

Multidimensional physiological reserve and long-term cardiovascular risk among breast cancer survivors: a prospective UK Biobank study

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Supplementary Table 1. Association of continuous Physical Reserve Index with clinical outcomes according to breast cancer status.

Outcome	NBC HR ^a (95% CI)	NBC P ^a	BC HR ^a (95% CI)	BC P ^b	P for interaction ^c
Heart failure	0.57 (0.55–0.59)	<0.001	0.60 (0.52–0.69)	<0.001	0.490
Atrial fibrillation	0.80 (0.78–0.82)	<0.001	0.77 (0.69–0.85)	<0.001	0.395
All-cause death	0.76 (0.74–0.77)	<0.001	0.89 (0.83–0.95)	<0.001	<0.001

^a HRs represent the association per 1-standard-deviation higher PRI within each breast cancer stratum.

^b P values for within-stratum associations were calculated using Wald tests from Cox proportional hazards models.

^c P for interaction was calculated from the multiplicative interaction term between continuous PRI and breast cancer status in the Cox model.

Abbreviations: BC, breast cancer; NBC, No breast cancer; CI, confidence interval; HR, hazard ratio; PRI, Physical Reserve Index.

Supplementary Table 2. Associations of Physical Reserve Index tertiles with clinical outcomes according to breast cancer status.

Outcome	Group	PRI group	HR (95% CI)	P value^b	Overall P for interaction^c
Heart failure	NBC	Low ^a	Reference		0.257
		Middle	0.53 (0.48–0.57)	<0.001	
		High	0.36 (0.32–0.41)	<0.001	
	BC	Low ^a	Reference		
		Middle	0.62 (0.45–0.84)	0.002	
		High	0.53 (0.33–0.87)	0.012	
Atrial fibrillation	NBC	Low ^a	Reference		0.589
		Middle	0.78 (0.74–0.82)	<0.001	
		High	0.72 (0.67–0.77)	<0.001	
	BC	Low ^a	Reference		
		Middle	0.70 (0.56–0.87)	0.002	
		High	0.73 (0.54–1.01)	0.055	
All-cause death	NBC	Low ^a	Reference		<0.001
		Middle	0.71 (0.68–0.74)	<0.001	
		High	0.62 (0.58–0.65)	<0.001	
	BC	Low ^a	Reference		
		Middle	0.80 (0.70–0.92)	0.001	
		High	0.98 (0.83–1.17)	0.852	

^a Low PRI is the reference category within each breast cancer stratum.

^b P values for Middle and High PRI compare each category with Low PRI within the corresponding breast cancer stratum and were calculated using Wald tests from Cox proportional hazards models.

^c Overall P for interaction was based on the joint Wald test for interaction terms between PRI tertiles and breast cancer status.

Abbreviations: BC, breast cancer; NBC, no breast cancer; CI, confidence interval; HR, hazard ratio; PRI, Physical Reserve Index.

Supplementary Table 3. Two-year lag sensitivity analysis of continuous Physical Reserve Index and clinical outcomes among women with breast cancer.

Outcome	Model	N^a	Events (%)	HR (95% CI)^b	P value^d
Heart failure	Crude ^c	5595	216 (3.9%)	0.47 (0.41–0.54)	<0.001
	Adjusted ^d	5595	216 (3.9%)	0.54 (0.47–0.63)	<0.001
Atrial fibrillation	Crude ^c	5576	377 (6.8%)	0.60 (0.54–0.66)	<0.001
	Adjusted ^d	5576	377 (6.8%)	0.74 (0.66–0.84)	<0.001
All-cause death	Crude ^c	5513	995 (18.0%)	0.70 (0.66–0.74)	<0.001
	Adjusted ^d	5513	995 (18.0%)	0.76 (0.71–0.82)	<0.001

^a The two-year lag analysis excluded events occurring within the first 2 years of follow-up.

^b Hazard ratios are presented per 1-standard-deviation increment in the Physical Reserve Index.

^c Crude models were unadjusted.

^d Adjusted models were fully adjusted for prespecified sociodemographic (age, Townsend Deprivation Index, education college), lifestyle (smoking, alcohol consumption, sleep duration, physical activity), and cardiovascular risk factors (hypertension, diabetes, and hyperlipidaemia).

^e P values were calculated using Wald tests from Cox proportional hazards models.

Abbreviations: CI, confidence interval; HR, hazard ratio; PRI, Physical Reserve Index.

Supplementary Table 4. Association of continuous Physical Reserve Index with clinical outcomes among women with breast cancer: complete-case analysis.

Outcome	N	Events, n (%)	HR (95% CI)^a	P value^b
Heart failure	4207	144 (3.4%)	0.51 (0.42–0.61)	<0.001
Atrial fibrillation	4207	279 (6.6%)	0.74 (0.64–0.85)	<0.001
All-cause death	4207	746 (17.7%)	0.77 (0.71–0.84)	<0.001

^a HRs are reported per 1-SD increment in PRI. Models were fully adjusted for prespecified sociodemographic, lifestyle, and cardiovascular risk factors.

^b P values were calculated using Wald tests from Cox proportional hazards models.

Abbreviations: CI, confidence interval; HR, hazard ratio; PRI, Physical Reserve Index.

Supplementary Table 5. Competing-risk sensitivity analysis of continuous Physical Reserve Index and clinical outcomes among women with breast cancer.

Outcome	Model	N	Events (%)	Competing deaths	sHR (95% CI)^a	P value^d
Heart failure	Crude ^b	5605	226(4.0%)	982	0.49 (0.43–0.56)	<0.001
	Adjusted ^c	5605	226(4.0%)	982	0.56 (0.48–0.65)	<0.001
Atrial fibrillation	Crude ^b	5605	406(7.2%)	961	0.61 (0.56–0.67)	<0.001
	Adjusted ^c	5605	406(7.2%)	961	0.77 (0.69–0.86)	<0.001

^a Subdistribution hazard ratios are reported per 1-standard-deviation increment in PRI.

^b Crude models were unadjusted.

^c Adjusted models were fully adjusted for prespecified sociodemographic (age, Townsend Deprivation Index, education college), lifestyle (smoking, alcohol consumption, sleep duration, physical activity), and cardiovascular risk factors (hypertension, diabetes, and hyperlipidaemia).

^d P values for heart failure and atrial fibrillation were calculated using Wald tests from Fine-Gray subdistribution hazard models, with death treated as a competing event.

Abbreviations: CI, confidence interval; PRI, Physical Reserve Index; sHR, subdistribution hazard ratio.

Supplementary Table 6. Global SHAP feature importance for prediction of heart failure, atrial fibrillation, and all-cause death.

Outcome	Model	Rank	Predictor	SHAP value^c
All-cause death	Model B^a	1	Smoking status: Never	0.272
		2	Smoking status: Previous	0.254
		3	FEV1	0.172
		4	Sleep duration: short-sleep	0.129
		5	Sleep duration: normal-sleep	0.126
		6	Waist circumference	0.110
		7	Age	0.072
		8	Grip strength	0.047
		9	Hypertension: Yes	0.033
		10	Physical activity: Middle	0.025
		11	Townsend deprivation index	0.019
		12	Physical activity: High	0.018
		13	Diabetes: Yes	0.017
		14	Drinking status: Previous	0.009
		15	Hyperlipidemia: Yes	0.008
		16	Drinking status: Never	0.003
	Model C^b	17	College education: Yes	0.000
		1	PRI	0.214
		2	Smoking status: Never	0.198
		3	Smoking status: Previous	0.175
		4	Age	0.068
		5	Hypertension: Yes	0.026
		6	Diabetes: Yes	0.016
		7	Drinking status: Previous	0.003
		8	Sleep duration: short-sleep	0.002
		9	Drinking status: Never	0.000
		10	College education: Yes	0.000
		11	Hyperlipidemia: Yes	0.000
		12	Physical activity: Middle	0.000
		13	Physical activity: High	0.000
		14	Sleep duration: normal-sleep	0.000
		15	Townsend deprivation index	0.000
Atrial fibrillation	Model B^a	1	Age	0.450
		2	Waist circumference	0.175
		3	Hypertension: Yes	0.114
		4	FEV1	0.108
		5	Smoking status: Never	0.042
		6	Townsend deprivation index	0.012
		7	Grip strength	0.010
		8	Diabetes: Yes	0.003
		9	Drinking status: Never	0.000
		10	Drinking status: Previous	0.000
		11	Smoking status: Previous	0.000
		12	College education: Yes	0.000
		13	Hyperlipidemia: Yes	0.000

Heart failure	Model C ^b	14	Physical activity: Middle	0.000
		15	Physical activity: High	0.000
		16	Sleep duration: normal-sleep	0.000
		17	Sleep duration: short-sleep	0.000
		1	Age	0.450
		2	PRI	0.217
		3	Hypertension: Yes	0.126
		4	Smoking status: Never	0.064
		5	Townsend deprivation index	0.018
		6	Diabetes: Yes	0.006
		7	Hyperlipidemia: Yes	0.001
		8	Drinking status: Never	0.000
		9	Drinking status: Previous	0.000
	Model B ^a	10	Smoking status: Previous	0.000
		11	College education: Yes	0.000
		12	Physical activity: Middle	0.000
		13	Physical activity: High	0.000
		14	Sleep duration: normal-sleep	0.000
		15	Sleep duration: short-sleep	0.000
		1	Sleep duration: normal-sleep	0.303
		2	Waist circumference	0.276
		3	Smoking status: Never	0.275
		4	FEV1	0.269
		5	Sleep duration: short-sleep	0.241
		6	Smoking status: Previous	0.227
		7	Age	0.157
	Model C ^b	8	Grip strength	0.156
		9	Hypertension: Yes	0.113
		10	Physical activity: Middle	0.091
		11	Physical activity: High	0.036
		12	Townsend deprivation index	0.028
		13	College education: Yes	0.021
		14	Diabetes: Yes	0.021
		15	Drinking status: Previous	0.020
		16	Hyperlipidemia: Yes	0.008
		17	Drinking status: Never	0.007
		1	PRI	0.480
		2	Sleep duration: normal-sleep	0.338
		3	Smoking status: Never	0.323
		4	Sleep duration: short-sleep	0.278
		5	Smoking status: Previous	0.264
		6	Age	0.159
		7	Hypertension: Yes	0.121
		8	Physical activity: Middle	0.105
		9	Physical activity: High	0.049
		10	Townsend deprivation index	0.035
		11	College education: Yes	0.025
		12	Diabetes: Yes	0.022
		13	Drinking status: Previous	0.021

14	Hyperlipidemia: Yes	0.009
15	Drinking status: Never	0.009

^a Model B included conventional clinical variables (age, Townsend Deprivation Index, educational attainment, smoking, alcohol consumption, sleep duration, physical activity, hypertension, diabetes, and hyperlipidaemia) plus FEV₁, handgrip strength, and waist circumference.

^b Model C included the same clinical variables (age, Townsend Deprivation Index, educational attainment, smoking, alcohol consumption, sleep duration, physical activity, hypertension, diabetes, and hyperlipidaemia) plus PRI.

^c Global feature importance was quantified as the mean absolute SHAP value across participants; larger values indicate greater contribution to model predictions.

Abbreviations: FEV₁, forced expiratory volume in 1 second; PRI, Physical Reserve Index; SHAP, SHapley Additive exPlanations.

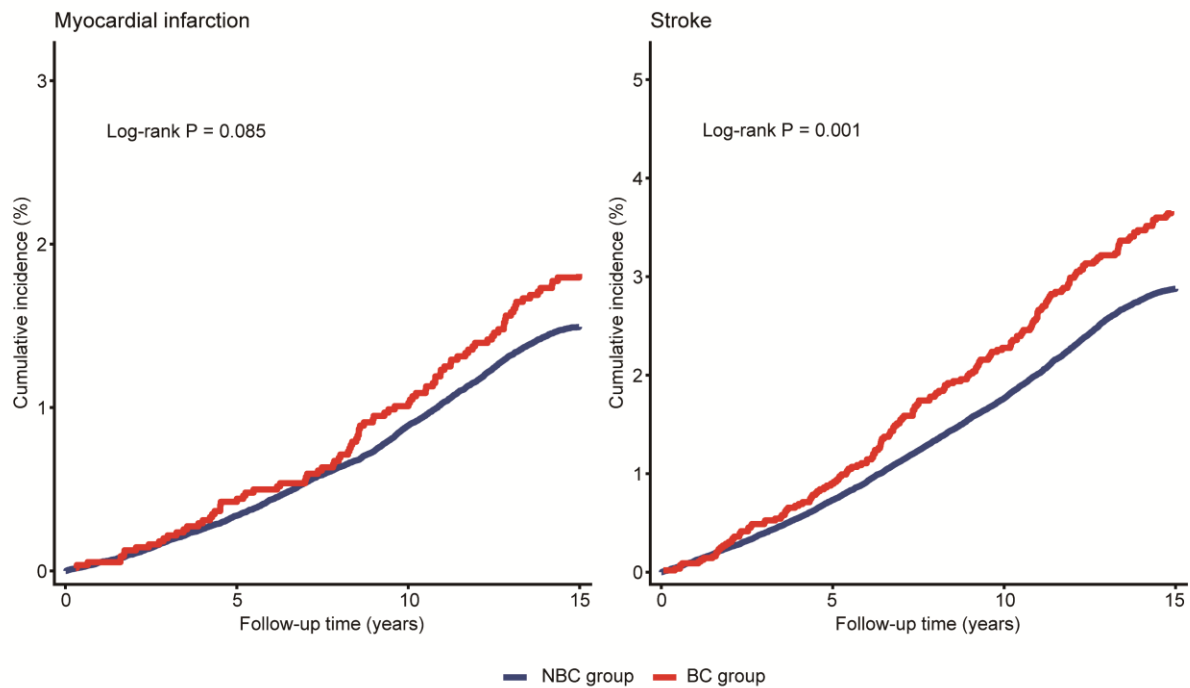
Supplementary Table 7. Missingness of variables in the analytical cohort.

Variable	Missing, n	Total, n	Missing, %
Physical activity	44459	183283	24.26%
BMI	1998	183283	1.09%
Education college	1375	183283	0.75%
Sleep duration	964	183283	0.53%
Smoking status	576	183283	0.31%
TDI	210	183283	0.11%
Drinking status	134	183283	0.07%

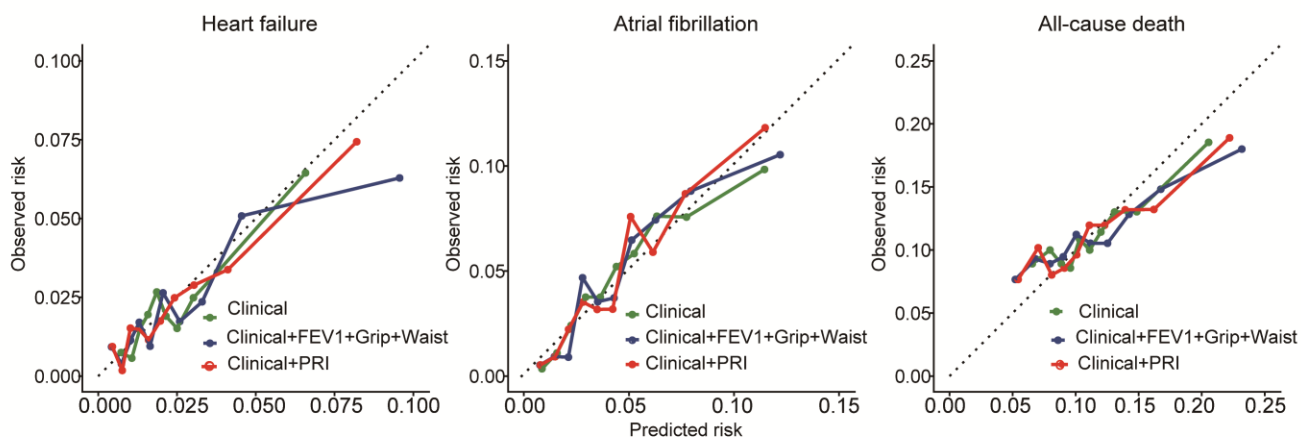
Missingness is presented for the analytical dataset (n=183,283).

Abbreviations: TDI, Townsend Deprivation Index.

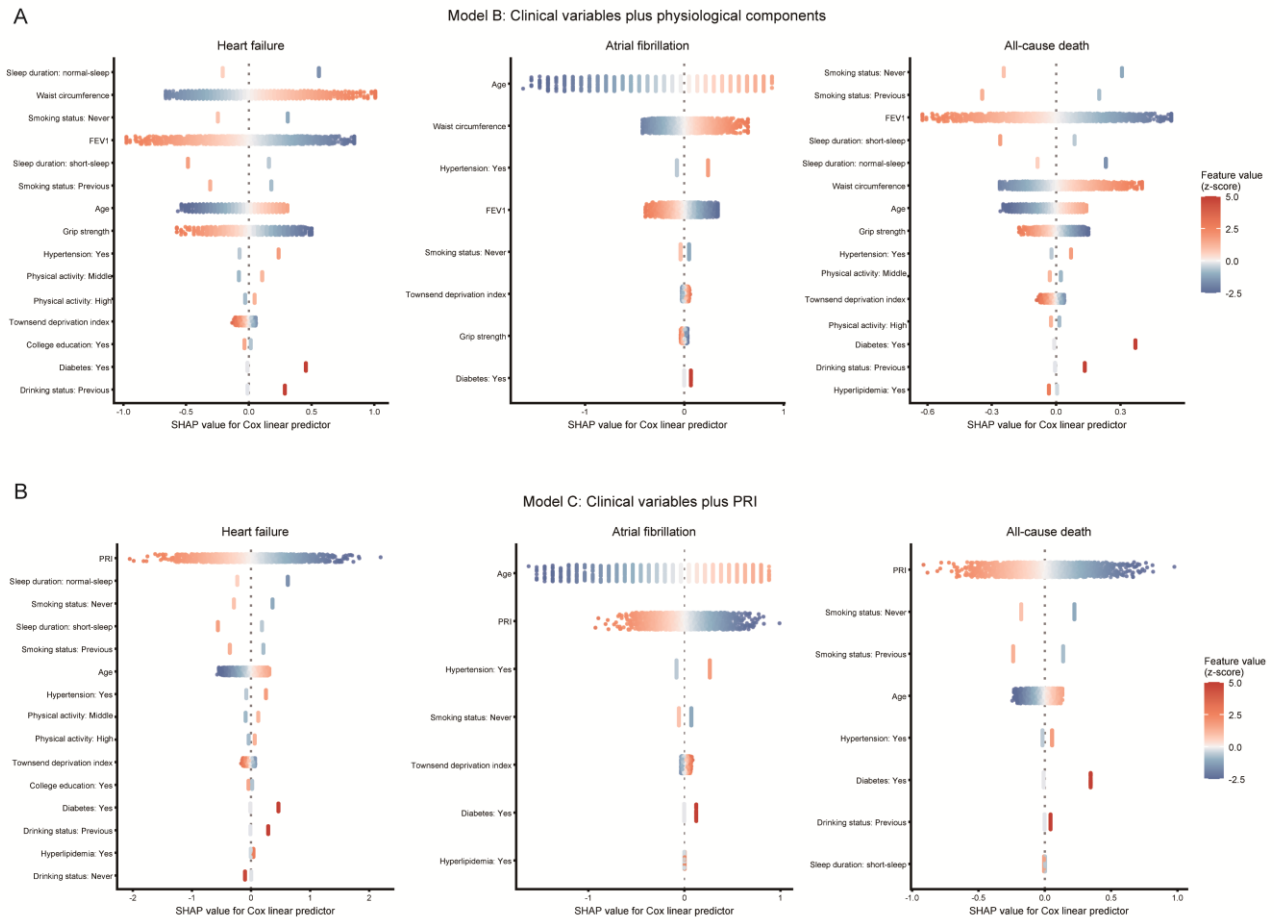
Supplementary Figure 1. Cumulative incidence of myocardial infarction and stroke according to breast cancer status. Cumulative incidence curves compare women with breast cancer (BC) and women without breast cancer (NBC). P values are from log-rank tests. BC, breast cancer; NBC, no breast cancer.



Supplementary Figure 2. Calibration of 10-year risk prediction models for heart failure, atrial fibrillation and all-cause death. Observed and predicted risks are shown across risk groups; the dotted diagonal line represents ideal calibration. The clinical model included conventional clinical variables; the component model additionally included FEV1, handgrip strength and waist circumference; and the PRI model additionally included PRI. FEV1, forced expiratory volume in 1 s; PRI, Physical Reserve Index.



Supplementary Figure 3. SHAP summary plots for Models B and C across clinical outcomes. (A) Model B included conventional clinical variables plus FEV1, handgrip strength and waist circumference. (B) Model C included the same clinical variables plus PRI. SHAP values quantify each predictor's contribution to the Cox linear predictor; point colour indicates the standardised feature value. FEV1, forced expiratory volume in 1 s; PRI, Physical Reserve Index; SHAP, SHapley Additive exPlanations.



Supplementary Figure 4. Participant selection flow diagram. Flow diagram showing derivation of the analytical cohort from UK Biobank. Baseline cardiovascular disease (CVD) comprised heart failure, atrial fibrillation, myocardial infarction and stroke.

