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Research Article

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Posted Date: November 24th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11401682/v1

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Additional Declarations: No competing interests reported.

Association Between Peak Expiratory Flow Trajectory and Risk Of Sarcopenia : A Multi-National Cross-Cohort Comparative Study

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Abstract

Background: Sarcopenia can affect 10%-27% of adults ≥60 years, which is a major public health challenge. Peak expiratory flow (PEF) reflects the function of respiratory muscle. The associations between repeated PEF measurements and sarcopenia are unclear.

Methods: This prospective cohort study included three nationally representative aging cohorts: China Health and Retirement Longitudinal Study (CHARLS, n=3,806), English Longitudinal Study of Ageing (ELSA, n=2,231) and Health and Retirement Study (HRS, n=724). Statistical analyses were conducted using R 4.2.0 and Stata 17.0, encompassing K-means trajectory clustering, Cox proportional hazards regression with Schoenfeld residual verification and random-effects meta-analysis with I^2 heterogeneity quantification.

Results: Three PEF trajectories (low-stable, moderate-stable, high-stable) were identified in all cohorts. High-stable PEF was associated with a 62%-73% lower risk of sarcopenia (CHARLS: HR=0.31; ELSA: HR=0.38; HRS: HR=0.27), with consistent direction across cohorts and no heterogeneity (I^2=0%). Trajectory clustering showed more stable dose-response relationships than single-point measurements, whereas prediction-equation-derived PEF metrics showed cross-cohort heterogeneity.

Conclusions: Repeatedly measured PEF levels were stably associated with incident sarcopenia across Chinese, British and American older adults, supporting PEF as a low-cost screening indicator. Differences among single-time, cumulative and prediction-equation-derived PEF metrics highlight the need for population-specific validation.

Keywords: Peak expiratory flow; Risk of sarcopenia; Trajectory clustering; Cohort study; Cross-national comparison; Prediction equation

Introduction

Sarcopenia is a progressive and generalized syndrome characterized by loss of skeletal muscle mass and function, closely associated with falls, fractures, disability, hospitalization and mortality[1–3]. The global prevalence of sarcopenia among adults aged ≥60 years is estimated at 10%-27%, increasing exponentially with age[4]. With accelerating population aging worldwide, sarcopenia has emerged as a major public health challenge,which brings significant social and economic burden[5,6].

Peak expiratory flow (PEF) is the maximum flow rate during forced expiration, serving as a composite indicator reflecting large airway patency, respiratory muscle strength (particularly expiratory muscles) and pulmonary ventilation function[7,8]. Because the respiratory muscles are fundamentally skeletal muscles, PEF is closely related not only to pulmonary function but also to overall physical function. Previous studies have shown that PEF is associated with grip strength, gait speed and body composition and have suggested a link between PEF and sarcopenia[9–14]. PEF measurement is simple, non-invasive and low-cost, making it a promising tool for community-based assessment of muscle status[7,15].

Existing studies have several limitations. First, most studies have relied on single-point PEF measurements and lack repeated measurement information, which cannot capture dynamic patterns of pulmonary function change. Second, large-scale validation across national aging cohorts is lacking, limiting the generalizability of findings. Third, it remains unclear whether different ways of expressing PEF—single-time, cumulative and prediction-equation-derived measures—show consistent associations with sarcopenia, as the prediction equations were predominantly developed in Western White populations and their applicability in Chinese populations has not been fully validated[16,17]. Additionally, socioeconomic status is an important determinant of sarcopenia, which is particularly relevant in cross-national comparison[18–20].

Based on three large aging cohorts from China (CHARLS), the United Kingdom (ELSA) and the United States (HRS), this study aimed to: (1) examine the associations of repeated PEF patterns and conventional PEF metrics with incident sarcopenia across CHARLS, ELSA and HRS; and (2) explore whether prediction-equation-derived PEF metrics showed consistent associations across populations.

Materials and Methods

Study Design

This prospective cohort study utilized three nationally representative aging cohorts. The China Health and Retirement Longitudinal Study (CHARLS) was launched in 2011, covering 28 provinces, 150 county-level units and 450 village-level units using multi-stage stratified cluster sampling[21]. This study included participants with complete PEF data from Wave 1 (2011) and Wave 2 (2013), with sarcopenia status at Wave 3 (2015) as the outcome. The English Longitudinal Study of Ageing (ELSA) was launched in 2002, with samples drawn from the British Household Panel Survey (BHPS) and the Postcode Address File, with biennial follow-up[22]. This study included PEF data from Wave 2 (2004-2005) and Wave 4 (2008-2009), predicting sarcopenia incidence at Wave 6 (2012-2013) and Wave 8 (2016-2017). The Health and Retirement Study (HRS) was launched in 1992, funded by the National Institute on Aging (NIA) and the Social Security Administration (SSA), using time-stratified probability sampling[23]. This study included PEF data from Wave 8 (2006) and Wave 10 (2010), predicting sarcopenia incidence at Wave 12 (2014) and Wave 14 (2018).

Study Participants

Inclusion criteria were: (1) age >=50 years; (2) complete baseline PEF measurement data; and (3) no sarcopenia diagnosis at baseline. Exclusion criteria were: (1) age <50 years; (2) missing baseline PEF data; (3) sarcopenia diagnosed at baseline; (4) missing sarcopenia status during follow-up; and (5) missing key covariates (age, sex, education, marital status, smoking, alcohol consumption, depression, hypertension, diabetes, activities of daily living limitation, stroke, heart disease, chronic lung disease(BMI). The final sample comprised 3,806 participants from CHARLS, 2,231 from ELSA and 724 from HRS.

Exposure Variable Definitions

PEF was expressed using four metrics. PEF trajectory clustering (PEF_cluster) was derived by applying K-means clustering to standardized PEF values from two follow-up assessments within each cohort; prior to clustering, Z-score standardization was performed to eliminate scale differences, the optimal cluster number was determined using the elbow method and silhouette coefficient and principal component analysis (PCA) visualization was applied to validate the clustering results[24,25]. PEF single-point measurement (PEF_w2) was defined as the measured PEF value at the second follow-up assessment, categorized into quartiles (Q1-Q4) and PEF cumulative exposure (PEF_cum) was defined as the cumulative average of PEF values from the two follow-up assessments, also categorized into quartiles.

Percent predicted, the ratio of measured PEF to predicted PEF×100%, was categorized into tertiles. The prediction equations were as follows. For Western populations (ELSA, HRS), the Nunn-Gregg equation[7] was used: males, PEF = exp(0.544× ln(age) - 0.0151×age - 74.7/height + 5.48); females, PEF = exp(0.376×ln(age) - 0.0120× age - 58.8/height + 5.63). For the Chinese population (CHARLS), the equation developed by the Zhong Nanshan team[11] was used: males, PEF = 75.6 + 20.4×age - 0.41×age2 + 0.002×age3 + 1.19×height; females, PEF = 282.0 + 1.79×age - 0.046×age2 + 0.68×height.

The standardized residual (SR) was calculated as (measured PEF - predicted PEF)/residual standard deviation and categorized into four percentile groups: >=80%, 50%-79%, 10%-49% and <10%. An SR <10% indicates that the measured value is substantially below the predicted value, suggesting severe pulmonary function impairment.

Outcome Variable Definition

Sarcopenia was defined according to the European Working Group on Sarcopenia in Older People (EWGSOP2) and the Asian Working Group on Sarcopenia (AWGS) consensus,[1,9] adapted to each cohort's available measures (Table 1). For CHARLS: based on grip strength (males <28 kg, females <18 kg) and gait speed (<1.0 m/s) or low muscle mass indicators, participants were classified as no sarcopenia, probable sarcopenia or sarcopenia. Those with no sarcopenia were defined as the reference group and the remaining categories were combined as sarcopenia. Similar criteria combining grip strength and gait speed assessment were applied in analyzing data from ELSA. For HRS: the operational definition was adapted from the study by Bing et al., which used EWGSOP2 criteria with gait speed threshold <0.8 m/s, grip strength threshold <27 kg for males and <16 kg for females, simplified estimation for muscle mass and European population-based muscle mass thresholds[4].

Table 1. Operational Definitions of Sarcopenia Across Three Cohorts

Characteristic	CHARLS (China)	ELSA (UK)	HRS (USA)
Diagnostic criteria	AWGS 2019	EWGSOP2	EWGSOP2
Gait speed threshold	<1.0 m/s	<=0.8 m/s	<0.8 m/s
Grip strength threshold (male)	<28 kg	<27 kg	<27 kg
Grip strength threshold (female)	<18 kg	<16 kg	<16 kg
Muscle mass formula	Wen equation (China-validated)	Lee equation	Simplified estimation
Case screening	SARC-F questionnaire	No	No
Chair stand test	Yes	Yes	No
Muscle mass threshold source	Asian population/lowest 20th percentile	European population	European population

Statistical Analysis

Statistical analyses were conducted using R 4.2.0 and Stata 17.0. K-means clustering was applied to standardized PEF values from two follow-up assessments within each cohort to identify trajectory groups, with the optimal cluster number determined by the elbow method and silhouette coefficient and validated by principal component analysis[25]. Associations between each PEF metric and incident sarcopenia were estimated using Cox proportional hazards regression and the proportional hazards assumption was verified using Schoenfeld residuals. Three progressively adjusted models were fitted. Model 1 was adjusted for age and sex. Model 2 was additionally adjusted for education, marital status, smoking status and alcohol consumption. Model 3 was further adjusted for body mass index, stroke, heart disease and chronic lung disease. Cohort-specific estimates were pooled using random-effects meta-analysis with I^2 heterogeneity quantification[26]. Stratified and sensitivity analyses (competing risk models and exclusion of baseline chronic lung disease) were also performed, with statistical significance set at $P<0.05$.

Results

Baseline Characteristics

The three cohorts differed significantly in age structure, education level and lifestyle, reflecting the sociodemographic characteristics of older adults in China, the United Kingdom and the United States. The HRS cohort had the oldest mean age (75.53 years) and the highest proportion of females (77.5%); the CHARLS cohort had the lowest education level (88.6% below high school) and the highest smoking rate (49.1%) (Table 2).

Table 2. Baseline Characteristics of the Three Cohorts

Characteristic	CHARLS (n=3,806)	ELSA (n=2,231)	ELSA vs CHARLS（significant difference）	HRS (n=724)	HRS vs CHARLS（significant difference）

Age, years, mean (SD)	60.70 (7.24)	66.69 (7.32)	**＜0.001**	75.53 (5.26)	**＜0.001**
Education below high school, n (%)	3,373 (88.6)	720 (32.3)	**＜0.001**	52 (7.2)	**＜0.001**
Married, n (%)	3,276 (86.1)	1,623 (72.7)	**＜0.001**	526 (72.7)	**＜0.001**
Female, n (%)	1,617 (42.5)	1,161 (52.0)	**＜0.001**	561 (77.5)	**＜0.001**
Depression, n (%)	1,121 (29.5)	212 (9.5)	**＜0.001**	40 (5.5)	**＜0.001**
Chronic lung disease, n (%)	468 (12.3)	110 (4.9)	**＜0.001**	67 (9.3)	**0.052**
Smoking, n (%)	1,870 (49.1)	217 (9.7)	**＜0.001**	46 (6.4)	**＜0.001**
Alcohol consumption, n (%)	1,880 (49.4)	1,614 (72.3)	**＜0.001**	436 (60.2)	**＜0.001**
Asthma, n (%)	-	293 (13.1)	**13.1**	-	**-**
ADL limitation, n (%)	543 (14.3)	278 (12.5)	**0.312**	14 (1.9)	**＜0.001**

ADL：Activities of Daily Living

PEF Trajectory Clustering Characteristics

Figure 1 summarizes the determination and validation of the PEF trajectory clusters in the three cohorts. In the elbow method plots (Figure 1A-1C), the total within-cluster sum of squares showed a marked inflection at k=3 in CHARLS, ELSA and HRS, identifying three as the optimal cluster number in all three cohorts. Principal component analysis visualization (Figure 1D-1F) confirmed that the three clusters formed clearly separated groups in the reduced-dimensional space, with the first principal component explaining 77.5%, 88.9% and 90% of the total variance in CHARLS, ELSA and HRS, respectively. The resulting PEF trajectories (Figure 1G-1I) showed a consistent level-based stratification across cohorts, with a low PEF cluster, a medium PEF cluster and a high PEF cluster; mean standardized PEF values remained largely parallel between the two follow-up waves within each cohort, indicating that the clusters primarily reflected differences in PEF level rather than divergent within-person change over time.

As shown in Table 3, the PEF levels of each trajectory group demonstrated clear natural stratification: the low-stable group had mean standardized PEF values of 215.4±78.3 L/min (CHARLS), 268.7±89.5 L/min (ELSA), and 312.5±95.6 L/min (HRS); the moderate-stable group had 348.6±62.1 L/min, 412.3±71.4 L/min, and 445.8±68.3 L/min; and the high-stable group had 498.2±55.7 L/min, 562.1±48.9 L/min, and 578.3±52.1 L/min, corresponding to approximate ranges of 210–310, 350–450, and 500–580 L/min across cohorts. All three groups remained relatively stable during follow-up, with mean within-subject standard deviations of 12.4, 15.6, and 18.3 L/min and intraclass correlation coefficients (ICC) of 0.92, 0.89, and 0.87, indicating good temporal stability of trajectory classification and suggesting identifiable pulmonary function phenotypes.

Table 3. Characteristics of PEF Trajectory Clusters

Trajectory Group	CHARLS (n=3,806)	ELSA (n=2,231)	HRS (n=724)	Mean PEF, L/min (SD)
Low-stable	1,348 (35.4)	761 (34.1)	151 (20.9)	215.4±78.3 / 268.7±89.5 / 312.5±95.6
Moderate-stable	1,671 (43.9)	956 (42.9)	323 (44.6)	348.6±62.1 / 412.3±71.4 / 445.8±68.3
High-stable	787 (20.7)	514 (23.0)	250 (34.5)	498.2±55.7 / 562.1±48.9 / 578.3±52.1
P	CHARLS vs ELSA	ELSA vs HRS	CHARLS vs HRS	
	＜0.001	＜0.001	＜0.001	

Note: PEF = peak expiratory flow; SD = standard deviation. Mean PEF values are presented as CHARLS / ELSA / HRS. Silhouette scores for the three-cluster solution were 0.58 (CHARLS), 0.61 (ELSA) and 0.55 (HRS); Calinski-Harabasz indices were 284.3, 312.7 and 198.5; and between-cluster sum of squares to total sum of squares ratios (BSS/TSS) were 0.875, 0.880 and 0.858, respectively.

Comparison of Baseline Characteristics by Incident Sarcopenia Status (CHARLS)

To describe the baseline profile of participants who developed incident sarcopenia during follow-up, we compared their baseline characteristics with those who remained sarcopenia-free in the CHARLS cohort (Table 4). Participants who developed sarcopenia were older (66.12 vs. 60.46 years) and more likely to be female (50.3% vs. 42.1%), unmarried (21.5% vs. 13.6%) and to have an education below high school (95.7% vs. 88.3%). They were also more likely to follow a low-stable PEF trajectory (51.5% vs. 34.7%) and far less likely to maintain a high-stable trajectory (9.2% vs. 21.2%) and had a lower mean measured PEF (272.38 vs. 324.50 L/min); all differences were statistically significant (all P<0.05). Similar patterns were observed in the ELSA and HRS cohorts. These baseline differences motivated the multivariable-adjusted Cox regression analyses examining the prospective association between PEF and incident sarcopenia.

Table 4. Comparison of Baseline Characteristics Between Sarcopenia and Non-Sarcopenia Groups (CHARLS)

Variable	Non-sarcopenia (n=3,643)	Sarcopenia (n=163)	*P*-value
Age, years	60.46 (7.15)	66.12 (7.16)	<0.001
Female, n (%)	1,535 (42.1%)	82 (50.3%)	0.047
Unmarried, n (%)	495 (13.6%)	35 (21.5%)	0.006
Education below high school, n (%)	3,217 (88.3%)	156 (95.7%)	0.005
Low-stable PEF, n (%)	1,264 (34.7%)	84 (51.5%)	<0.001
High-stable PEF, n (%)	772 (21.2%)	15 (9.2%)	<0.001
Measured PEF, L/min	324.50 (125.98)	272.38 (115.35)	<0.001

Note: The moderate-stable PEF group served as the reference category and was therefore omitted from this descriptive comparison.

Cox Regression Analysis

In all three cohorts, higher PEF trajectory groups were associated with a lower risk of sarcopenia in a dose-response manner (Table 5). Compared with the low-stable group, the high-stable group was associated with HRs of 0.31 (95% CI: 0.18–0.56), 0.38 (0.27–0.54) and 0.27 (0.17–0.41) in CHARLS, ELSA and HRS, respectively (all P<0.001) and the moderate-stable group with HRs of 0.57 (0.41–0.80), 0.60 (0.47–0.75) and 0.50 (0.36–0.71). Random-effects meta-analysis showed no heterogeneity (I^2=0%).

Single-point measurement (PEF_w2) was also associated with a lower risk of sarcopenia: compared with Q1, Q4 HRs were 0.34 (95% CI: 0.20–0.58), 0.34 (0.24–0.48) and 0.28 (0.18–0.44) in CHARLS, ELSA and HRS, respectively (all P<0.001). In CHARLS, the Q3 estimate (HR=0.57, 95% CI: 0.38–0.87) was higher than Q4, indicating some non-monotonicity in this cohort; the dose-response gradient of trajectory clustering was more stable across cohorts.

By contrast, cumulative exposure (PEF_cum) showed weaker and less consistent associations (Table 5). In CHARLS, the association was limited to Q3 (HR=0.44, 95% CI: 0.26–0.73, P=0.001), while Q4 showed no association (HR=1.06, 95% CI: 0.72–1.56, P=0.771). In ELSA and HRS, Q4 HRs were 0.64 (0.48–0.87) and 0.67 (0.45–0.98), respectively.

The prediction-equation-derived metrics were also less consistent. Percent predicted PEF showed protective associations in ELSA (T3 HR=0.43, 95% CI: 0.30–0.61, P<0.001) and HRS (T3 HR=0.43, 0.28–0.65, P<0.001), but the association was attenuated and non-significant in CHARLS (T3 HR=0.71, 0.46–1.11, P=0.135; T2 HR=0.87, 0.56–1.37, P=0.561) (Table 5).

Similarly, standardized residual (SR) showed significant cross-cohort differences: SR<10% was associated with a higher risk of sarcopenia in HRS (HR=3.66, 95% CI: 2.17–6.17, P<0.001) and ELSA (HR=2.65, 1.24–5.68, P=0.012), but not in CHARLS (HR=0.77, 0.38–1.57, P=0.476).

Table 5. Cox Regression Analysis of PEF Metrics and Sarcopenia Risk Across Three Cohorts

Variable	CHARLS HR (95% CI)	P	ELSA HR (95% CI)	P	HRS HR (95% CI)	P
PEF_cluster						
Low-stable	1.00(Ref)		1.00（Ref）		1.00（Ref）	
Moderate-stable	0.57 (0.41-0.80)	0.001	0.60 (0.47-0.75)	<0.001	0.50 (0.36-0.71)	<0.001
High-stable	0.31 (0.18-0.56)	<0.001	0.38 (0.27-0.54)	<0.001	0.27 (0.17-0.41)	<0.001
PEF_w2						
Q1	1.00（Ref）		1.00（Ref）		1.00（Ref）	
Q2	0.64 (0.43-0.95)	0.025	0.74 (0.57-0.96)	0.025	0.63 (0.44-0.90)	0.01
Q3	0.57 (0.38-	0.009	0.51 (0.38-	<0.001	0.34 (0.22-	<0.001

	0.87)		0.68)		0.52)	
Q4	0.34 (0.20-0.58)	<0.001	0.34 (0.24-0.48)	<0.001	0.28 (0.18-0.44)	<0.001
PEF_cum						
Q1	1.00（Ref）		1.00（Ref）		1.00（Ref）	
Q2	0.75 (0.49-1.14)	0.174	0.82 (0.62-1.09)	0.167	0.91 (0.63-1.31)	0.611
Q3	0.44 (0.26-0.73)	0.001	0.75 (0.56-1.00)	0.053	0.66 (0.44-0.98)	0.041
Q4	1.06 (0.72-1.56)	0.771	0.64 (0.48-0.87)	0.004	0.67 (0.45-0.98)	0.041
% Predicted						
T1	1.00（Ref）		1.00（Ref）		1.00（Ref）	
T2	0.87 (0.56-1.37)	0.561	0.62 (0.48-0.80)	<0.001	0.41 (0.29-0.60)	<0.001
T3	0.71 (0.46-1.11)	0.135	0.43 (0.30-0.61)	<0.001	0.43 (0.28-0.65)	<0.001
SR percentile						
>=80%	1.00（Ref）		1.00（Ref）		1.00（Ref）	
50%-79%	0.92 (0.44-1.89)	0.811	1.10 (0.47-2.59)	0.822	1.02 (0.62-1.68)	0.926
10%-49%	0.93 (0.48-1.80)	0.826	1.65 (0.77-3.53)	0.197	2.30 (1.45-3.63)	<0.001
<10%	0.77 (0.38-1.57)	0.476	2.65 (1.24-5.68)	0.012	3.66 (2.17-6.17)	<0.001

Note: Estimates are from Model 3, adjusted for age, sex, education, marital status, smoking, alcohol consumption, body mass index, stroke, heart disease and chronic lung disease. PEF_cluster = peak expiratory flow trajectory clustering; PEF_w2 = PEF at the second follow-up assessment; PEF_cum = cumulative average of PEF from two follow-up assessments; percent predicted = ratio of measured PEF to predicted PEF × 100%; SR = standardized residual. PEF_w2 and PEF_cum were categorized into quartiles (Q1–Q4) based on the distribution within each cohort. Percent predicted was categorized into tertiles (T1–T3) based on the distribution within each cohort. SR percentiles were categorized as ≥80%, 50%–79%, 10%–49% and <10%. HR = hazard ratio; CI = confidence interval.

Figures 2-4 present the cohort-specific forest plots for percent predicted PEF, corroborating the patterns described above (Table 5). Notably, the consistency between ELSA and HRS—both employing the Nunn-Gregg equation in White populations—supports the validity of Western prediction equations within their derivation populations[7,16].

Kaplan-Meier Survival Curves

Figure 5A-5C shows Kaplan-Meier survival curves across the three cohorts. Survival curves stratified by PEF trajectory clustering showed that in all three cohorts, the low-stable group had the poorest survival and the high-stable group the best, with all Log-rank P<0.001. In the CHARLS cohort, the moderate-stable group showed a sharp decline at 30 months, suggesting potential heterogeneity within

this group; in contrast, the ELSA and HRS cohorts showed earlier curve separation with constant separation, reflecting longer follow-up duration allowing full manifestation of effects.

Figure 6A-6D presents comparative Kaplan-Meier curves for alternative PEF metrics in CHARLS. Single-point measurement (Figure 6D) showed clear dose-response separation (Q4>Q3>Q2>Q1, Log-rank P<0.001), performing comparably to trajectory clustering. In contrast, cumulative exposure (Figure 6C) displayed an inverted J-shaped pattern inconsistent with monotonic risk gradients. Prediction equation-based metrics showed poor discrimination: percent predicted (Figure 6B) had minimal separation between lower tertiles, while standardized residual (Figure 6A) showed less distinct intermediate group separation. These visual findings confirm that trajectory clustering and single-point measurement outperform cumulative and prediction-based metrics for risk stratification.

Stratified Analysis

To evaluate whether the association between PEF trajectory clustering and the risk of sarcopenia was modified by key demographic, lifestyle and clinical characteristics, we conducted stratified analyses across predefined subgroups in each cohort. As the optimal PEF metric identified in the primary analysis, PEF trajectory clustering was used as the exposure variable for all stratified analyses. The high-stable trajectory group was compared against the low-stable group (reference) in each subgroup, with the moderate-stable group excluded from this comparison to focus on the contrast between extreme phenotypes.

The direction of the protective effect was consistent across BMI and chronic lung disease subgroups in all three cohorts, with no statistically significant effect modification (all P for interaction >0.05; Table 6).

For lifestyle factors, the association between PEF trajectories and the risk of sarcopenia remained consistent across subgroups defined by alcohol consumption and smoking status in all three cohorts (all P for interaction >0.05; Table 6). In the CHARLS cohort, the protective effect was observed among both non-drinkers (HR=0.51, 95% CI: 0.32-0.80) and drinkers (HR=0.66, 95% CI: 0.41-1.08), with no significant interaction (P=0.139); the effect among drinkers did not reach statistical significance, likely attributable to the smaller event numbers in this subgroup. Similarly, the association was consistent between never-smokers and ever/current smokers in all three cohorts (all P for interaction >0.70), though some subgroup estimates were imprecise because of small event numbers, including current smokers in ELSA (HR=0.45, 95% CI: 0.20-1.03) and HRS (HR=0.72, 95% CI: 0.22-2.44), the latter reflecting the very low smoking prevalence (6.4%) in this older American cohort.

Table 6. Stratified Analysis of PEF Trajectory Clustering (Selected Results)

Stratification Variable	Subgroup	CHARLS HR (95% CI)	P for interaction	ELSA HR (95% CI)	P for interaction	HRS HR (95% CI)	P for interaction
Alcohol consumption	No	0.51 (0.32-0.80)	0.139	0.56 (0.39-0.80)	0.893	0.55 (0.35-0.87)	0.723
	Yes	0.66 (0.41-1.08)		0.53 (0.39-0.71)		0.44 (0.28-0.68)	
Smoking	No	0.52 (0.33-	0.796	0.51 (0.41-	0.916	0.48 (0.34-	0.863

		0.82)		0.65)		0.67)	
	Yes	0.63 (0.39-1.02)		0.45 (0.20-1.03)		0.72 (0.22-2.44)	
BMI	Normal	0.59 (0.42-0.85)	0.426	0.36 (0.22-0.59)	0.138	0.72 (0.36-1.41)	0.586
	Overweight	0.37 (0.16-0.85)		0.57 (0.44-0.73)		0.46 (0.32-0.66)	
Chronic lung disease	No	0.57 (0.40-0.82)	0.296	0.52 (0.41-0.67)	0.932	0.46 (0.32-0.65)	0.387
	Yes	0.75 (0.33-1.73)		0.46 (0.22-0.98)		0.84 (0.37-1.94)	

Meta-Analysis

Figure 7A-7C shows the meta-analysis forest plot. Random-effects meta-analysis confirmed that PEF trajectory clustering exhibited good cross-cohort consistency: pooled HRs were 0.32 (95% CI: 0.24–0.42) for high-stable and 0.56 (95% CI: 0.49–0.64) for moderate-stable trajectories, with I^2=0% for both. Single-point measurement (PEF_w2 Q4) similarly showed good consistency (pooled HR 0.32, 95% CI: 0.26–0.39; I^2=0%). In contrast, prediction equation–based metrics displayed substantial heterogeneity: percent predicted T3 yielded a pooled HR of 0.52 (95% CI: 0.28–0.97; I^2=85.3%), reflecting the attenuated, non-significant association in CHARLS (HR=0.71) and SR<10% yielded a pooled HR of 1.71 (95% CI: 0.72–4.06; I^2=88.7%), reflecting the null effect in CHARLS (HR=0.77) versus significant effects in HRS (HR=3.66) and ELSA (HR=2.65).

Discussion

In three nationally representative cohorts from China, the United Kingdom and the United States, repeatedly measured higher PEF levels were associated with a lower risk of incident sarcopenia. This association was directionally consistent across the CHARLS, ELSA and HRS cohorts, with no heterogeneity in meta-analysis. Direct PEF measures (trajectory clustering and single-point measurement) showed more consistent cross-cohort associations than prediction-equation-derived metrics. Consistent with previous reports that lower socioeconomic status is associated with sarcopenia[19,20], participants who developed sarcopenia in this study had markedly lower educational attainment.

Several mechanisms may explain the association between PEF and sarcopenia. Respiratory muscles, including the diaphragm and intercostals, are skeletal muscles that undergo parallel decline in sarcopenia, a phenomenon termed “respiratory sarcopenia.”[10,11] Because systemic skeletal muscle loss and respiratory muscle weakness share common pathways, PEF may serve as an integrated marker of overall muscle status. Systemic inflammation is one such shared pathway: elevated TNF-α, IL-6 and CRP promote concurrent muscle protein catabolism and lung tissue injury, linking inflammation to muscle loss and pulmonary function decline[27–29]. Finally, physical inactivity, often driven by dyspnea, exacerbates disuse atrophy in both respiratory and limb muscles[30–36].

Despite differences in sarcopenia definitions, follow-up schedules and sociodemographic profiles, the direction of the PEF-sarcopenia association was consistent across the three cohorts, supporting the

robustness of the main finding. In contrast, prediction-equation-derived metrics showed clear heterogeneity: percent predicted and standardized residuals performed well in ELSA and HRS but were attenuated in CHARLS. This pattern suggests that the transportability of prediction equations across populations requires formal validation rather than direct application; otherwise, individuals with genuinely compromised respiratory muscle function may be misclassified and falsely reassured by "normal" percent predicted values. Developing geographically and ethnically stratified reference equations based on large-scale multi-center studies remains a priority[16,17,37,38].

This study has several strengths, including the use of three nationally representative prospective cohorts from different countries, the simultaneous evaluation of multiple PEF expressionsand meta-analytic pooling of cohort-specific estimates. Several limitations should be noted. First, only two PEF measurements were available, so the trajectories identified reflect level differences rather than change velocity or morphology. Second, sarcopenia definitions were not identical across cohorts because of differences in available measures, which may affect cross-cohort comparability. Third, as an observational study, residual confounding cannot be excluded despite multivariable adjustment. Fourth, the HRS sample was relatively small (n=724), limiting the precision of cohort-specific estimates. Finally, the prediction equations were not formally recalibrated within each cohort. Future studies with three or more PEF measurements, harmonized sarcopenia assessmentand locally validated prediction equations are warranted.

Conclusion

Based on three large aging cohorts from China, the United Kingdom and the United States, this study confirms that repeatedly measured PEF levels are stably associated with incident sarcopenia, with consistent direction across cohorts and clear dose-response relationships and that trajectory-based classification showed more stable dose-response patterns than single-point measurements. Differences among single-time, cumulative and prediction-equation-derived PEF metrics suggest that population-specific validation of reference equations is needed to accurately assess respiratory muscle function and identify high-risk sarcopenia populations.

Acknowledgements

The authors thank the China Health and Retirement Longitudinal Study (CHARLS), the English Longitudinal Study of Ageing (ELSA) and the Health and Retirement Study (HRS) teams for making the data publicly available. We also thank all participants in these three cohorts for their valuable contributions.

Funding

This work was supported by the Shenzhen "Three Famous Medical Projects" (Grant No. SZZYSM202401018) and the Shenzhen Hospital of Traditional Chinese Medicine Clinical Research Center (Grant No. 2025JCTJC123). The funding sources had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

Mingshumei Liu: Conceptualization, Methodology, Formal analysis, Writing—Original Draft, Visualization.Ying Ma: Conceptualization, Methodology, Formal analysis, Writing—Original Draft, Visualization.Xiahui Cai: Data curation, Formal analysis, Software.Junlin Wu: Data curation, Formal analysis, Software.Xiaoyang Hu: Data curation, Investigation.Xubo Hong: Data curation, Investigation.Anbang Hu: Data curation, Investigation.Huaqiong Qi: Data curation, Investigation.Linfeng Meng: Writing—Review & Editing, Validation.Xiuzhe Mo: Writing—Review & Editing, Validation.Jiewen Chen: Writing—Review & Editing, Validation.Xin Zhang: Writing—Review & Editing, Validation.Sheng Chen: Supervision, Project administration, Funding acquisition, Writing—Review & Editing.Hong Li: Supervision, Project administration, Funding acquisition, Writing—Review & Editing.

Mingshumei Liu and Ying Ma contributed equally to this work and should be considered as co-first authors. All authors have read and agreed to the published version of the manuscript.

Data Availability

The data that support the findings of this study are openly available: CHARLS (http://charls.pku.edu.cn/), ELSA (https://www.elsa-project.ac.uk/) and HRS (https://hrs.isr.umich.edu). Restrictions apply to the availability of these data, which were used under license for this study.

Trial registration

Clinical trial number: not applicable. This study is an observational cohort study based on three population-based aging cohorts and is not a clinical trial.

Ethics Approval

This study used publicly available de-identified data from three nationally representative aging cohorts. The CHARLS study was approved by the Institutional Review Board of Peking University (IRB00001052-11015). The ELSA study was approved by the National Research Ethics Service (NRES) Committee South Central—Berkshire. The HRS study was approved by the Institutional Review Board of the University of Michigan (HUM00061128). All participants provided informed consent. This study was conducted in accordance with the Declaration of Helsinki.

Consent to Participate

Informed consent was obtained from all participants in the original CHARLS, ELSA and HRS cohort studies at the time of data collection. The present study is a secondary analysis of publicly available, de-identified data and did not involve any new data collection from human participants.

Consent for Publication

Not applicable.

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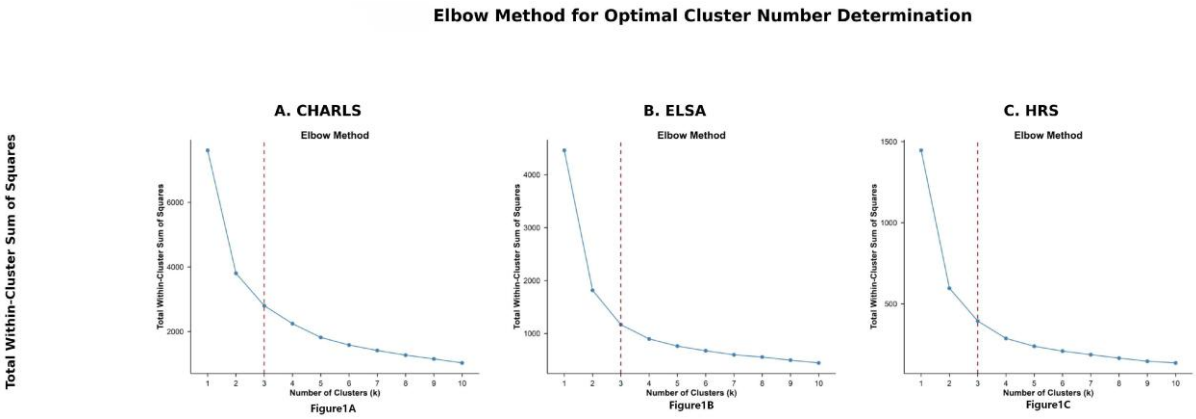
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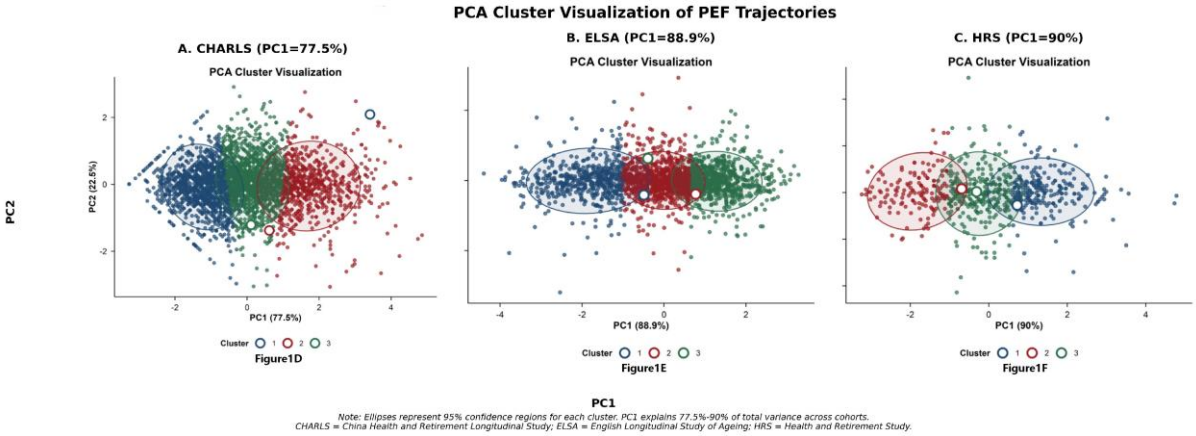
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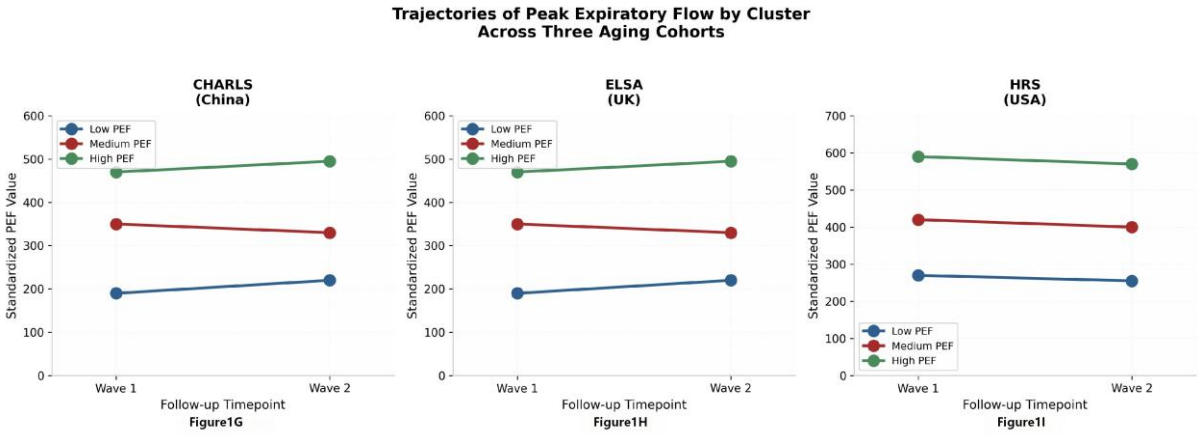
Figure 1. Determination and Characterization of PEF Trajectory Clusters in the Three Cohorts. (A-C) Elbow method for optimal cluster number selection; (D-F) principal component analysis (PCA) visualization of the three PEF trajectory clusters; (G-I) mean standardized PEF trajectories of the low, medium and high PEF clusters across the two follow-up waves. CHARLS = China Health and Retirement Longitudinal Study; ELSA = English Longitudinal Study of Ageing; HRS = Health and Retirement Study.



Note: The red dashed line indicates the optimal cluster number (k=3) for all three cohorts.
CHARLS = China Health and Retirement Longitudinal Study; ELSA = English Longitudinal Study of Ageing; HRS = Health and Retirement Study.



Note: Ellipses represent 95% confidence regions for each cluster. PC1 explains 77.5%-90% of total variance across cohorts.
CHARLS = China Health and Retirement Longitudinal Study; ELSA = English Longitudinal Study of Ageing; HRS = Health and Retirement Study.



Note: Clusters are reordered by baseline PEF level (Low/Medium/High) for cross-cohort comparability.
Original cluster numbering varies across cohorts due to K-means algorithm initialization.

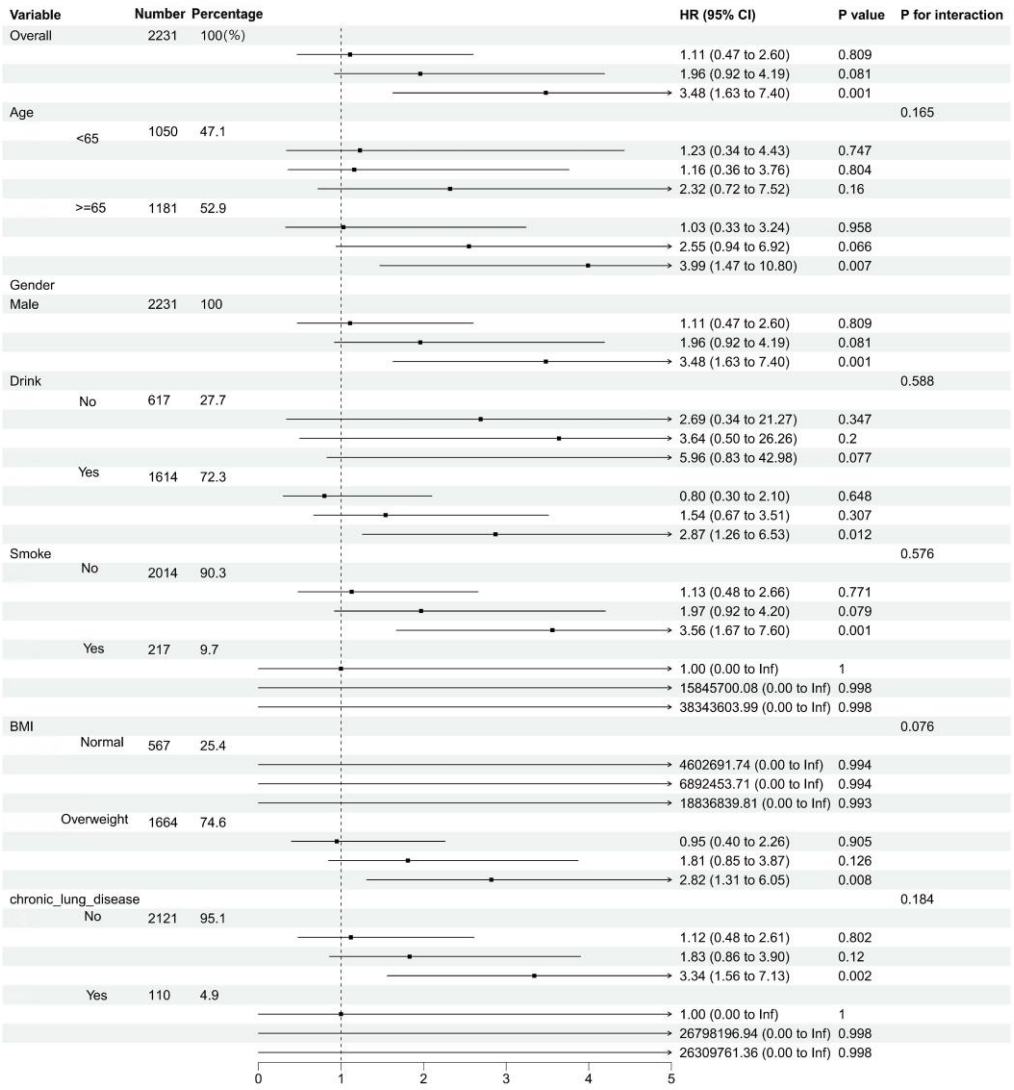


Figure 2. Forest Plot for Percent Predicted PEF - CHARLS Cohort

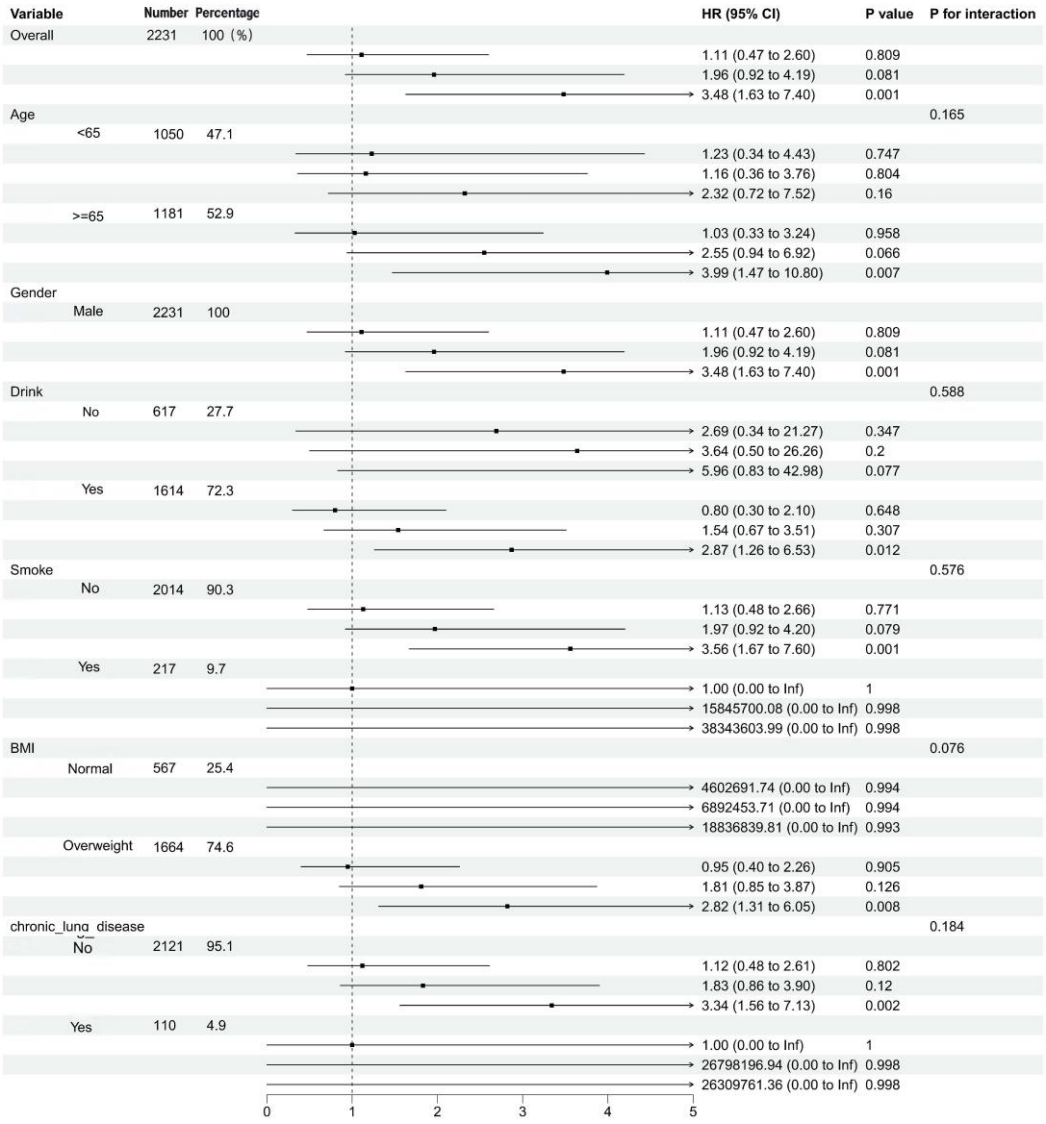


Figure 3. Forest Plot for Percent Predicted PEF - ELSA Cohort

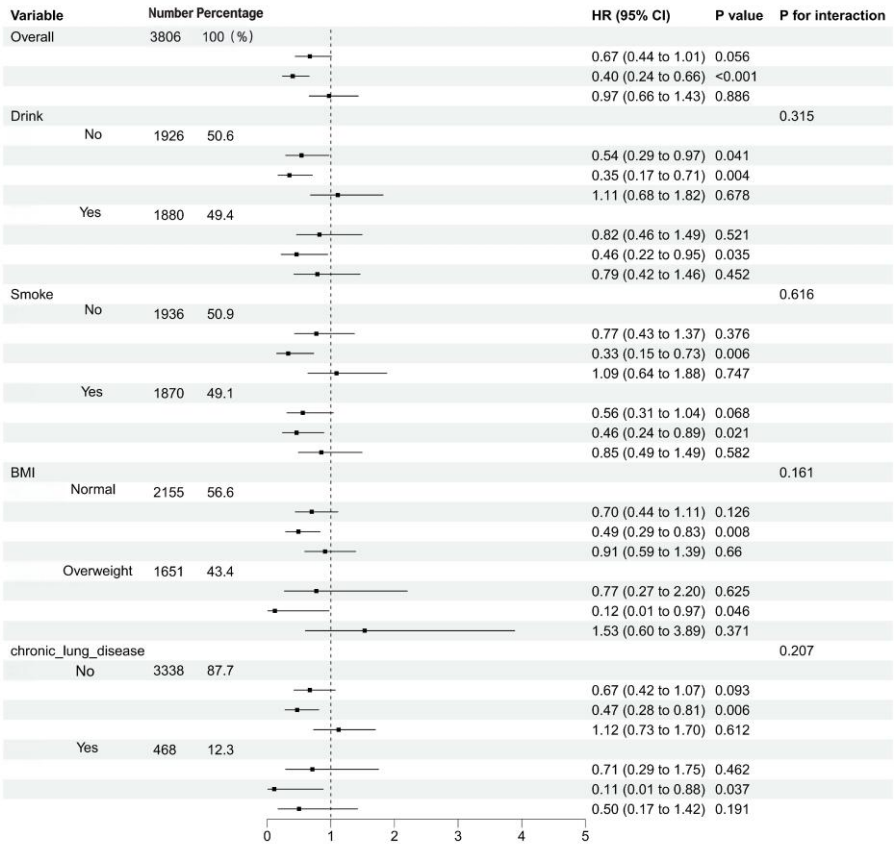


Figure 4. Forest Plot for Percent Predicted PEF - HRS Cohort

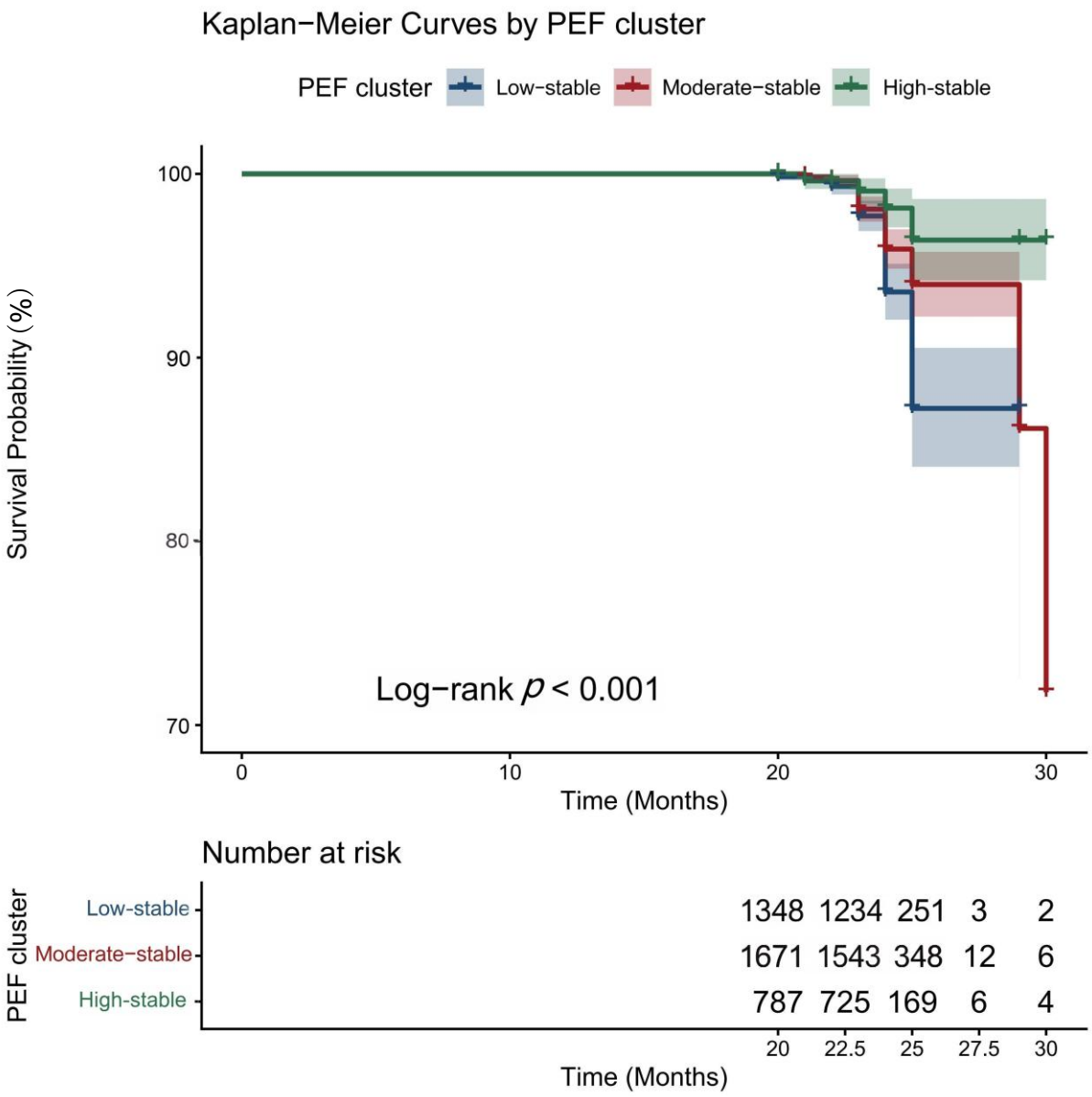


Figure 5A. Kaplan-Meier Curves by PEF Cluster (CHARLS)

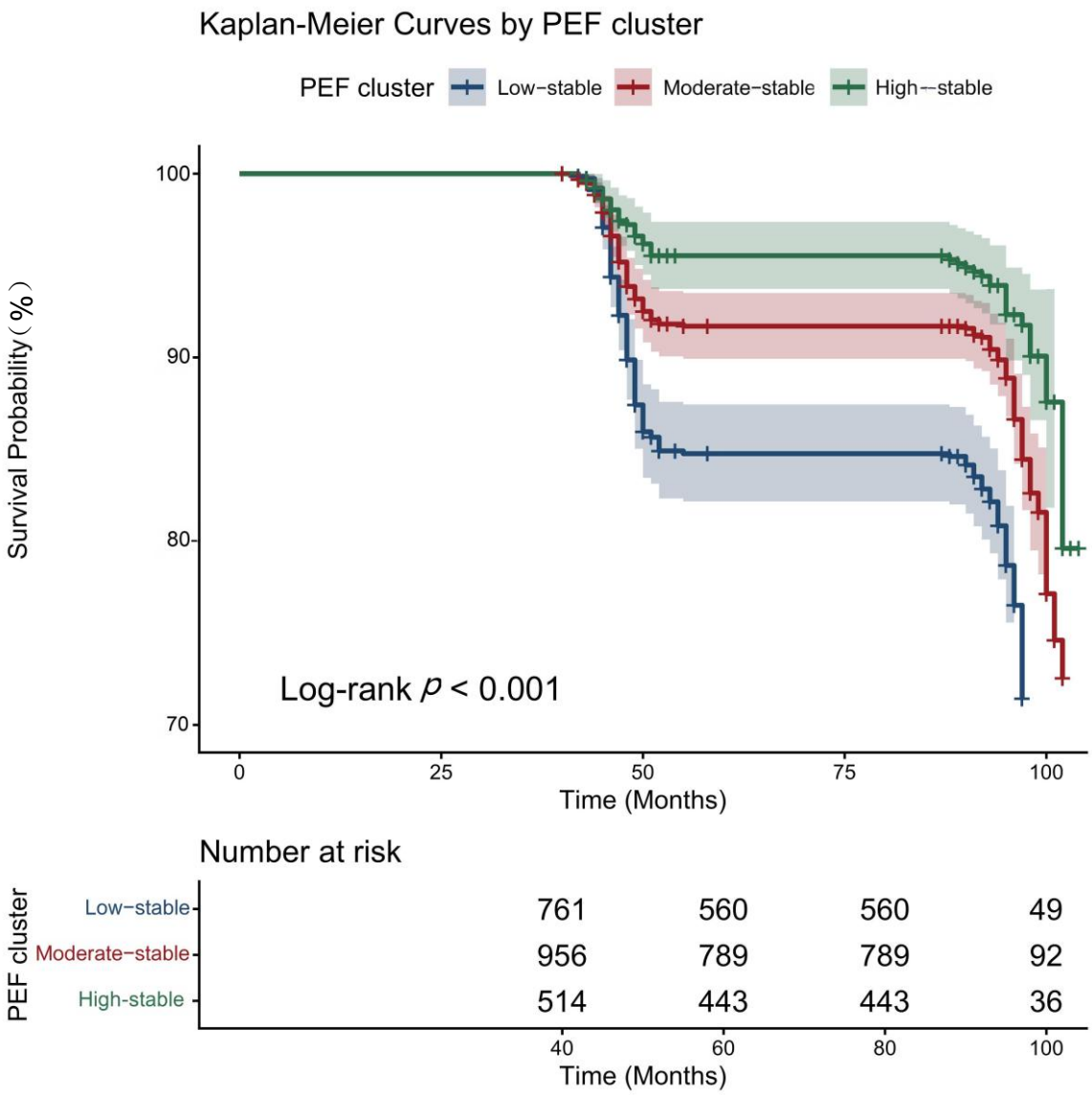


Figure 5B. Kaplan-Meier Curves by PEF Cluster (ELSA)

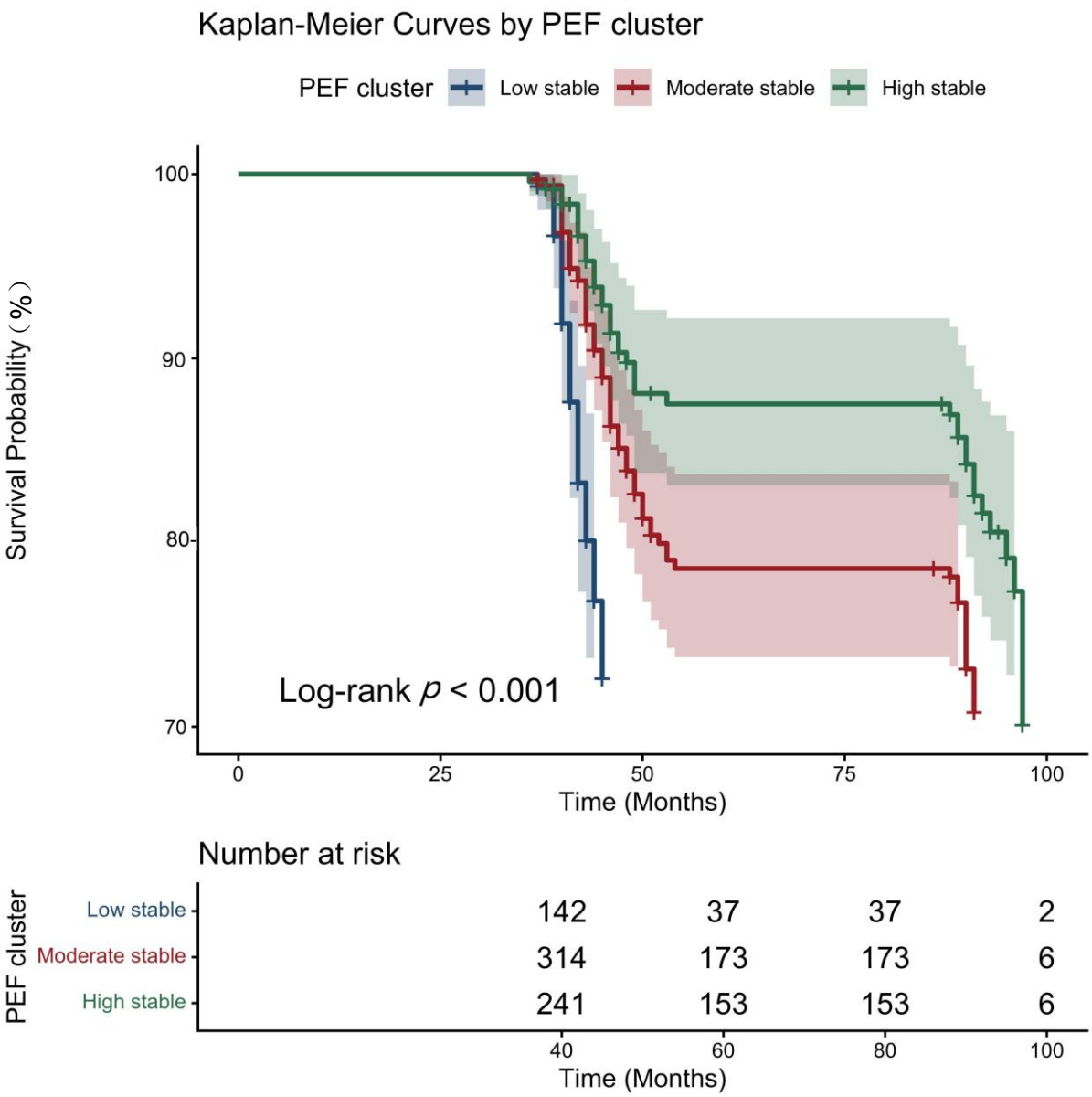


Figure 5C. Kaplan-Meier Curves by PEF Cluster (HRS)

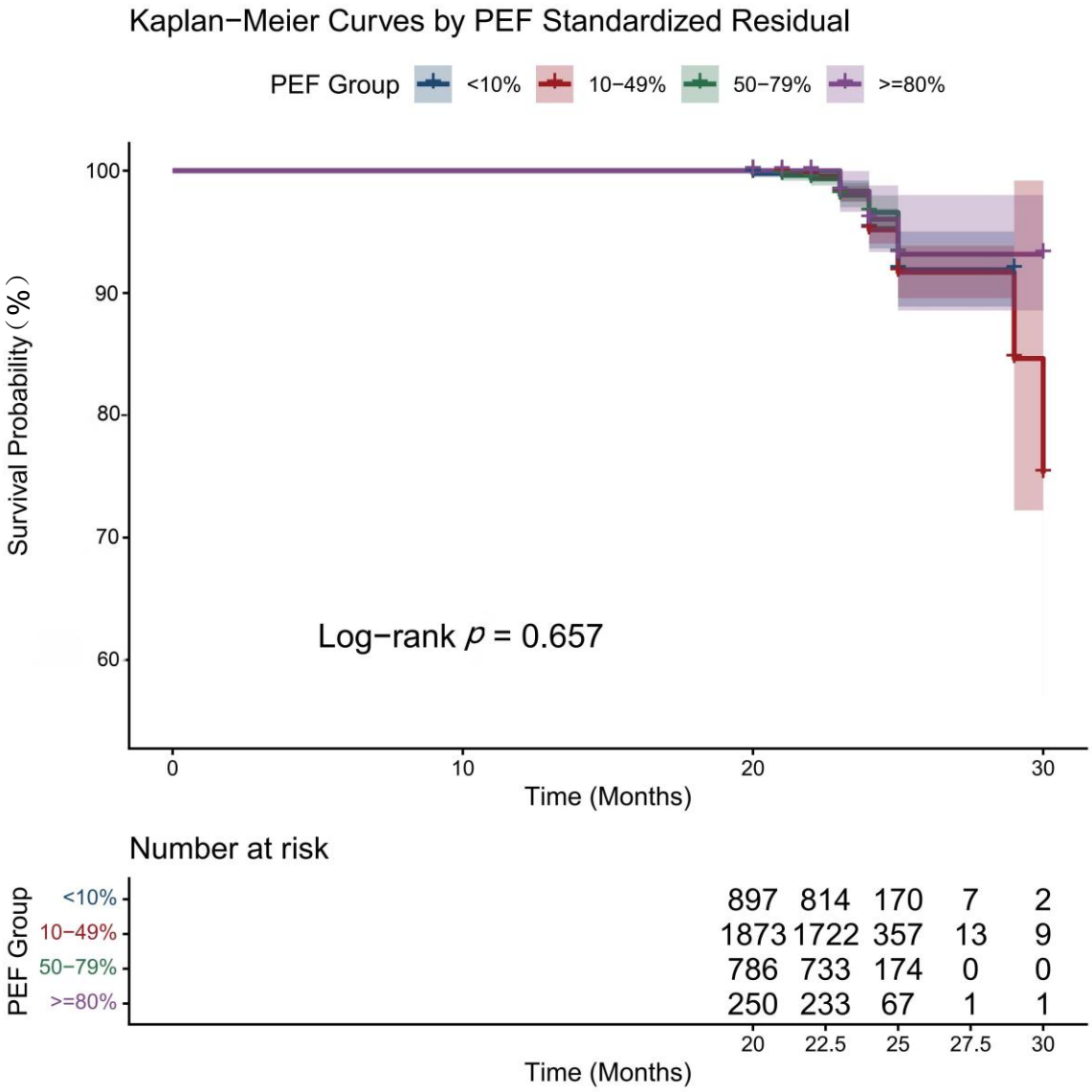


Figure 6A. KM Curves by PEF Standardized Residual (CHARLS)

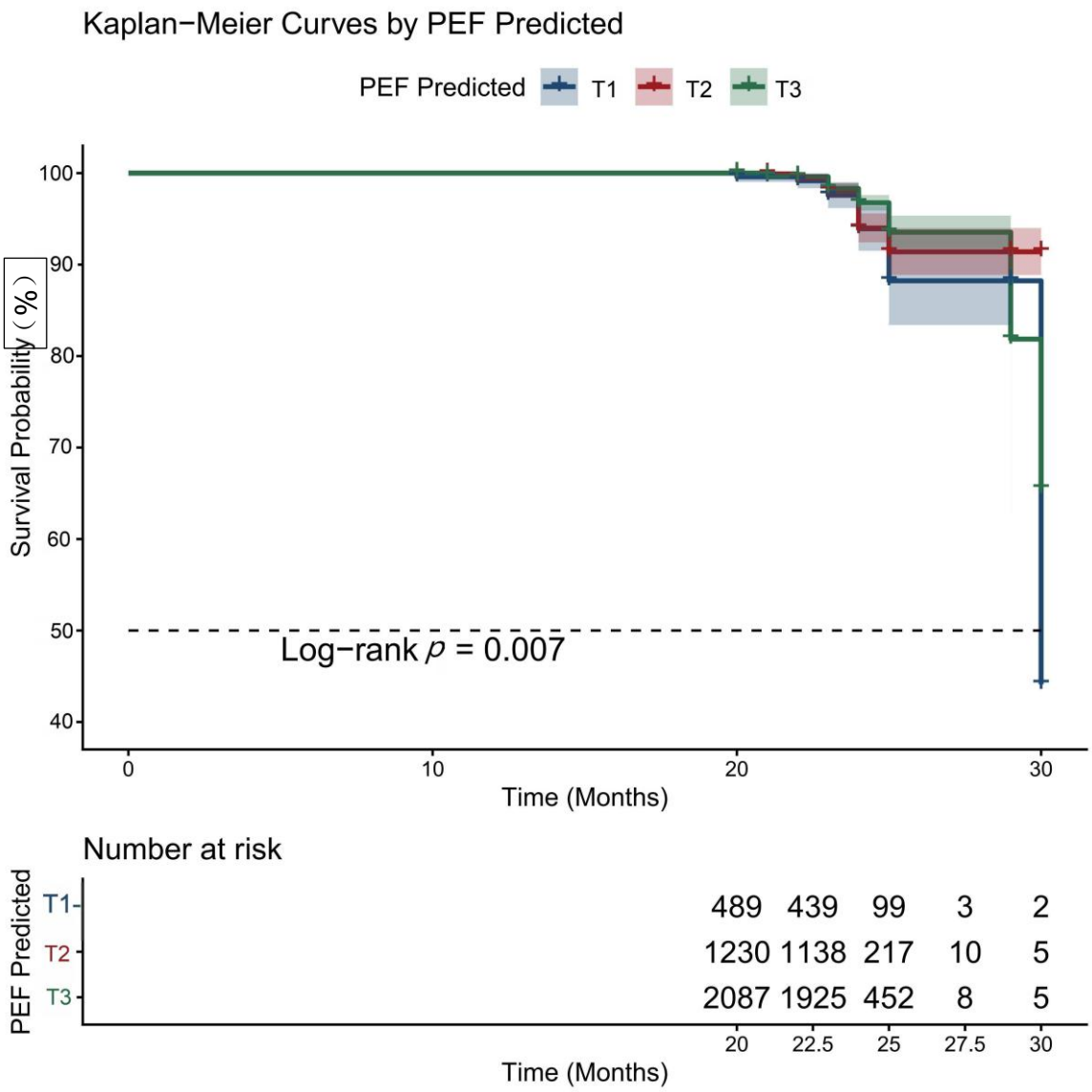


Figure 6B. KM Curves by PEF Predicted (CHARLS)

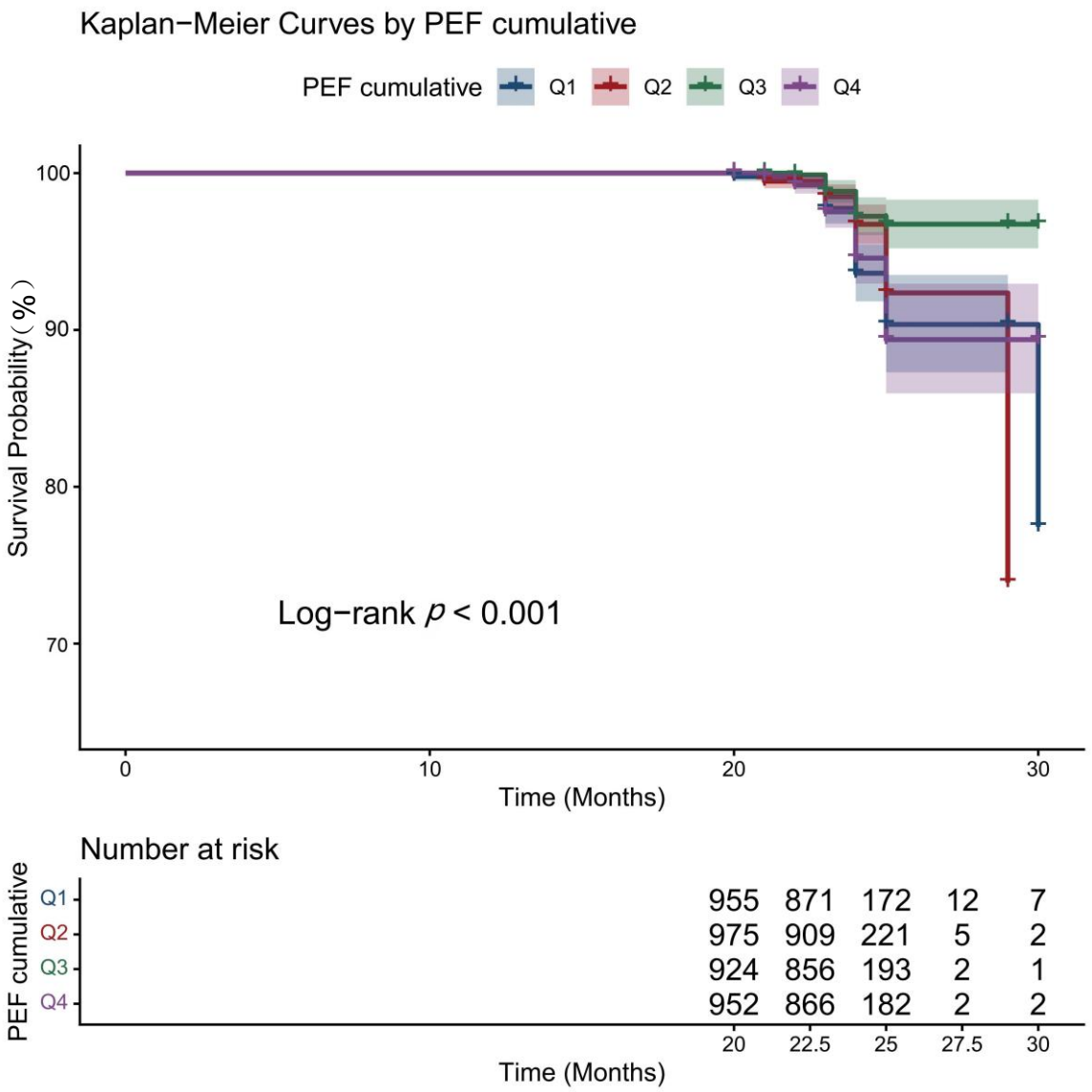


Figure 6C. KM Curves by PEF Cumulative (CHARLS)

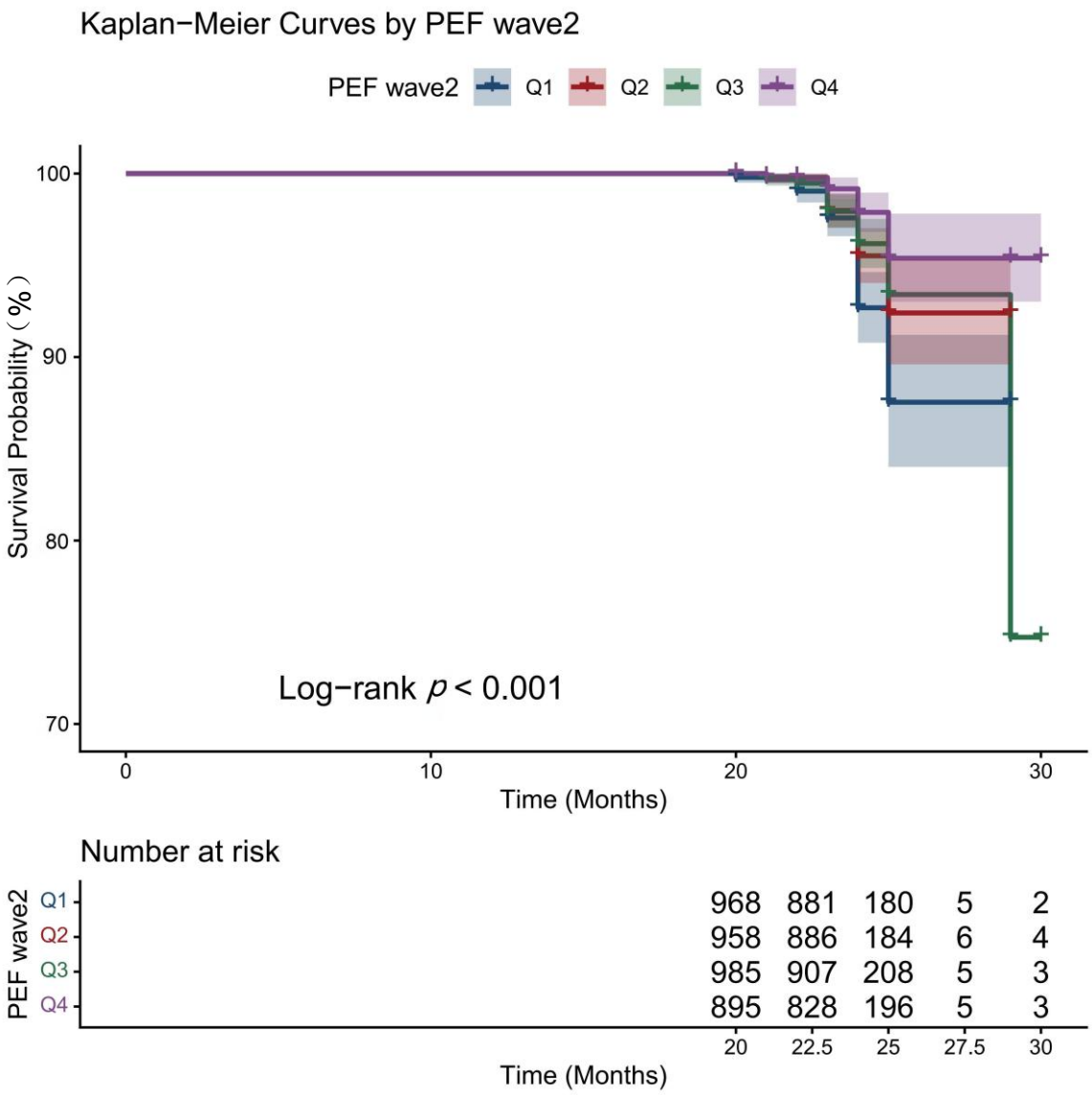


Figure 6D. KM Curves by PEF Wave2 (CHARLS)

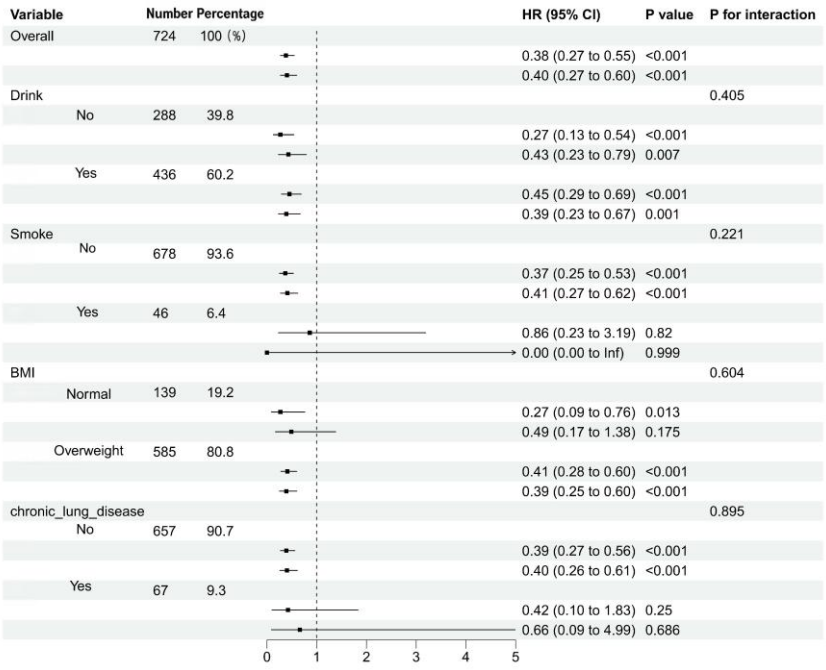


Figure 7A. Meta-Analysis Forest Plot - PEF Trajectory Clustering

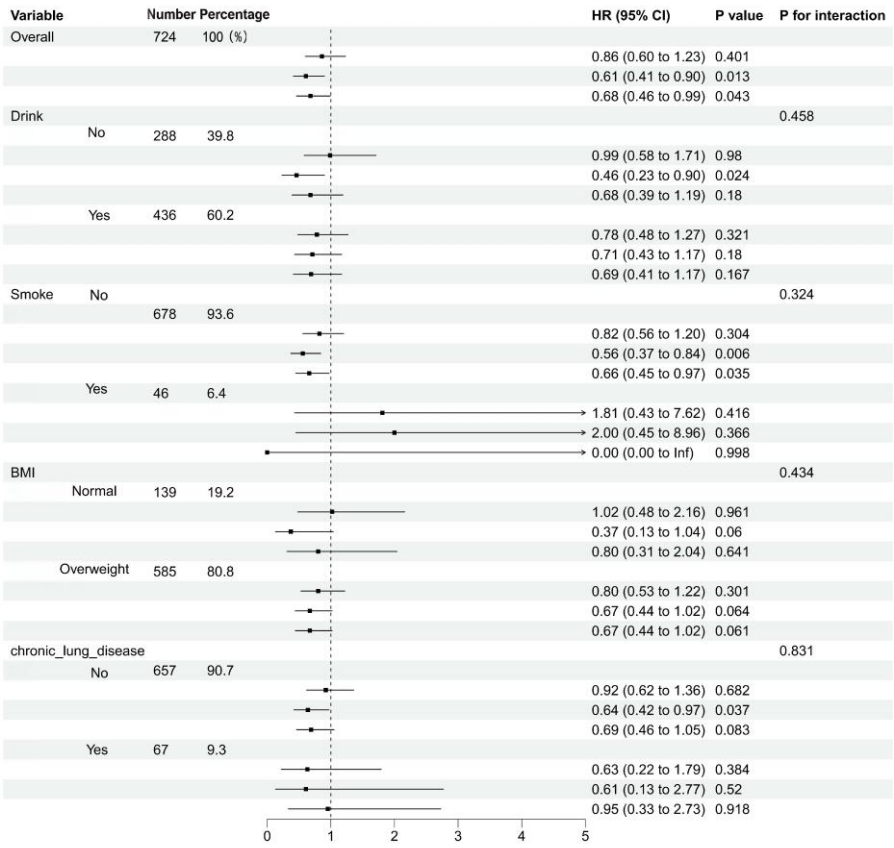


Figure 7B. Meta-Analysis Forest Plot - Single-Point Measurement

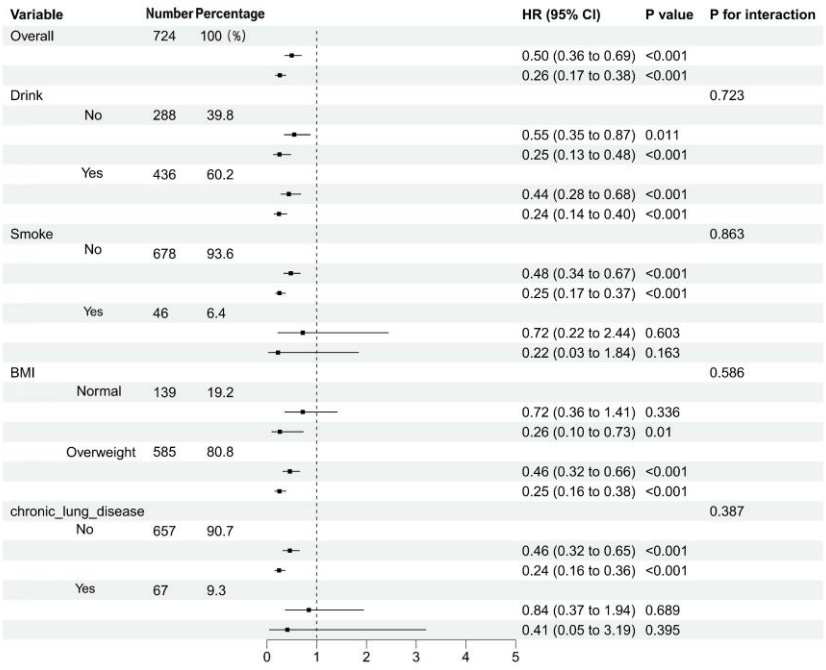


Figure 7C. Meta-Analysis Forest Plot - Percent Predicted