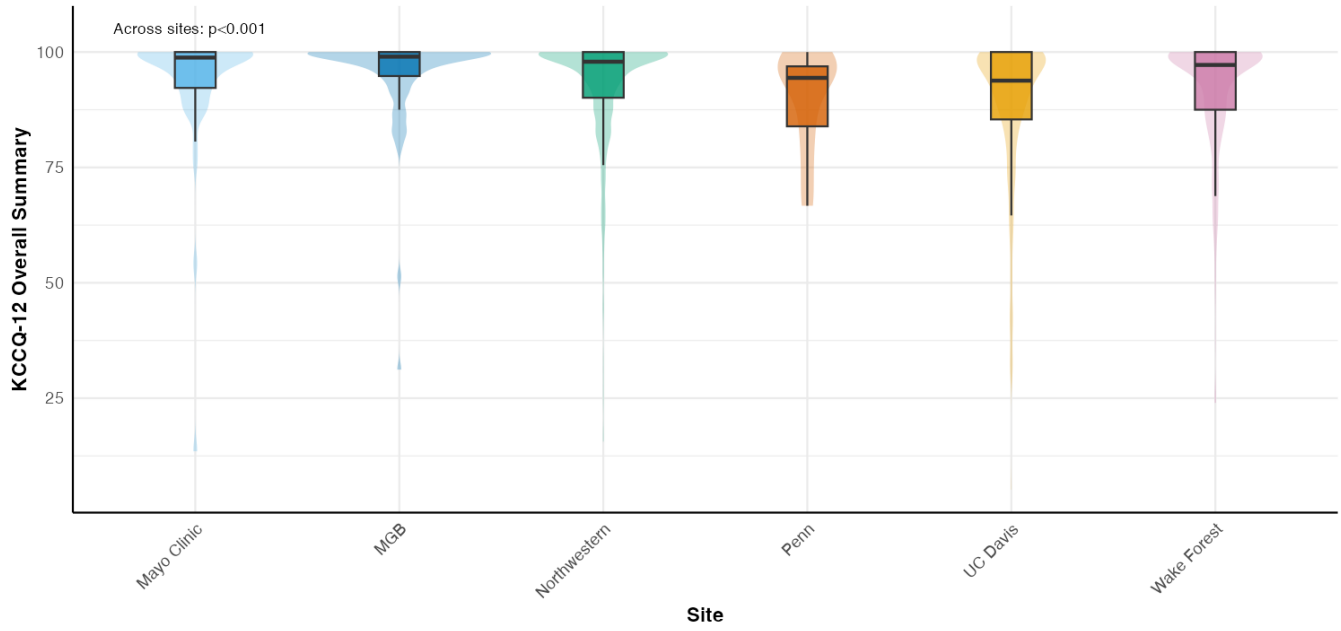
¹ Mean (SD); n (%)

² Kruskal-Wallis rank sum test; NA; Pearson's Chi-squared test; Fisher's exact test

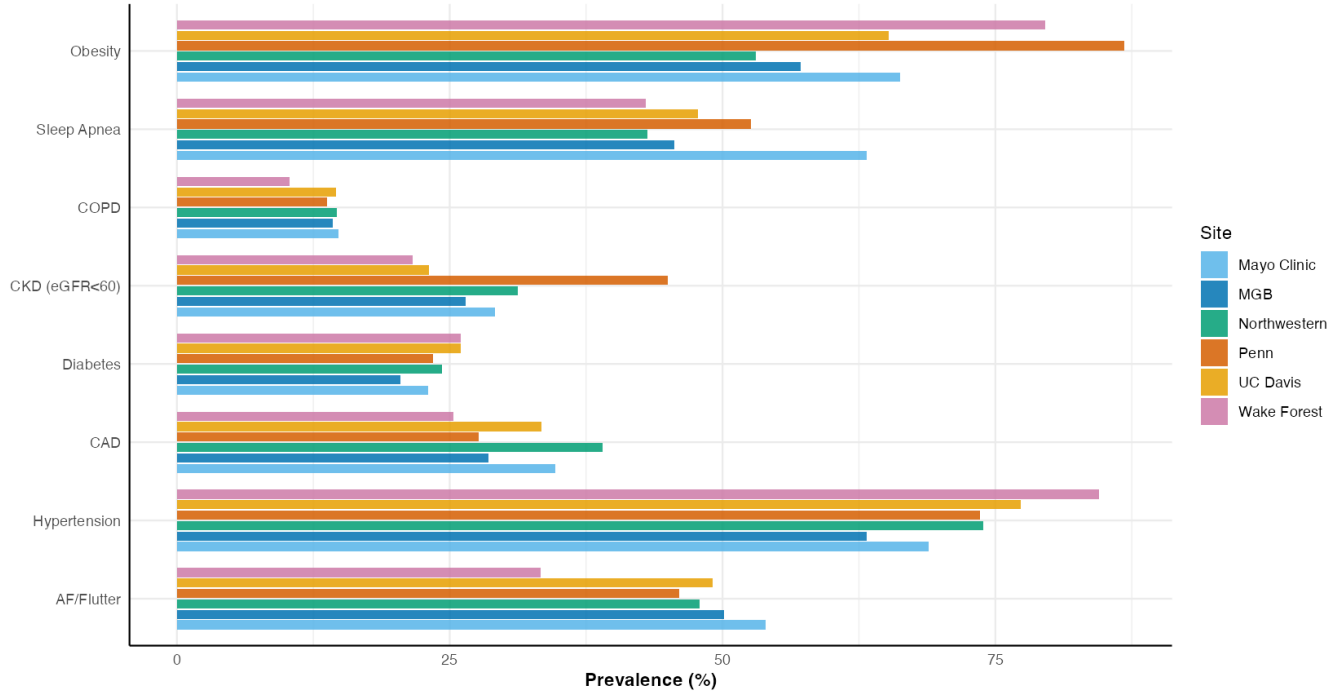
KCCQ Overall Summary in HF by Site – Registry



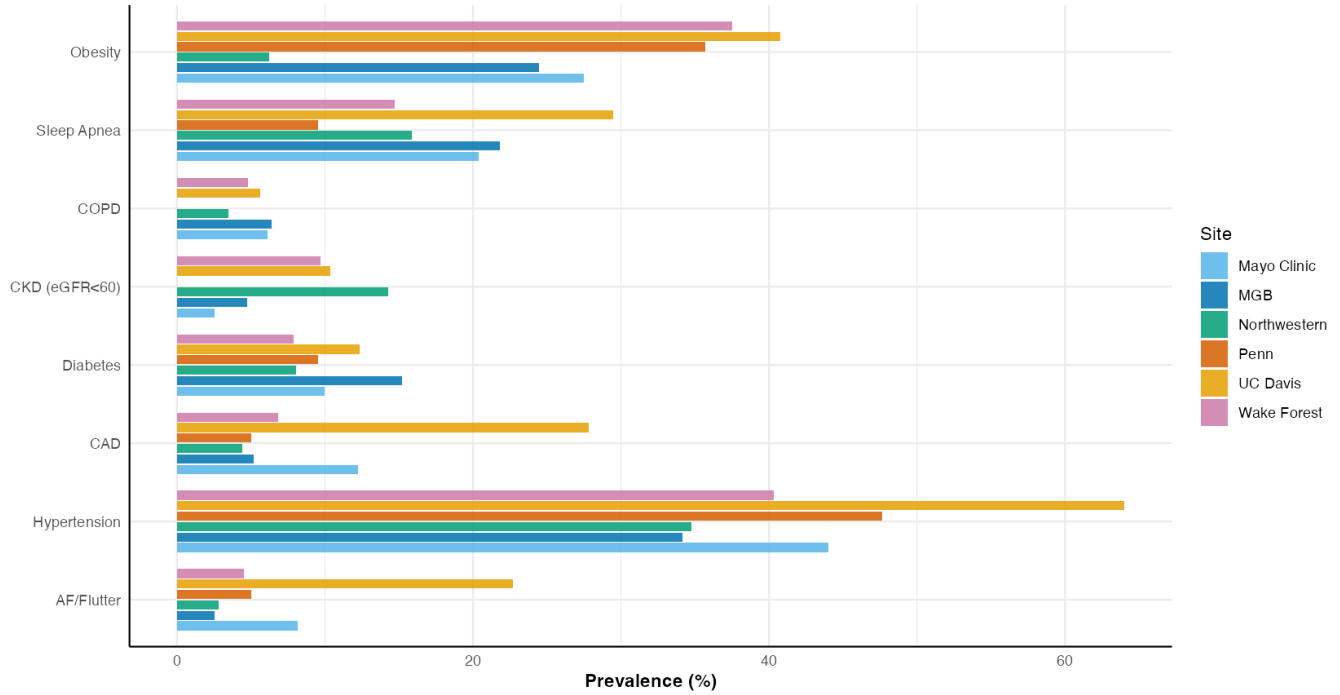
KCCQ Overall Summary in Comparators by Site – Registry



Comorbidity Prevalence in HF by Site – Registry



Comorbidity Prevalence in Comparators by Site – Registry

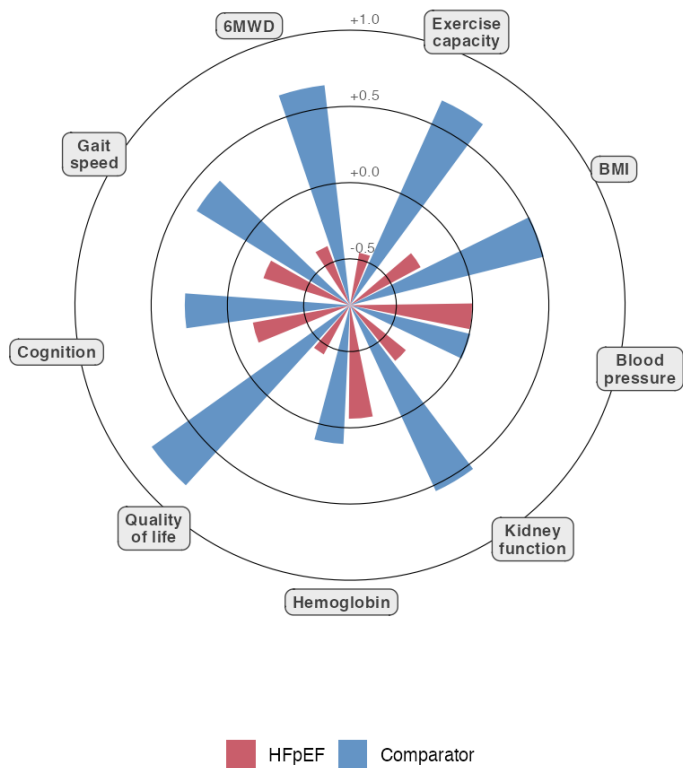


4 Summary Figures

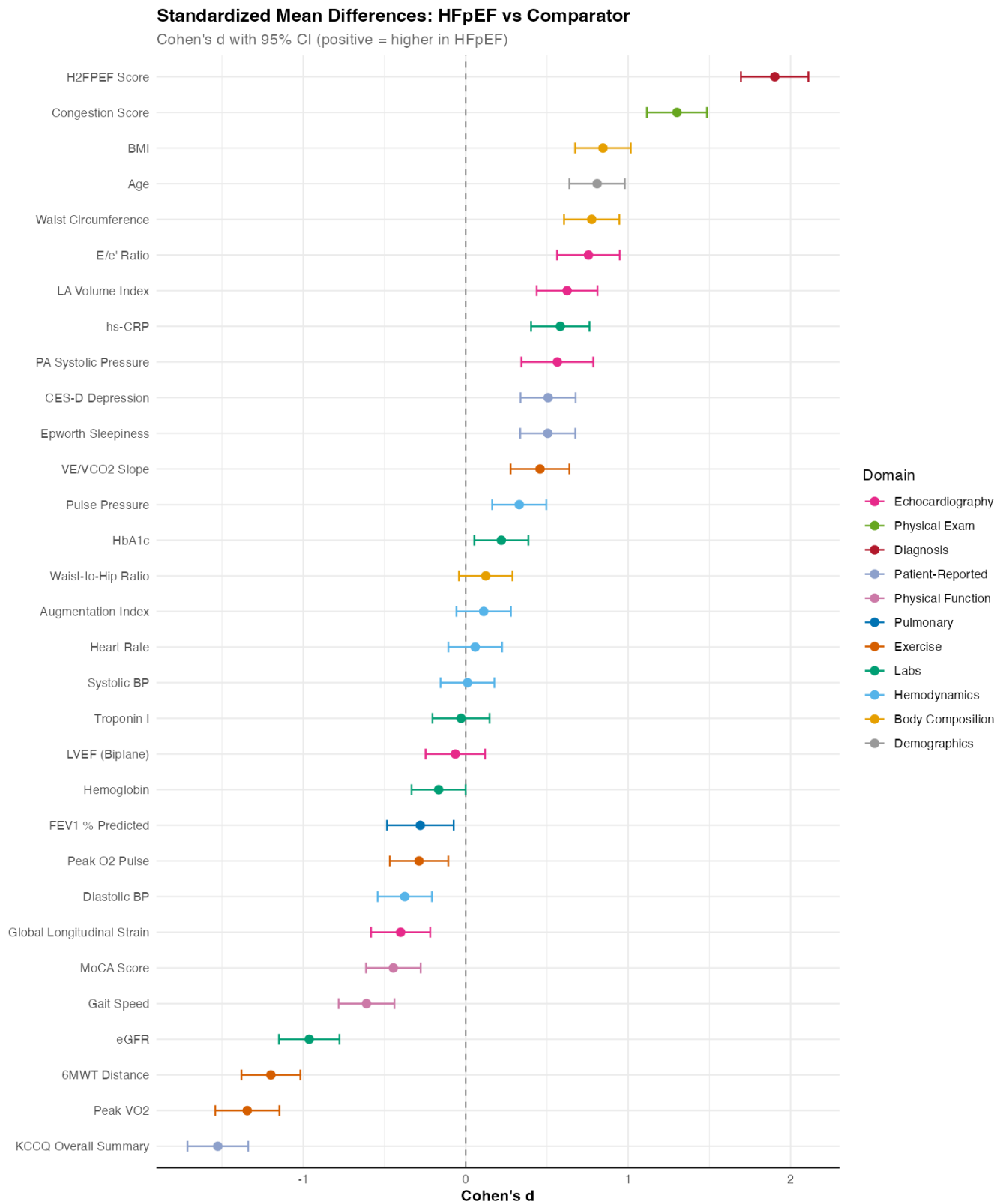
4.1 Radial Bar Plot: Multi-Domain Phenotypic Profile

Multi-Domain Phenotypic Profile: HFpEF vs Comparator

Standardized domain scores (higher = better; displayed as radial bars)



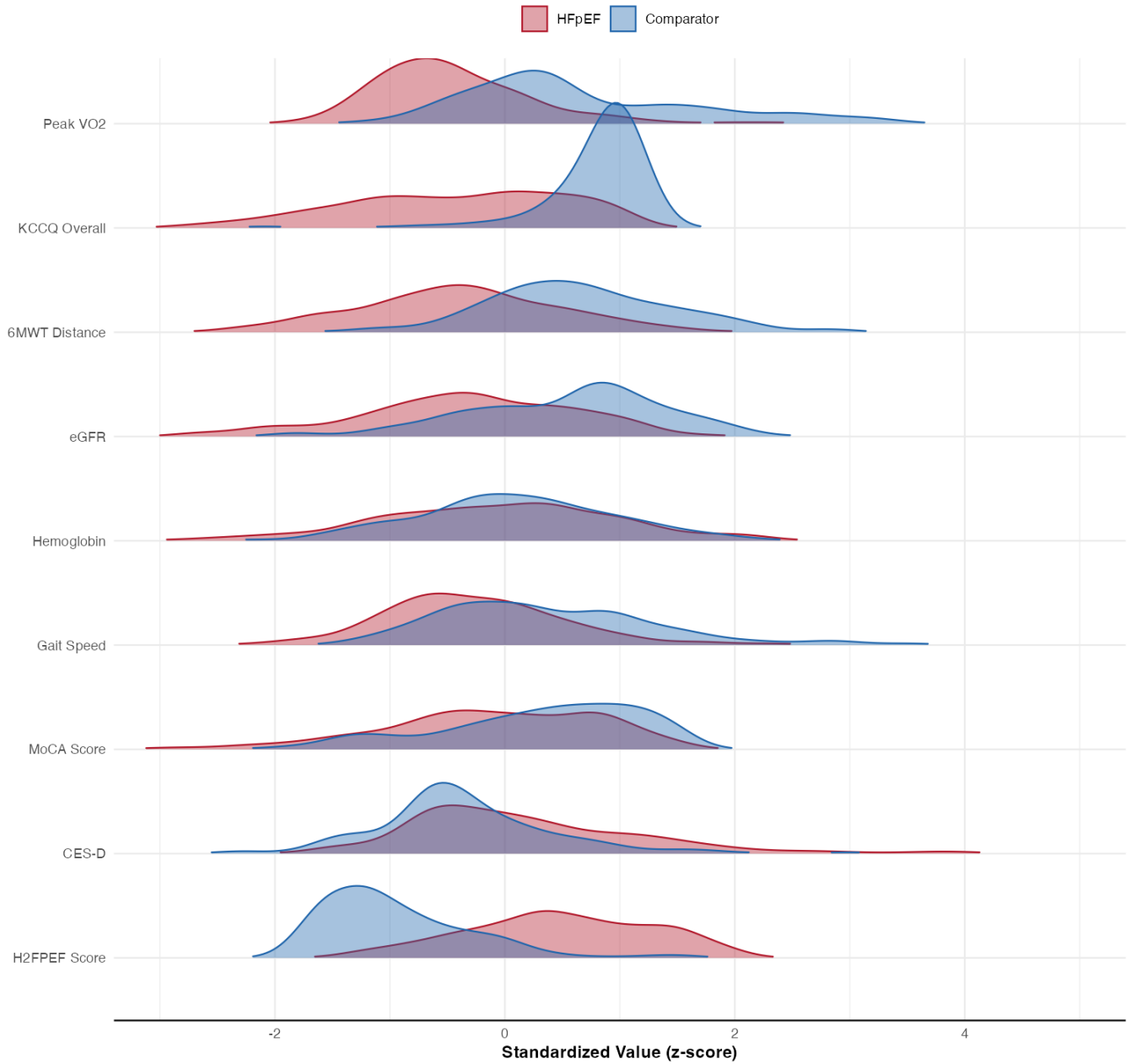
4.2 Forest Plot: Standardized Mean Differences



4.3 Ridgeline Density Plots

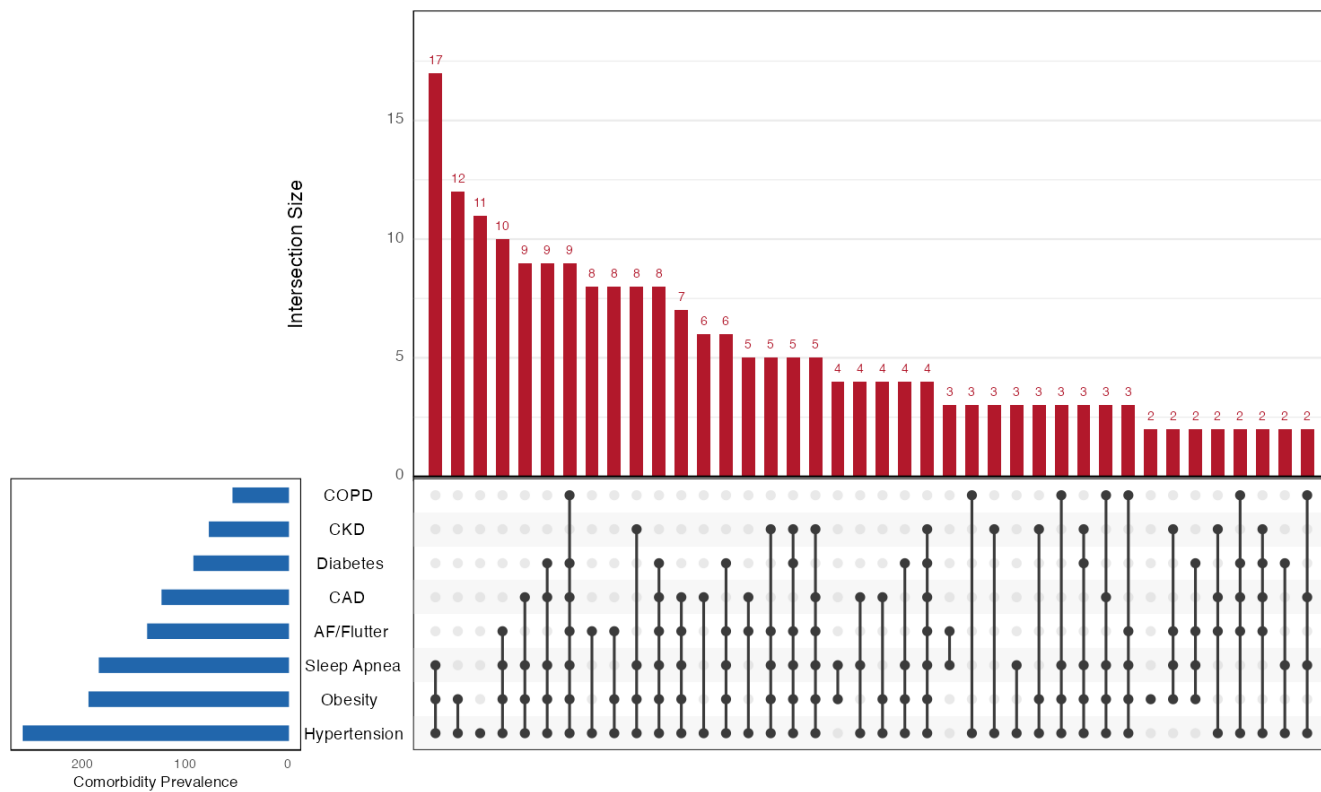
Distribution of Key Phenotypic Measures: HFpEF vs Comparator

Standardized values (z-scores) for cross-domain comparison

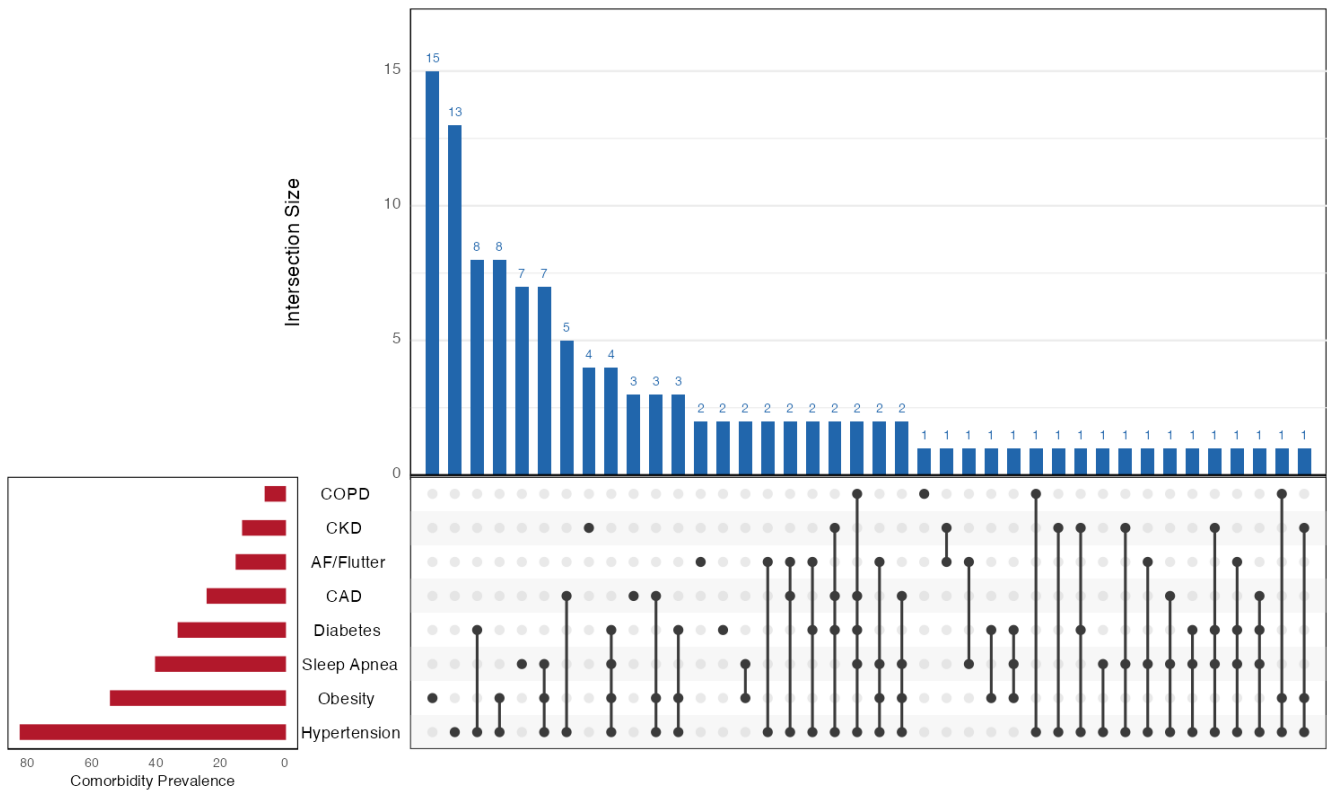


4.4 UpSet Plot: Comorbidity Combinations

4.4.1 HFpEF



4.4.2 Comparator

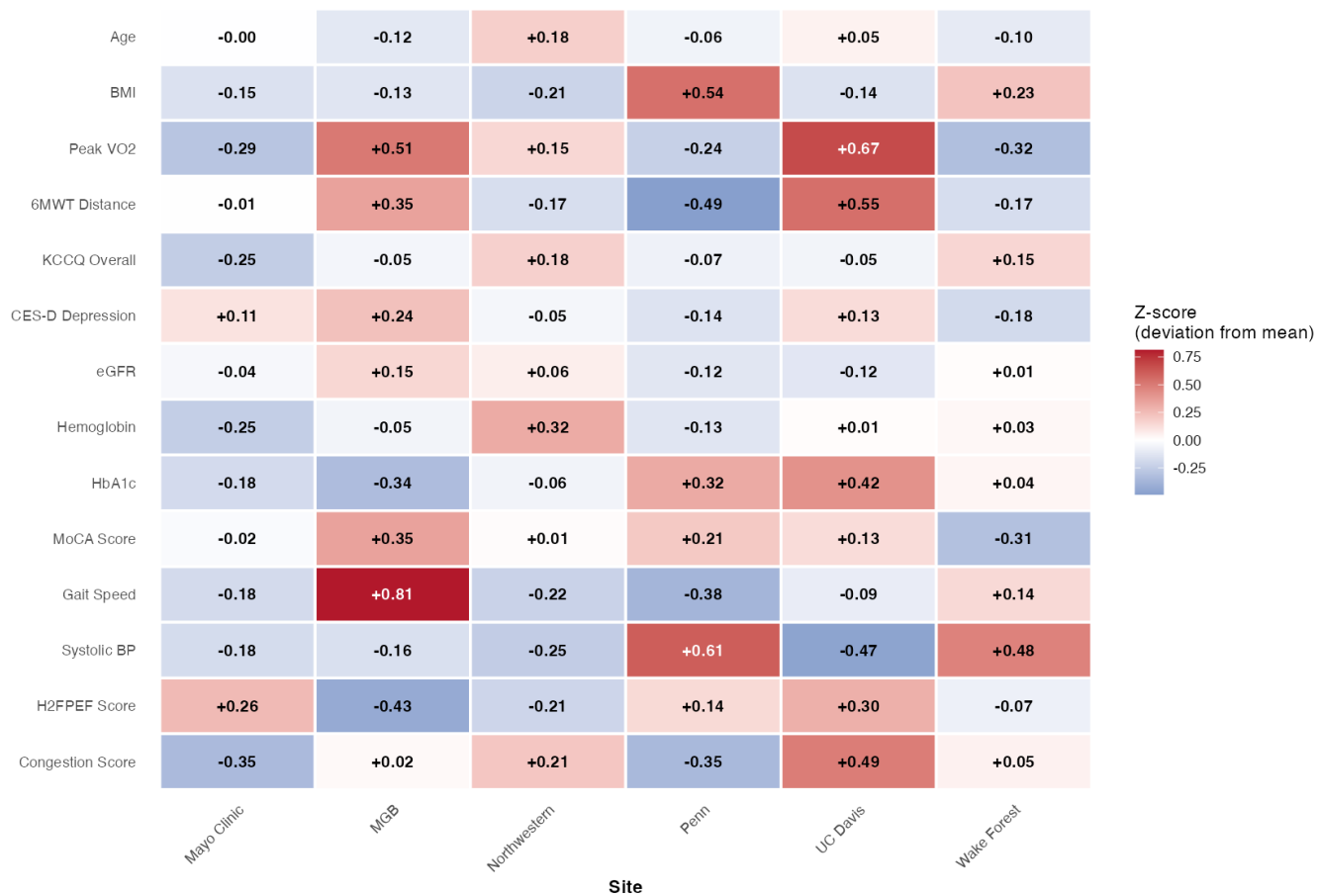


4.5 Site Heterogeneity Heatmap

4.5.1 HFpEF

Site Heterogeneity in HFpEF: Deviation from Overall Mean

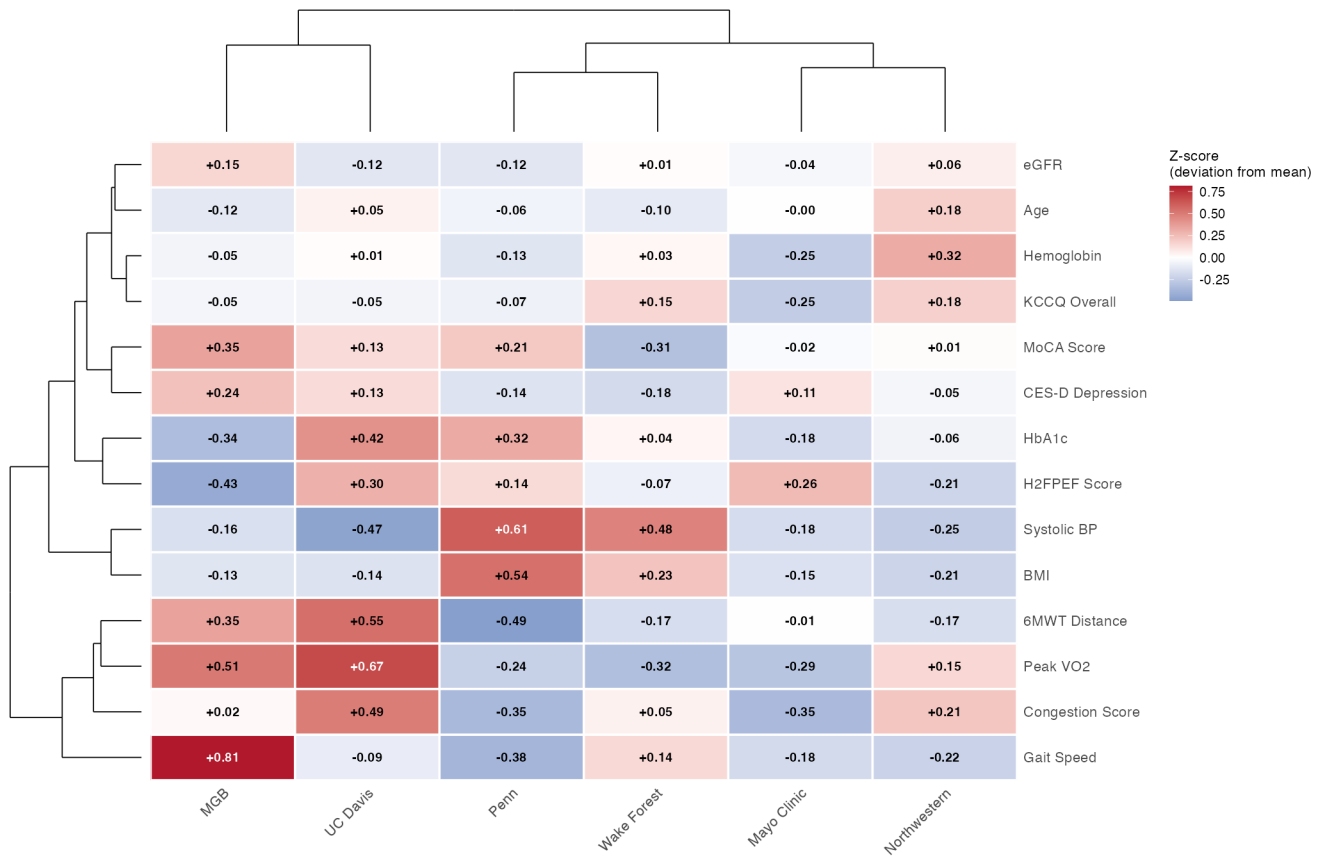
Z-scores of site means relative to overall HFpEF mean



4.5.2 HFpEF (Clustered with Dendrograms)

Site Heterogeneity in HFpEF (Clustered)

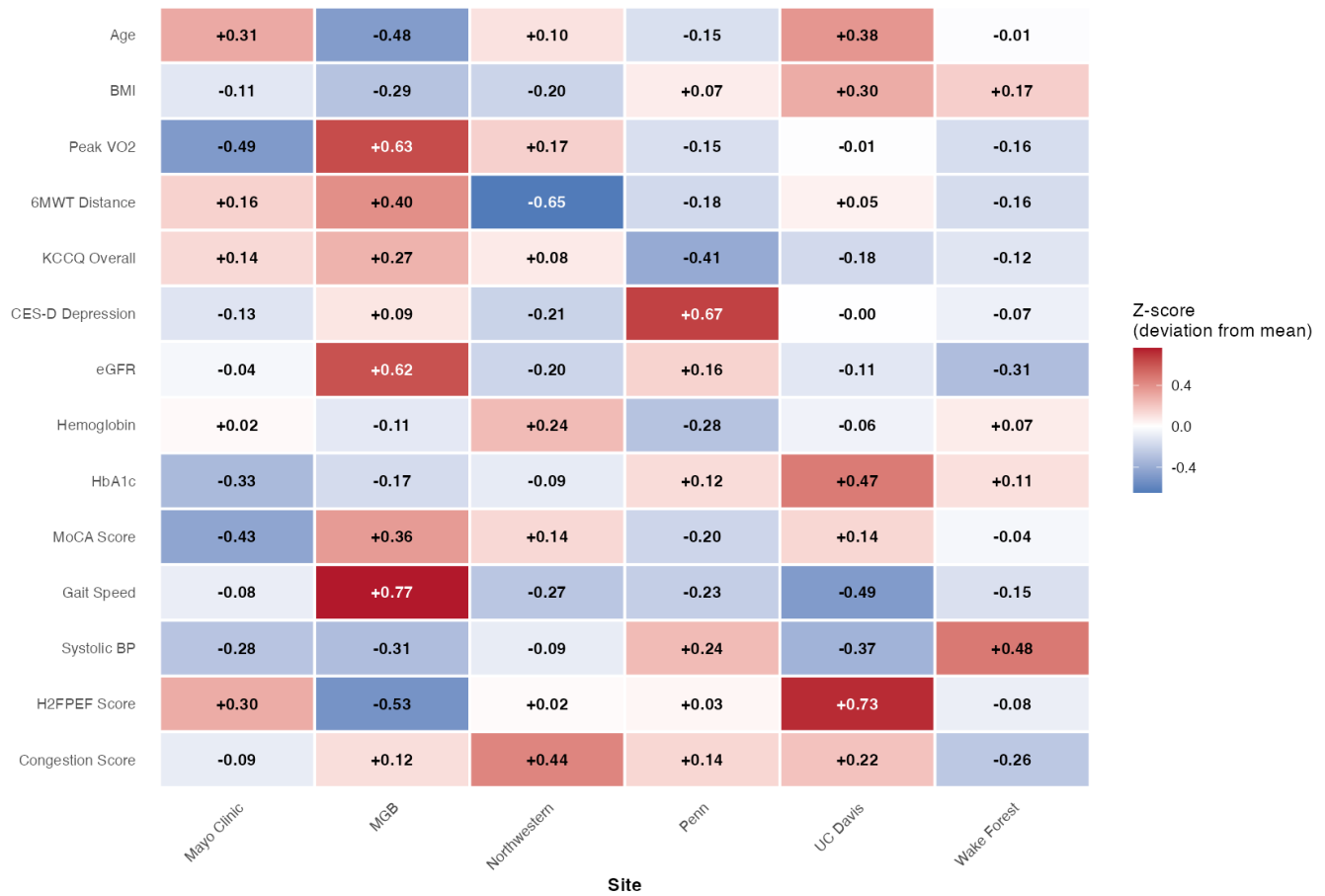
Hierarchically clustered; HFpEF



4.5.3 Comparator

Site Heterogeneity in Comparators: Deviation from Overall Mean

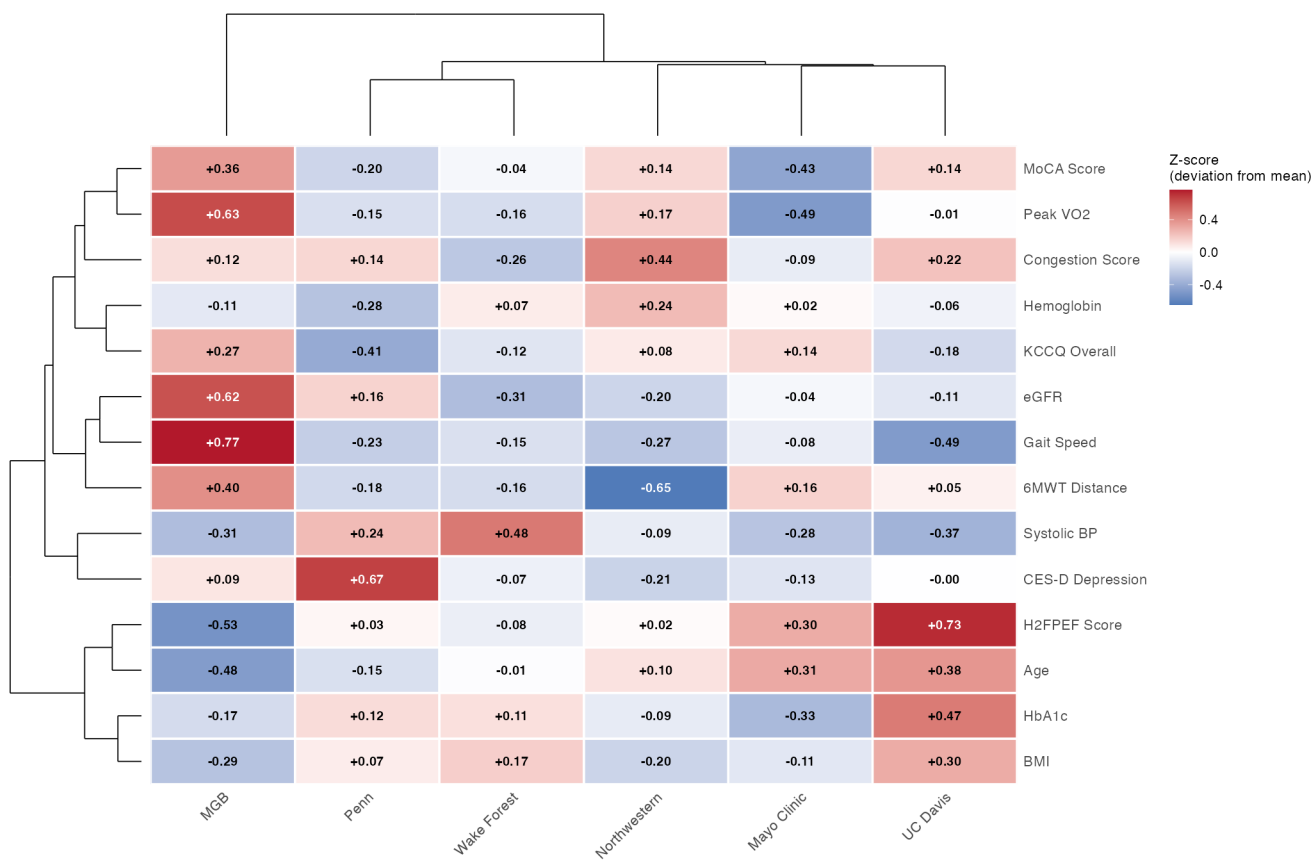
Z-scores of site means relative to overall Comparator mean



4.5.4 Comparator (Clustered with Dendrograms)

Site Heterogeneity in Comparators (Clustered)

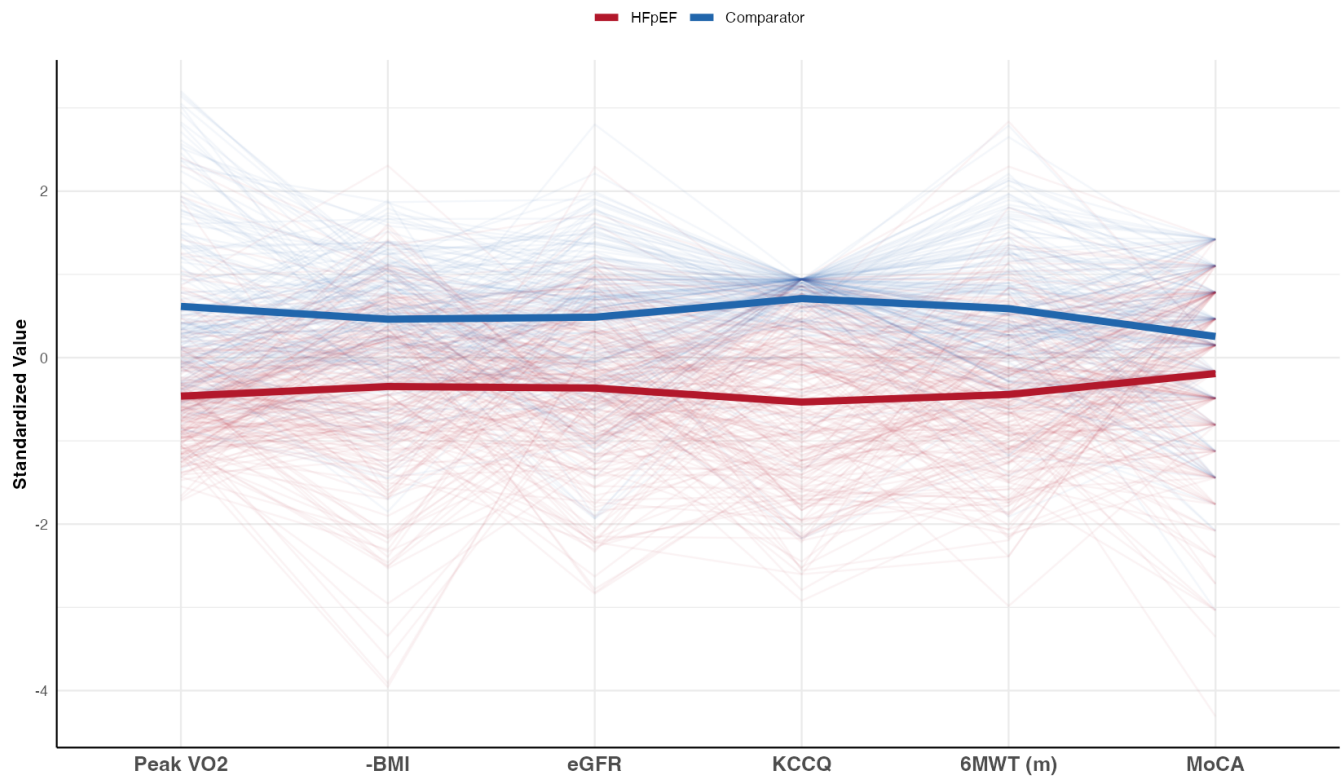
Hierarchically clustered; Comparator



4.6 Parallel Coordinates Plot

Parallel Coordinates: Multivariate Phenotypic Profiles

Individual trajectories (faint) and group means (bold); all axes: higher = better



4.7 Correlation Network

Phenotype Correlation Network in HFpEF

Node size = HFpEF vs Comparator effect size; edges = correlations ($|r| > 0.25$)

