

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

Minyi Xing

First Affiliated Hospital of Dalian Medical University

Minghui Yang

First Affiliated Hospital of Dalian Medical University

Bingjie Li

Huazhong University of Science and Technology

Xiaojie Wang

First Affiliated Hospital of Dalian Medical University

Yiheng Yang

First Affiliated Hospital of Dalian Medical University

Siting Feng

First Affiliated Hospital of Dalian Medical University

Dongyang Xu

First Affiliated Hospital of Dalian Medical University

Yingxin Bi

First Affiliated Hospital of Dalian Medical University

Jinbo Fan

First Affiliated Hospital of Dalian Medical University

Jiaqi Chai

First Affiliated Hospital of Dalian Medical University

Rujia Han

First Affiliated Hospital of Dalian Medical University

Yuner Guo

First Affiliated Hospital of Dalian Medical University

Xiamei Zhu

First Affiliated Hospital of Dalian Medical University

Yunlong Xia

First Affiliated Hospital of Dalian Medical University

Rongfeng Zhang

zr-f0088@126.com

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Abstract

Background

Cardio-oncology risk assessment has focused largely on treatment-related cardiac injury, whereas the prognostic significance of physiological reserve in breast cancer survivors remains uncertain. We investigated whether a multidimensional Physiological Reserve Index (PRI) identifies long-term cardiovascular vulnerability and improves risk stratification.

Methods

We analyzed 183,283 women in the UK Biobank, including 5,605 breast cancer survivors. PRI combined standardized forced expiratory volume in 1 second (FEV₁), grip strength, and waist circumference. Cox proportional hazards models assessed associations with heart failure, atrial fibrillation, and all-cause mortality. Population-attributable fractions and incremental predictive performance using Harrell's concordance index (C-index) and 10-year time-dependent area under the receiver operating characteristic curve (AUC) were also evaluated.

Results

During a median follow-up of 16.7 years, breast cancer survivors had higher risks of heart failure (hazard ratio [HR] 1.59, 95% confidence interval [CI] 1.39–1.81), atrial fibrillation (HR 1.29, 95% CI 1.17–1.43), and all-cause mortality (HR 2.36, 95% CI 2.22–2.51) than women without breast cancer. Among survivors, each 1-standard-deviation higher PRI was associated with lower risks of heart failure (HR 0.55, 95% CI 0.47–0.63), atrial fibrillation (HR 0.75, 95% CI 0.67–0.84), and mortality (HR 0.76, 95% CI 0.71–0.81). Ten-year heart failure risk ranged from 0.80% to 3.61% across PRI strata. Under a hypothetical shift to the highest PRI category, the population-attributable fraction for heart failure was 49.8%. Adding PRI to conventional clinical factors increased the C-index for heart failure from 0.642 to 0.695 and the 10-year AUC from 0.668 to 0.712.

Conclusions

Physiological reserve captures substantial heterogeneity in long-term cardiovascular risk among breast cancer survivors and provides prognostic information beyond conventional clinical factors. Simple functional and anthropometric measures may complement cardio-oncology risk assessment and support future evaluation of reserve-oriented survivorship strategies.

Background

Breast cancer is the most commonly diagnosed malignancy among women worldwide[1], with advances in detection and treatment substantially increasing the number of long-term survivors[2]. As survival improves, cardiovascular disease has emerged as an important determinant of long-term health. Breast cancer survivors experience elevated risks of heart failure, atrial fibrillation, and cardiovascular mortality, although the magnitude and pattern of risk vary considerably across individuals[3–5]. This heterogeneity reflects the combined influence of pre-existing cardiovascular risk factors, shared biological pathways between cancer and cardiovascular disease, and the direct and indirect effects of cancer treatment[6]. Identifying which survivors remain vulnerable to cardiovascular complications is therefore becoming a central component of long-term cancer care.

Contemporary cardio-oncology has appropriately focused on treatment-related cardiovascular toxicity. Current strategies emphasize baseline cardiovascular risk assessment before potentially cardiotoxic treatment[7–10]. During therapy, surveillance commonly integrates clinical assessment with cardiac imaging and circulating biomarkers to detect early myocardial injury[11–13]. These approaches are essential for patients exposed to radiotherapy and systemic therapies with recognized cardiovascular effects, including anthracyclines and HER2-directed treatment[14, 15]. Breast cancer and its treatment can also be accompanied by reduced physical activity, impaired cardiorespiratory fitness, loss of muscular function and progressive physical deconditioning, suggesting that the physiological capacity retained after cancer treatment may represent an additional dimension of long-term cardiovascular health[16].

Emerging evidence supports the relevance of several routinely available measures that capture complementary aspects of this physiological capacity. Forced expiratory volume in 1 second (FEV₁), a marker of respiratory function, may decline after breast cancer radiotherapy and remain impaired during long-term follow-up[17]. Cardiorespiratory fitness itself is also inversely associated with mortality among adults with cancer[18]. Handgrip strength provides a simple measure of muscular function, and lower grip strength has been associated with higher cardiovascular and all-cause mortality in large prospective populations[19]. Body composition is similarly relevant: Abdominal obesity has been associated with increased cardiovascular and stroke risk[20], while greater waist circumference has been linked to heart failure among postmenopausal breast cancer survivors[21].

However, these physiological domains have largely been investigated separately, and whether their integration can provide a more comprehensive assessment of cardiovascular vulnerability among breast cancer survivors remains unknown. Although emerging molecular biomarkers may improve cardiovascular risk stratification[22], simple functional and anthropometric measures are inexpensive, widely accessible and potentially suitable for repeated assessment in survivorship care. We therefore integrated FEV₁, grip strength and waist circumference into a pragmatic Physiological Reserve Index (PRI) to capture multidimensional physiological reserve. Using the UK Biobank, we examined the associations of PRI with heart failure, atrial fibrillation and mortality, characterized absolute and population-level risk gradients across PRI levels, and evaluated whether PRI provided incremental prognostic information beyond conventional clinical factors. By moving beyond individual physiological

measures and treatment exposure alone, this study aimed to determine whether multidimensional physiological reserve can identify a clinically relevant and potentially actionable dimension of long-term cardiovascular vulnerability among breast cancer survivors.

Results

Physiological reserve components differ between women with and without breast cancer

Among 183,283 women included in the analytic cohort, 5,605 participants had a history of breast cancer. Breast cancer (BC) patients were older (59.4 vs 56.1 years, $P<0.001$) and had a higher prevalence of hypertension (23.9% vs 20.9%, $P<0.001$), diabetes (2.3% vs 1.3%, $P<0.001$), and hyperlipidemia (11.3% vs 10.2%, $P=0.005$) compared with women without breast cancer. Lifestyle-related characteristics also differed between groups. Importantly, breast cancer survivors exhibited evidence of reduced multidimensional physiological reserve. Compared with women without breast cancer, survivors had lower lung function (FEV_1 : 2.3 vs 2.4 L, $P<0.001$) and reduced muscular strength (mean grip strength: 22.2 vs. 23.8 kg, $P<0.001$). Conversely, waist circumference was higher among breast cancer survivors (85.2 vs 84.2 cm, $P<0.001$), suggesting greater metabolic burden (**Table 1**).

Women with breast cancer had significantly lower FEV_1 (beta -0.03 , 95% CI -0.05 to -0.01) and grip strength (beta -0.13 , 95% CI -0.15 to -0.10) than women without breast cancer. Waist circumference was modestly higher in women with breast cancer (beta 0.03 , 95% CI 0.00 to 0.05). The largest between-group difference was observed for grip strength, suggesting a particularly pronounced reduction in muscular reserve among women with breast cancer. (**Fig. 1a**).

Table 1. Baseline characteristics of women with and without breast cancer

	NBC group	BC group	
Variable	N = 177,678	N = 5,605	p-value
Demographic characteristics			
Age, years	56.1 (7.90)	59.4 (6.62)	<0.001 ^a
Breast cancer diagnosis age	NA	52.2 (7.42)	
TDI	-1.6 (2.90)	-1.6 (2.85)	0.074 ^a
Education college	57,828 (32.5%)	1,710 (30.5%)	0.001 ^b
Lifestyle			
Smoking			<0.001 ^b
Current	15,495 (8.7%)	420 (7.5%)	
Never	103,576 (58.3%)	3,122 (55.7%)	
Previous	58,607 (33.0%)	2,063 (36.8%)	
Alcohol			0.320 ^b
Current	164,730 (92.7%)	5,167 (92.2%)	
Never	7,134 (4.0%)	239 (4.3%)	
Previous	5,814 (3.3%)	199 (3.6%)	
Sleep			0.001 ^b
long-sleep	2,752 (1.5%)	131 (2.3%)	
normal sleep	133,956 (75.4%)	4,083 (72.8%)	
short-sleep	40,970 (23.1%)	1,391 (24.8%)	
Physical activity			0.028 ^b
low	30,818 (17.3%)	1,043 (18.6%)	
middle	75,832 (42.7%)	2,392 (42.7%)	
high	71,028 (40.0%)	2,170 (38.7%)	
Cardiovascular risk factors			
Hypertension	37,081 (20.9%)	1,337 (23.9%)	<0.001 ^b
Diabetes	2,309 (1.3%)	130 (2.3%)	<0.001 ^b

	NBC group	BC group	
Variable	N = 177,678	N = 5,605	p-value
Hyperlipidemia	18,116 (10.2%)	636 (11.3%)	0.005 ^b
Physiological reserve components			
FEV ₁ , L	2.4 (0.51)	2.3 (0.48)	<0.001 ^a
Mean Grip Strength, kg	23.8 (5.98)	22.2 (5.75)	<0.001 ^a
Waist circumference, cm	84.2 (11.96)	85.2 (11.53)	<0.001 ^a

Continuous variables are expressed as mean (SD, standard deviation), and categorical variables are expressed as number (percentage).

^a P values were calculated using Welch's two-sample t-test.

^b P values were calculated using Pearson's chi-squared test.

Abbreviations: BC, breast cancer; NBC, no breast cancer; TDI, Townsend Deprivation Index; FEV₁, forced expiratory volume in 1 second.

Heterogeneous cardiovascular risk among breast cancer survivors

During a median follow-up of 16.7 years, breast cancer patients exhibited a higher incidence of multiple adverse clinical outcomes relative to women without breast cancer. Multivariable Cox regression analyses revealed that a history of breast cancer was independently associated with elevated risks of heart failure, atrial fibrillation, and all-cause mortality (**Fig. 1b**). Patients had a greater risk of heart failure (hazard ratio [HR], 1.59; 95% confidence interval [CI], 1.39-1.81; $P < 0.001$) and atrial fibrillation (HR, 1.29; 95% CI, 1.17-1.43; $P < 0.001$). By contrast, breast cancer history was not linked to higher risks of ischemic cardiovascular events, including myocardial infarction (HR, 0.95; 95% CI, 0.77-1.17; $P = 0.620$) and stroke (HR, 0.99; 95% CI, 0.86-1.15; $P = 0.927$). Additionally, breast cancer patients exhibited a higher risk of all-cause mortality (HR, 2.36; 95% CI, 2.22-2.51; $P < 0.001$).

Women with breast cancer had higher cumulative incidences of heart failure and atrial fibrillation than women without breast cancer (both Gray's $P < 0.001$), with differences progressively widening during follow-up (**Fig. 1c, Supplementary Figure 1**). A modest difference was also observed for stroke (Gray's $P = 0.027$), whereas myocardial infarction did not differ significantly between groups (Gray's $P = 0.318$). All-cause mortality was substantially higher among women with breast cancer (log-rank $P < 0.001$).

Individual physiological reserve components are associated with cardiovascular outcomes among breast cancer survivors

Multivariable Cox regression models revealed that each 1-standard-deviation (SD) increment in FEV₁ was independently associated with lower risks of all-cause mortality (adjusted HR, 0.78; 95% CI, 0.73-0.84; P<0.001), heart failure (HR, 0.66; 95% CI, 0.56-0.76; P<0.001), and atrial fibrillation (HR, 0.84; 95% CI, 0.75-0.94; P=0.003). Per 1-SD higher grip strength was associated with reduced risk of all-cause mortality (HR, 0.90; 95% CI, 0.85-0.96; P=0.001) and heart failure (HR, 0.76; 95% CI, 0.66-0.87; P<0.001), with no significant association for atrial fibrillation (HR, 0.94; 95% CI, 0.84-1.04; P=0.217). In contrast, each 1-SD increase in waist circumference predicted higher risks of all-cause mortality (HR, 1.17; 95% CI, 1.10-1.24; P<0.001), heart failure (HR, 1.46; 95% CI, 1.29-1.67; P<0.001), and atrial fibrillation (HR, 1.30; 95% CI, 1.18-1.44; P<0.001). The forest plot of these associations is presented in **Fig. 2a**.

Restricted cubic spline models were used to explore the dose-response patterns and nonlinear associations between standardized physiological reserve indicators (FEV₁, grip strength, and waist circumference) and the study outcomes (**Fig. 2b**). Overall, FEV₁ and grip strength exhibited inverse correlations with heart failure, atrial fibrillation, and all-cause mortality; the protective risk reductions gradually plateaued at elevated levels of these two markers. Significant nonlinear associations were detected between FEV₁ and atrial fibrillation as well as all-cause mortality, and between grip strength and atrial fibrillation. By contrast, higher waist circumference was continuously linked to increased risks of all adverse outcomes, with no evident nonlinear trend identified.

Multidimensional physiological reserve is associated with lower cardiovascular risk

To quantify overall physiological reserve capacity, we constructed a composite Physiological Reserve Index (PRI), calculated as: $PRI = Z(\text{grip strength}) - Z(\text{waist circumference}) + Z(\text{FEV}_1)$. Participants were stratified into low, middle, and high physiological reserve groups based on PRI tertiles. In multivariable Cox regression models, a higher PRI was independently associated with reduced risks of all prespecified adverse outcomes. Per one-standard-deviation (1-SD) increment in PRI was linked to lower risks of all-cause mortality (HR, 0.76; 95% CI, 0.71-0.81; P<0.001), heart failure (HR, 0.55; 95% CI, 0.47-0.63; P<0.001), and atrial fibrillation (HR, 0.75; 95% CI, 0.67-0.84; P<0.001) (**Fig. 3a**).

Cumulative incidence curves showed progressively higher event risks across descending PRI tertiles for heart failure, atrial fibrillation, and all-cause mortality (all log-rank P < 0.001). Participants in the lowest PRI tertile exhibited the highest cumulative incidence of each endpoint, while those in the highest PRI tertile had the lowest risk (**Fig. 3b**).

Ten-year absolute risks of heart failure, atrial fibrillation, and all-cause death increased progressively with decreasing PRI in both women with and without breast cancer. Women with breast cancer and low PRI consistently had the highest risks, reaching 3.61% (95% CI 2.92-4.46) for heart failure, 6.96% (5.99-8.08) for atrial fibrillation, and 13.98% (12.68-15.41) for all-cause death. In contrast, women without breast cancer and high PRI had the lowest corresponding risks of 0.27% (0.23-0.32), 1.26% (1.18-1.36), and 1.43% (1.34-1.53), respectively (**Fig. 3c**). Notably, even among women with breast cancer, higher PRI was associated with substantially lower absolute risks, supporting a marked gradient in long-term cardiovascular and mortality risk according to physiological reserve.

We estimated population attributable fractions (PAFs) under two hypothetical intervention scenarios: shifting participants from the lowest PRI tertile to the middle tertile (worst-to-middle), and shifting all individuals to the highest PRI tertile (shift-to-best). Under the worst-to-middle scenario, the PAFs were 23.6% for heart failure, 16.1% for atrial fibrillation, and 14.9% for all-cause death. Under the more ambitious shift-to-best scenario, corresponding PAFs increased substantially to 49.8% for heart failure, 33.1% for atrial fibrillation, and 22.7% for all-cause death. Across both intervention strategies, the largest potential risk reduction was observed for heart failure. These PAF estimates are visualized in **Fig. 3d**.

Effect modification by breast cancer status

Associations between PRI and outcomes were further examined according to breast cancer status (**Supplementary Table 1**). Each 1-SD higher PRI was associated with lower risks of heart failure in women without and with breast cancer (HR 0.57, 95% CI 0.55-0.59 and HR 0.60, 95% CI 0.52-0.69, respectively; Interaction P = 0.490) and atrial fibrillation (HR 0.80, 95% CI 0.78-0.82 and HR 0.77, 95% CI 0.69-0.85; Interaction P = 0.395), with no evidence of effect modification by breast cancer status. For all-cause mortality, the inverse association was weaker among women with breast cancer (HR 0.89, 95% CI 0.83-0.95) than among those without breast cancer (HR 0.76, 95% CI 0.74-0.77; Interaction P <0.001). Analyses using PRI tertiles showed broadly consistent findings, with no significant overall interaction for heart failure (Interaction P = 0.257) or atrial fibrillation (Interaction P = 0.589), but significant heterogeneity for all-cause mortality (Interaction P < 0.001; **Supplementary Table 2**).

Sensitivity analyses

Sensitivity analyses yielded results consistent with the primary findings (**Supplementary Tables 3-5**). After excluding events occurring within the first 2 years of follow-up, each 1-SD increment in PRI remained associated with lower risks of all-cause mortality (HR, 0.76; 95% CI, 0.71-0.82), heart failure (HR, 0.54; 95% CI, 0.47-0.63), and atrial fibrillation (HR, 0.74; 95% CI, 0.66-0.84; all P<0.001). Complete-case analyses produced similar estimates for all-cause mortality (HR, 0.77; 95% CI, 0.71-0.84), heart failure (HR, 0.51; 95% CI, 0.42-0.61), and atrial fibrillation (HR, 0.74; 95% CI, 0.64-0.85). In Fine-Gray competing-risk analyses, the inverse associations remained robust for heart failure (subdistribution HR, 0.56; 95% CI, 0.48-0.65) and atrial fibrillation (subdistribution HR, 0.77; 95% CI, 0.69-0.86; both P < 0.001), with death from other causes treated as a competing event. Collectively, these findings support the robustness of the primary results.

PRI improves cardiovascular risk stratification beyond conventional clinical factors

Adding physiological reserve measures improved model discrimination, with the greatest gain observed for heart failure. The C-index increased from 0.642 (95% CI 0.606-0.677) for the clinical model to 0.688 (0.654-0.724) after adding the individual physiological reserve components and to 0.695 (0.659-0.732) after adding PRI. Corresponding C-indices were 0.685, 0.698, and 0.699 for atrial fibrillation, and 0.577, 0.594, and 0.596 for all-cause death (**Fig. 4a**).

Similar improvements were observed for 10-year discrimination (**Fig. 4b**). For heart failure, the AUC increased from 0.668 for the clinical model to 0.704 with the individual components and 0.712 with PRI. The corresponding AUCs were 0.689, 0.710, and 0.707 for atrial fibrillation, and 0.568, 0.579, and 0.580 for all-cause death. Calibration plots showed generally good agreement between predicted and observed 10-year risks across the three models, although some deviation was apparent at the extremes of predicted risk (Supplementary Figure 2). Decision curve analyses suggested modest additional net benefit from incorporating physiological reserve information, particularly at lower clinically relevant risk thresholds (**Fig. 4c**).

SHapley Additive explanations (SHAP) analyses further demonstrated the prognostic importance of physiological reserve (**Supplementary Figure 3; Supplementary Table 6**). When FEV₁, grip strength, and waist circumference were entered separately, their relative contributions varied across outcomes, with FEV₁ and waist circumference showing prominent contributions. When these components were integrated into PRI, PRI emerged as one of the leading predictors, particularly for heart failure and all-cause death, and also contributed substantially to atrial fibrillation prediction. Higher PRI values were generally associated with lower predicted risk, supporting the ability of the composite index to capture clinically relevant physiological reserve beyond conventional risk factors.

Discussion

In this prospective cohort, breast cancer survivors had higher risks of heart failure, atrial fibrillation, and death, but not myocardial infarction or stroke. Higher FEV₁ and grip strength were generally associated with lower risk, whereas greater waist circumference was associated with higher risk. Their integration into PRI identified marked risk gradients: each 1-SD higher PRI was associated with 45% lower heart failure risk, 25% lower atrial fibrillation risk, and 24% lower mortality. PRI also improved prediction beyond conventional clinical factors, most clearly for heart failure.

The individual PRI components appeared to contribute related but non-redundant information. Pulmonary function reflects not only respiratory capacity but also systemic and cardiovascular health[23, 24], while grip strength provides an objective marker of muscular function and global physical capacity[19]. Waist circumference, in turn, captures central adiposity and associated cardiometabolic burden[25]. This multidimensional interpretation is consistent with emerging evidence that reduced functional capacity in breast cancer survivors reflects abnormalities across several physiological systems rather than a single organ. A recent review highlighted both central and peripheral determinants of exercise intolerance in breast cancer survivors, including cardiac, vascular, and skeletal-muscle impairments[26]. Similarly, pre-existing frailty has recently been associated with greater cardiotoxicity during adjuvant breast cancer therapy, with progressively higher cardiovascular event rates among robust, prefrail, and frail patients[27]. These observations support the concept that host functional status may provide information complementary to treatment exposure itself. The restricted cubic spline analyses further suggested that some associations, particularly those of FEV₁ and grip strength with atrial fibrillation, were not uniformly linear. This finding cautions against treating any single component

as an isolated therapeutic target and supports a multidimensional assessment in which the combined pattern of functional capacity and body composition is more informative than any measure alone.

The composite PRI extends this interpretation. Its association was strongest for heart failure, for which each 1-SD higher PRI was associated with an approximately 45% lower risk. Heart failure can arise through several pathways relevant to breast cancer survivorship, including pre-existing cardiovascular risk, treatment-related myocardial injury, adverse body composition, and loss of cardiopulmonary and muscular conditioning[28]. Recent evidence supports this multisystem interpretation: long-term heart failure remains an important complication after trastuzumab with or without anthracyclines[29], systemic anticancer therapy can produce sustained reductions in cardiorespiratory fitness[30]. PRI may be better understood as an integrated phenotype of retained physiological capacity rather than a conventional risk score or a marker of treatment-related cardiotoxicity. Its strong association with heart failure suggests particular relevance to outcomes driven by cumulative myocardial, systemic, and functional impairment.

Importantly, PRI was also associated with heart failure and atrial fibrillation among women without breast cancer, and these associations were not significantly modified by breast cancer status on the multiplicative scale. This indicates that physiological reserve is unlikely to represent a mechanism specific to breast cancer. Instead, it appears to capture a broader dimension of cardiovascular vulnerability that remains especially relevant in survivors, who face the combined influence of aging, conventional cardiovascular risk factors, cancer-related exposures, and possible functional decline[31, 32]. The absence of multiplicative interaction does not imply an absence of clinical relevance. Breast cancer shifted the overall risk burden upward, while PRI stratified risk within both groups; moreover, because baseline risk was higher among survivors, comparable relative associations could translate into larger absolute risk differences[33]. Thus, breast cancer history and physiological reserve provide complementary rather than competing information: the former identifies a higher-risk clinical population, whereas the latter helps distinguish vulnerability within that population.

The population-attributable analyses extended these individual-level associations to a population perspective. Under the hypothetical shift-to-high-PRI scenario, the PAF for heart failure approached 50%, exceeding those for atrial fibrillation and all-cause death. These estimates should not be interpreted as the proportion of events that would necessarily be prevented by improving PRI. PAFs derived from observational data depend on assumptions regarding confounding, exposure redistribution, and causal interpretation, and may be biased when these assumptions are not met[34, 35]. Accordingly, our estimates are best interpreted as indicators of the population burden associated with low physiological reserve rather than projections of intervention effects. Nevertheless, the concentration of functional and metabolic deficits among survivors provides a rationale for prospectively evaluating exercise, nutritional, and weight-management strategies[36, 37].

Interaction analyses showed that the inverse associations of PRI with heart failure and atrial fibrillation were broadly similar in women with and without breast cancer, suggesting that physiological reserve

reflects a general dimension of cardiovascular vulnerability rather than a breast cancer-specific mechanism. By contrast, the association with all-cause mortality was significantly weaker among women with breast cancer, possibly because mortality in survivors is influenced by competing cancer-related and non-cardiovascular risks[38, 39]. Importantly, the absence of interaction for cardiovascular outcomes does not imply limited clinical relevance, because the higher baseline risk among breast cancer survivors may still result in larger absolute risk differences for comparable relative effects.

The incremental prediction analyses offer a complementary clinical perspective. Adding PRI to conventional clinical factors improved discrimination most clearly for heart failure, increasing the C-index from 0.642 to 0.695 and the 10-year time-dependent AUC from 0.668 to 0.712. Improvements were less pronounced for atrial fibrillation and all-cause mortality. Current cardio-oncology risk frameworks are based largely on clinical characteristics, conventional cardiovascular risk factors, and treatment-related exposures[8, 40, 41]. Recent analyses have shown that established cardiovascular risk scores generally perform less well in cancer survivors than in matched individuals without cancer and may underestimate cardiovascular risk in this population[42], merging approaches based on molecular or genetic information also illustrate the continuing search for better survivor-specific risk stratification; however, recent data suggest that the incremental predictive value of cardiovascular polygenic scores in breast cancer survivors remains limited[43]. PRI may provide pragmatic prognostic information by capturing functional and metabolic health beyond conventional clinical factors. The observed improvement in discrimination supports its potential value as a complementary tool for cardiovascular risk stratification. Further external validation and assessment across diverse populations will help clarify its broader clinical applicability and decision-making value.

These findings may have implications for rehabilitation-oriented survivorship care. Current follow-up after breast cancer understandably emphasizes cancer surveillance and management of treatment-related complications. Contemporary evidence increasingly supports cardiovascular prevention, cardiorespiratory fitness assessment, and rehabilitation as important components of care for cancer survivors[44–46]. Our results suggest that preservation of respiratory function, muscular strength, and favorable body composition may also deserve greater attention as markers of long-term cardiovascular health. Unlike fixed characteristics such as age or cancer history, several components contributing to physiological reserve are at least potentially amenable to physical activity, exercise-based rehabilitation, nutritional intervention, weight management, and prevention of functional decline. Randomized studies have shown that structured exercise or cardio-oncology rehabilitation can improve functional or cardiovascular intermediate outcomes in breast cancer populations[16, 47]. Observational survivorship data likewise support the relevance of physical activity and fitness[48]. The present observational findings cannot demonstrate that improving PRI will reduce cardiovascular events, but they provide a rationale for prospective studies testing whether preserving or improving multidimensional reserve translates into fewer cardiovascular complications.

Several limitations should be considered. First, this was an observational study, and causal relationships between physiological reserve and cardiovascular outcomes cannot be established. Residual

confounding and reverse causation remain possible, particularly because subclinical disease may influence FEV₁, grip strength, or body composition before overt cardiovascular events occur. Second, differences in reserve components between women with and without breast cancer should not be interpreted as evidence that breast cancer caused these differences, because the two groups also differed in age, cardiovascular risk factors, and lifestyle characteristics. Third, PRI was constructed from three pragmatic and clinically accessible measures rather than from a comprehensive assessment of physiological reserve; other domains, including exercise capacity, cardiac function, frailty, and psychosocial factors, were not incorporated. Fourth, detailed information on individual cancer treatments and treatment intensity was not integrated into the current analyses, limiting our ability to determine whether physiological reserve modifies the cardiovascular effects of specific cancer therapies. Fifth, all-cause mortality is not a cardiovascular-specific outcome and may reflect cancer-related and noncardiovascular deaths. Finally, the study population consisted of White women in the UK Biobank, which may limit generalizability to more diverse populations[49].

Conclusions

In conclusion, greater multidimensional physiological reserve was associated with substantially lower long-term risks of heart failure, atrial fibrillation, and all-cause mortality among breast cancer survivors, with the strongest association observed for heart failure. PRI also provided incremental prognostic information beyond conventional clinical factors and identified risk gradients in women both with and without breast cancer. These findings position physiological reserve as a complementary dimension of cardiovascular vulnerability rather than a breast cancer-specific mechanism or an established intervention target. Prospective validation is needed to determine whether incorporating physiological reserve into survivorship assessment can improve risk stratification and guide rehabilitation strategies that ultimately reduce cardiovascular events.

Methods

Study population and design

UK Biobank is a prospective population-based cohort comprising over 500,000 participants recruited between 2006 and 2010 across the United Kingdom[50]. Participants aged 37–73 years at enrollment underwent extensive baseline assessments, including sociodemographic questionnaires, physical measurements, lifestyle assessments, and biological sample collection. Longitudinal follow-up was achieved through linkage to national hospital inpatient records, primary care data, and death registries. All participants provided written informed consent, and ethical approval was obtained from the North West Multicenter Research Ethics Committee. This research was conducted using data from the UK Biobank under application number 928207.

Women with complete baseline measurements of FEV₁, handgrip strength, and waist circumference were eligible for this study. We excluded male participants, individuals with prevalent heart failure, atrial

fibrillation, myocardial infarction, or stroke at baseline, those with invalid follow-up records, and subjects with missing exposure data. The final analytical sample consisted of 183,283 participants. Full details of the inclusion and exclusion procedure and stepwise sample attrition are provided in Supplementary Fig. 4.

A history of breast cancer was ascertained before or at the baseline assessment through linkage to the national cancer registry and was defined using the International Classification of Diseases, Tenth Revision (ICD-10) code C50.

Incident heart failure, atrial fibrillation, myocardial infarction, and stroke were identified through linked hospital, primary care, and death registry data. These outcomes were defined by ICD-10 codes: heart failure (I50), atrial fibrillation (I48), myocardial infarction (I21-I22), and stroke (I60-I64, G45). The date of death was obtained from national death registries. The onset date was defined as the earliest recorded diagnosis across all sources. Follow-up time was calculated from baseline assessment to the earliest incident cardiovascular event, death, loss to follow-up, or the administrative censoring date (31 December 2025).

Exposure assessment of physiological reserve

Physiological reserve was assessed at baseline using handgrip strength, pulmonary function, and waist circumference. Mean bilateral grip strength was measured with a Jamar dynamometer; the best valid FEV₁ was obtained by spirometry; and waist circumference was measured by trained staff. Values were winsorized at the 1st and 99th percentiles and standardized as Z-scores for analysis.

Assessment of Covariates

Baseline covariates were collected at the initial assessment visit through self-administered touchscreen questionnaires and physical measurements. Sociodemographic variables included age at recruitment (years), socioeconomic position as indexed by the Townsend Deprivation Index (TDI), and educational attainment (dichotomized as college or university degree versus no degree). Lifestyle variables comprised smoking status (current, previous, or never smoker), drinking status (categorized as: current, previous, or never), sleep duration (short [< 7 h], normal [7–9 h], or long [9 h] per night), and physical activity level (derived from the International Physical Activity Questionnaire short form and categorized as low, middle, or high). Clinical covariates included blood pressure medication use and prevalent comorbidities at baseline: diabetes, hypertension, and hyperlipidemia were ascertained using inpatient hospital records, primary care data, death registries, and self-reports. Missing covariate data were handled via multiple imputation by chained equations[51]. with the proportion of missing data for each covariate summarized in Supplementary Table 7.

Statistical analysis

Differences in physiological reserve components between women with and without breast cancer were assessed using multivariable linear regression after standardization of FEV₁, grip strength, and waist circumference. Associations of breast cancer with incident cardiovascular outcomes and all-cause mortality were evaluated using multivariable Cox proportional hazards models. Cumulative incidences of cardiovascular outcomes were estimated using competing-risk methods with death as a competing event and compared using Gray's test, whereas all-cause mortality was assessed using the Kaplan-Meier method and log-rank test[52].

Among women with breast cancer, FEV₁, grip strength, and waist circumference were standardized using breast-cancer-specific means and SDs, and PRI was calculated as $Z(\text{FEV}_1) + Z(\text{grip strength}) - Z(\text{waist circumference})$. PRI was analyzed per 1-SD increment and by breast-cancer-specific tertiles. Cox models assessed associations of individual components and PRI with outcomes; four-knot restricted cubic splines assessed nonlinearity. Potential effect modification by breast cancer status was primarily assessed by including a multiplicative interaction term between breast cancer status and continuous PRI (per 1-SD increment) in multivariable Cox models. A single P value for interaction was obtained for each outcome, and HRs (95% CIs) for PRI were estimated separately for women with and without breast cancer from the interaction models. As a supplementary analysis, interactions were examined using PRI tertiles, with overall interaction assessed using a likelihood-ratio test.

For the joint breast cancer-PRI 10-year risk matrix only, components were re-standardized using the means and SDs among women without breast cancer. PRI tertile cutoffs derived from women without breast cancer were then applied to both groups, generating six joint breast cancer-PRI groups. Ten-year absolute risks were estimated as 1-S (10), with 95% CIs based on log-log transformation.

Among women with breast cancer, PAFs were estimated for two hypothetical PRI improvements: low-to-middle and low/middle-to-high. 95% CIs were obtained by non-parametric bootstrap resampling.

All multivariable models were adjusted for age, educational attainment, Townsend Deprivation Index, smoking status, alcohol consumption, physical activity, sleep duration, hypertension, type 2 diabetes, and hyperlipidaemia.

Prediction analysis

For each endpoint (heart failure, atrial fibrillation, and all-cause death), three elastic-net Cox proportional hazards models were developed: Model A included conventional clinical factors (age, Townsend Deprivation Index, education college, smoking, alcohol consumption, sleep duration, physical activity, hypertension, diabetes, and hyperlipidaemia); Model B included the clinical factors in Model A plus FEV₁, grip strength, and waist circumference; and Model C included the clinical factors in Model A plus PRI.

Elastic-net Cox regression ($\alpha = 0.5$) was implemented using stratified nested 5-fold cross-validation repeated three times. Within each outer training fold, λ was selected by inner 5-fold cross-validation

(lambda.min). Out-of-fold predictions were generated for hold-out participants and averaged across repetitions.

Model discrimination was assessed using the C-index, with 95% CIs, between-model differences, and P values derived from 500 bootstrap replicates. At the 10-year horizon, model performance was further evaluated using time-dependent receiver operating characteristic curve (ROC) curves and AUCs, calibration of predicted versus observed risks across deciles, and decision curve analysis of net clinical benefit across risk thresholds. SHAP were used to interpret Models B and C. Exact SHAP values for the Cox linear predictor were derived from fitted coefficients and mean-centered feature values, with global importance quantified by the mean absolute SHAP value.

All analyses were implemented in R software. Key packages included survival, glmnet, timeROC, purrr, and ggplot2. All analyses were conducted using R software (version 4.4.3).

Sensitivity analyses

Several sensitivity analyses were conducted to assess the robustness of the primary findings. First, participants who developed the cardiovascular outcome of interest within the first two years of follow-up were excluded to reduce the possibility of reverse causation. Second, complete-case analyses were restricted to participants with no missing covariate data. Third, Fine-Gray subdistribution hazard models were fitted for incident cardiovascular outcomes, treating death from other causes as a competing event.

Abbreviations

PRI, Physiological Reserve Index;

FEV₁, forced expiratory volume in 1 second;

BC, breast cancer;

NBC, no breast cancer;

HR, hazard ratio;

CI, confidence interval;

TDI, Townsend Deprivation Index;

RCS, restricted cubic spline;

PAF, population-attributable fraction;

C-index, Harrell's concordance index;

ROC, receiver operating characteristic;

AUC, area under the receiver operating characteristic curve;

SHAP, SHapley Additive exPlanations;

Declarations

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Research Board (IRB) at the Virginia Commonwealth University.

Consent for publication

Not applicable.

Availability of data and materials

The data used in this study are available from the UK Biobank but are not publicly available. This research was conducted using the UK Biobank Resource under Application Number 928207. Further information is available at the following URL: <https://www.ukbiobank.ac.uk/>. Eligible researchers may apply to UK Biobank for data access, subject to approval.

Competing interests

All authors declare no financial or non-financial competing interests.

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Author contributions

MX, RZ and BL designed the study. MX, DX and YB performed the data analyses. MX and MY drafted the manuscript. JF, JC, RH, YG and XZ contributed to the interpretation of the results, and XW, YY, SF and YX critically revised the manuscript for important intellectual content. MX, MY and BL contributed equally to

this work and should be considered as co-first authors. All authors read and approved the final manuscript.

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Figures

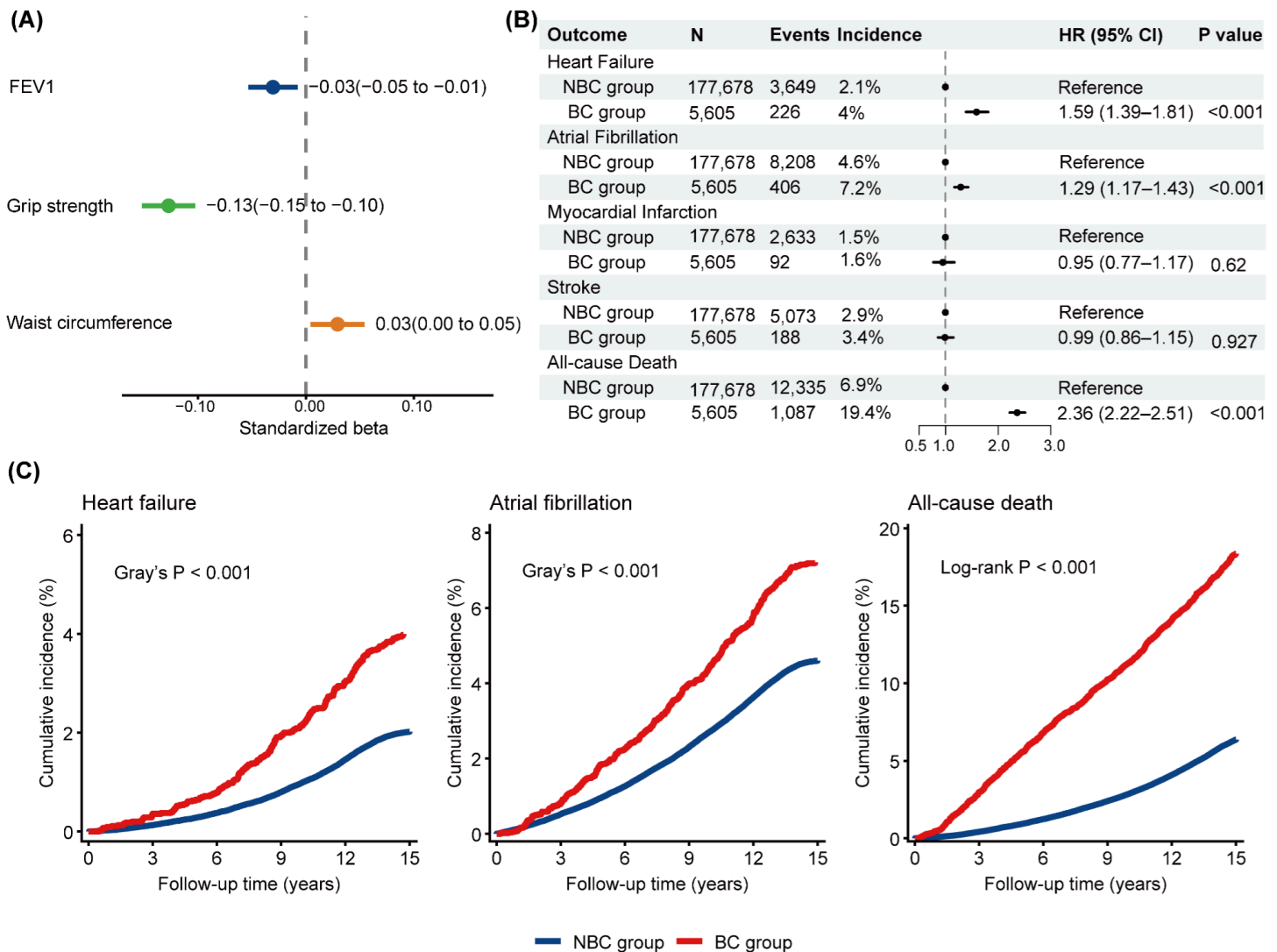


Figure 1

Physiological reserve and cardiovascular risk according to breast cancer status.

a. Standardized differences (beta, 95%CI) in FEV₁, grip strength, and waist circumference between women with and without breast cancer. **b.** Adjusted HRs (95%CI) for cardiovascular outcomes and all-cause death associated with breast cancer. **c.** Cumulative incidence of heart failure and atrial fibrillation and cumulative all-cause mortality according to breast cancer status; Gray's test was used for cardiovascular outcomes and the log-rank test for all-cause death. BC, breast cancer; NBC, no breast cancer; FEV₁, forced expiratory volume in 1 second; HR, hazard ratio.

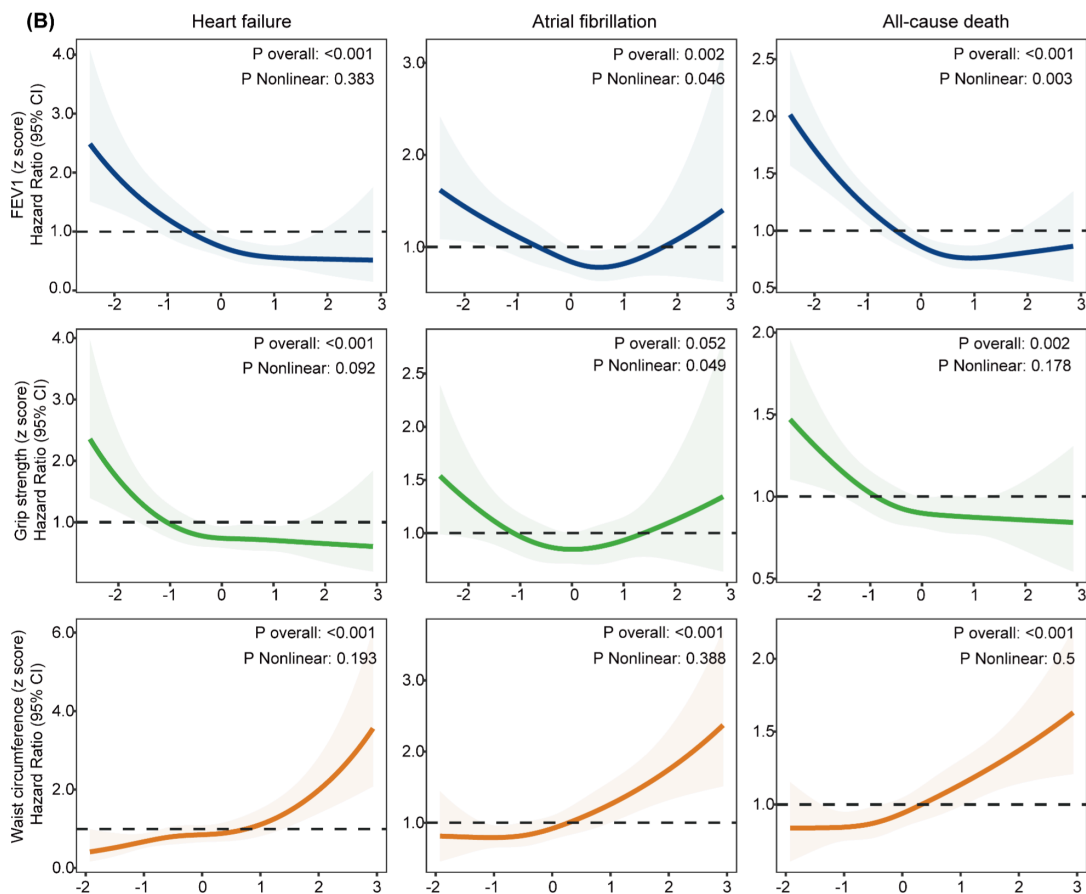
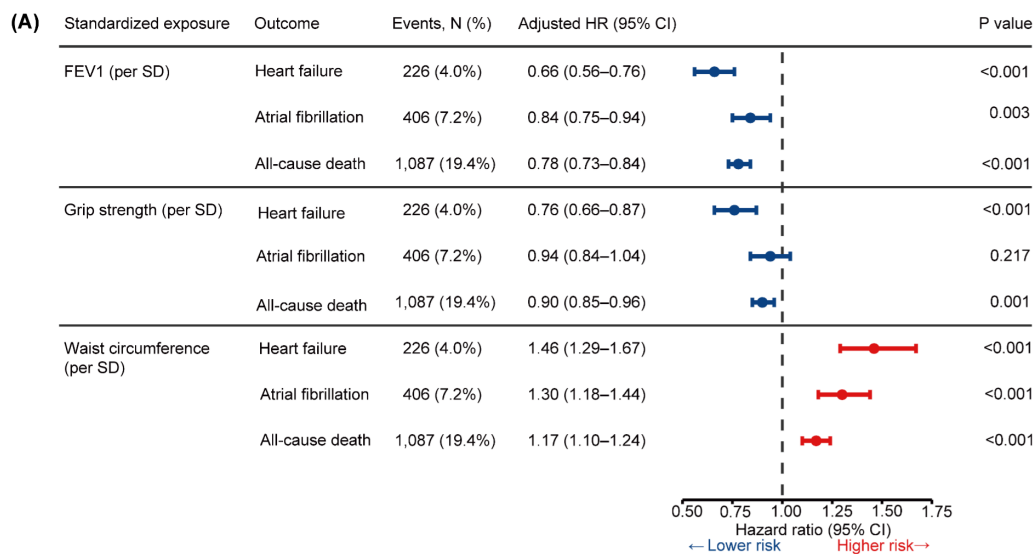


Figure 2

Associations of individual physiological reserve components with cardiovascular outcomes and mortality.

a. Forest plot showing adjusted HRs per standard-deviation (SD) increment for FEV₁, grip strength, and waist circumference with respect to heart failure, atrial fibrillation, and all-cause death. Blue symbols indicate protective effects (HR < 1), red symbols indicate higher risk (HR > 1). **b.** Restricted cubic spline (RCS) plots visualizing nonlinear relationships between z-score-standardized physical-function indicators and hazard rates of each outcome. Shaded areas correspond to 95% CIs.

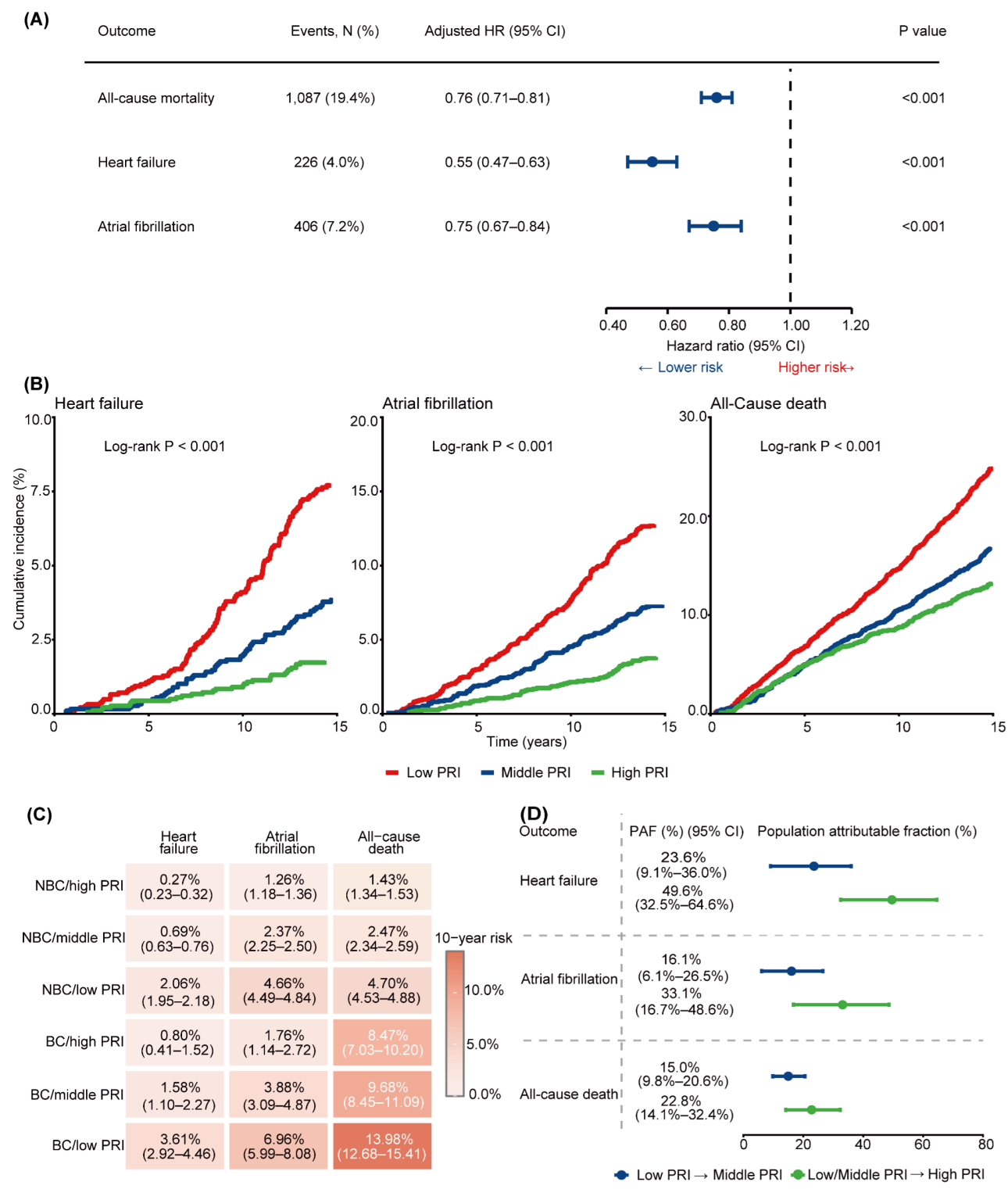


Figure 3

Physiological Reserve Index and long-term cardiovascular risk.

a. Forest plot of adjusted HRs for the PRI in relation to heart failure, atrial fibrillation, and all-cause mortality. **b.** Kaplan-Meier cumulative incidence curves stratified by low-PRI, middle-PRI, and high-PRI subgroups for heart failure, atrial fibrillation, and all-cause death. Log-rank P values are shown. **c.** Estimated 10-year absolute risks (95% CIs) of heart failure, atrial fibrillation, and all-cause death according to breast cancer status and PRI tertile. **d** Population attributable fractions (PAFs) and 95% CIs associated with impaired Physiological reserve, comparing low versus middle PRI and low/middle versus high PRI, for heart failure, atrial fibrillation, and all-cause death. BC, breast cancer; CI, confidence interval; HR, hazard ratio; NBC, no breast cancer; PAF, population attributable fraction; PRI, Physiological Reserve Index; SD, standard deviation.

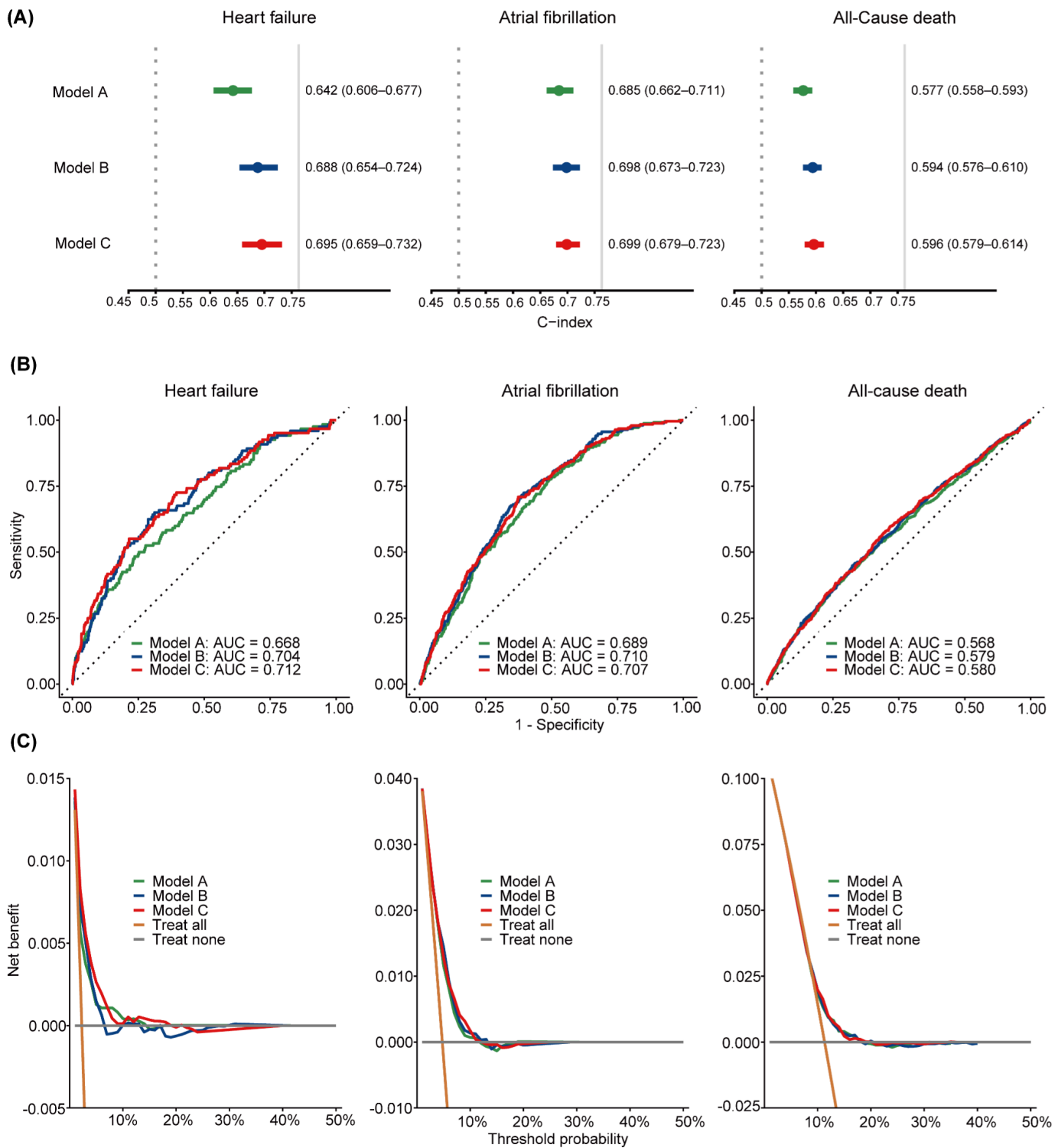


Figure 4

Predictive performance of models incorporating physiological reserve.

a. C-indices (95% CIs) for heart failure, atrial fibrillation, and all-cause death across Models A-C. **b.** Time-dependent ROC curves for 10-year risk prediction. **c.** Decision curve analyses comparing net benefit across threshold probabilities. Model A, clinical variables; Model B, clinical variables plus FEV₁, grip

strength, and waist circumference; Model C, clinical variables plus PRI. AUC, area under the curve; CI, confidence interval; FEV₁, forced expiratory volume in 1 s; PRI, Physiological Reserve Index; ROC, receiver operating characteristic.

Supplementary Files

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