Respiration

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Sex-Dependent Integration of Symptoms and Functional Vulnerability in Interstitial Lung Disease: eurILDreg Study

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Abstract

Introduction: In interstitial lung diseases (ILD), patient-centred disease burden is only partly explained by physiological impairment, with considerable variability in symptoms, psychological distress, and functional limitation among patients with similar lung function. We investigated whether sex modifies longitudinal patient-centred outcomes in ILD and whether differences emerge in outcome structure and cross-domain integration.

Methods: In a prospective multicentre eurILDreg cohort, repeated measures of lung function, patient-reported outcome measures (K-BILD, EQ-5D-5L, LCQ), and the Clinical Frailty Scale (CFS) were analysed. Longitudinal trajectories and time × sex interactions were assessed using linear mixed-effects models. Sex-stratified correlation analyses examined cross-domain outcome structure and symptom–physiology integration.

Results: Baseline global PROM scores and functional vulnerability were comparable between women and men, including EQ-5D-5L index ($p = 0.337$), K-BILD Total (66.4 ± 19.9 vs 68.2 ± 18.6; $p = 0.271$), LCQ Total (7.2 ± 3.0 vs 7.0 ± 3.0; $p = 0.107$), and CFS (mean 3.24 in both sexes). Despite similar global scores, EQ-5D-5L domain profiles differed: women reported greater limitations in usual activities (2.04 vs 1.90) and higher pain/discomfort (2.27 vs 2.07), while mobility and self-care were similar. Anxiety/depression (AD ≥ 2) was more frequent in women, reaching borderline significance ($\chi^2 = 3.71$, $p = 0.054$).

Sex differences were most evident in cross-domain outcome structure. Coupling between global health perception and ILD-specific psychological domains was stronger in women (EQ-5D × K-BILD Psychological: $r = 0.452$ vs 0.380; EQ-5D Anxiety/Depression × K-BILD Psychological: $r = -0.555$ vs -0.486), whereas men showed stronger coupling between psychological and physical cough domains (LCQ Psychological × LCQ Physical: $r = 0.635$ vs 0.560). Longitudinal trajectories were largely similar by sex: EQ-5D-5L ($p = 0.330$) and LCQ ($p = 0.105$) remained stable. A borderline sex interaction was observed for K-BILD (time × sex −0.243 points/month; $p = 0.053$). CFS increased modestly over time (+0.0172 points/month; $p = 0.0084$) without sex differences.

Conclusions: Sex differences in ILD are not primarily reflected in overall disease severity, functional vulnerability, or average PROM trajectories, but in how patient-centred outcomes are organised and interconnected. These findings suggest sex-specific patterns in the experience of ILD, with women showing stronger links between global health perception and psychological burden, and men between psychological and physical symptom domains. Recognising sex as a modifier of patient-reported outcomes may help refine interpretation of PROMs and support more personalised, sex-informed ILD care.

1. Introduction

Interstitial lung diseases (ILDs) impose a substantial and enduring burden on patients' everyday lives, but the lived experience of ILD is far from uniform [1]. Beyond known differences in incidence and ILD subtype distributions between women and men, evidence from other chronic diseases suggests that symptom perception, psychological responses, and functional adaptation are strongly shaped by sex [2]. Whether, and how, these sex-related patterns translate into distinct trajectories of patient-centred outcomes in ILD remains largely unexplored [3, 4].

Disease severity and progression in ILD have traditionally been described using physiological indices such as forced vital capacity (FVC), or diffusing capacity for carbon monoxide (DLCO), and exercise capacity measured by the six-minute walk distance [5]. While indispensable for staging, prognostication, and treatment decisions, these measures capture only part of the disease burden [6]. Symptoms such as cough, breathlessness, fatigue, psychological distress, and functional vulnerability may substantially impair daily functioning even when lung function is relatively preserved. These dimensions frequently correlate only weakly with physiological decline, giving rise to a symptom–physiology mismatch that may differ systematically by sex.

Multiple biological, clinical, and psychosocial mechanisms may contribute to sex-related differences in the experience of ILD. Women are more often affected by immune-mediated entities such as systemic autoimmune rheumatic disease–associated ILD (SARD-ILD), whereas exposure-related phenotypes, including idiopathic pulmonary fibrosis (IPF), and combined pulmonary fibrosis and emphysema (CPFE), tend to predominate in men [7]. These patterns likely interact with sex-specific immune regulation, hormonal factors, comorbidity profiles, and exposure histories, influencing symptom burden and psychological impact [8]. Functional vulnerability, assessed using the Clinical Frailty Scale (CFS), may further modify patient-centred outcomes differently in women and men, even at similar levels of physiological impairment [9].

Psychosocial and behavioural patterns may amplify or mitigate these biological differences. Women tend to report symptoms earlier and with greater sensory precision, particularly for fatigue, breathlessness, and psychological distress, and frequently carry caregiving and household responsibilities that magnify the functional consequences of ILD [10]. Men, in contrast, may under-report symptoms, delay help-seeking, and accumulate longer or more intense exposure histories, prioritising work-related functioning until relatively late stages of disease [11, 12]. Such sex-related differences in reporting, coping, and social role expectations are likely to shape how symptoms, psychological burden, functional limitation, and vulnerability interrelate, yet this internal organisation of patient-centred outcomes has rarely been examined in ILD [13].

To capture these multidimensional aspects, patient-centred outcomes can be assessed using a combination of patient-reported outcome measures (PROMs) and clinician-reported functional assessment. The King's Brief Interstitial Lung Disease Questionnaire (K-BILD) quantifies ILD-specific impacts on breathlessness, activities, chest symptoms, and psychological well-being [14]. The Leicester Cough Questionnaire (LCQ) assess cough burden and its physical, psychological, and social consequences, symptoms that may be experienced differently by women and men [15]. The EuroQol 5-Dimension 5-Level Questionnaire (EQ-5D-5L) captures generic Health-related Quality of Life (HRQoL) across mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [16, 17]. Last but not least, the CFS reflects functional reserve and vulnerability [18, 19].

Although these instruments are routinely collected in registries such as the European ILD Registry (eurILDreg), they are rarely analysed within a longitudinal, sex-focused analytical framework [20]. Consequently, key questions remain unresolved. Do women and men with ILD differ in longitudinal trajectories of patient-centred outcomes once physiological severity and ILD subtype are accounted for? Are sex differences primarily reflected in average outcome levels, or do they emerge at the level of domain composition and cross-domain coupling? Does functional vulnerability progress independently of patient-reported outcomes, and does this dissociation differ by sex?

In this multicentre, longitudinal eurILDreg cohort, we address these questions using a multidimensional outcome framework combining PROMs and clinician-reported functional vulnerability. By integrating repeated physiological measurements, longitudinal outcome trajectories, and sex-stratified analyses of cross-domain structure, we examine whether sex modifies not only the level and change of patient-centred outcomes, but their internal organisation and integration over time. This approach aims to identify sex-sensitive patterns of lived disease burden that remain obscured by physiology-centred assessment and global summary scores.

2. Study Objectives

The primary objective of this study was to determine whether sex differences in ILD are reflected in overall patient-centred outcome burden or functional vulnerability by comparing baseline levels and longitudinal trajectories of multidomain patient-reported outcome measures (K-BILD, EQ-5D-5L, LCQ) and clinician-reported frailty between women and men.

A key secondary objective was to characterise sex-specific differences in outcome domain composition by examining whether the distribution of functional, symptom-related, and psychological burden differs between women and men, potentially masking differences at the domain level despite similar global scores. We also assessed whether sex modifies longitudinal outcome trajectories using linear mixed-effects models with time × sex interaction terms, while anchoring changes to physiological severity (FVC, DLco, and resting pO_2). In addition, we explored sex-specific symptom–physiology coupling by analysing cross-domain relationships across outcome instruments.

Finally, we evaluated whether functional vulnerability progresses differently by sex and whether frailty trajectories diverge from patient-reported outcomes over time, helping to disentangle physical decline from perceived disease burden and identify sex-specific patterns of adaptation.

3. Materials and Methods

Study Design and Population

This prospective multicentre cohort study was conducted within the eurILDreg, which collects longitudinal clinical, physiological, and patient-reported data from ILD centres across Europe. Patients were enrolled from four tertiary care institutions: the Center for Interstitial and Rare Lung Diseases in Giessen (Germany), Hospital Clínic de Barcelona (Spain), Ludwig Maximilian University (LMU) Munich (Germany), and Policlinico University Catania (Italy).

The eurILDreg, originally established as the European Registry for Idiopathic Pulmonary Fibrosis (eurIPFreg, NCT02951416), was subsequently expanded to include a broader spectrum of ILDs (DRKS00028968) [21]. All participants provided written informed consent, and institutional ethics approval was granted at each site, including the Ethics Committee of the Justus Liebig University Giessen (AZ 111/08). ILD diagnoses were confirmed through multidisciplinary discussion, integrating clinical, radiologic, and (when available) histopathologic data according to ATS/ERS/JRS/ALAT international guidelines [22]. PROMs were collected longitudinally in line with registry protocol and contemporaneous clinical evaluations.

Eligibility Criteria

Eligible participants were aged 18 years or older, had a confirmed diagnosis of ILD, and were able to independently complete PROMs. At least two follow-up visits were required for inclusion in longitudinal modelling. Patients were excluded if they were pregnant, lacked core PROM data, or had comorbidities likely to confound interpretation, such as major neurodegenerative or psychiatric disorders.

Demographic and Clinical Covariates

Baseline demographic and clinical variables were extracted from eurILDreg and included ILD diagnosis, age, sex, body mass index (BMI), and smoking status. Pulmonary function parameters were assessed at each visit and included FVC % pred., and DLCO % pred.

Patient-Reported Outcome Measures (PROMs)

EQ-5D-5L- Questionnaire measures generic health status from the patient's perspective across five core life domains—mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain is scored on a five-level ordinal scale ranging from 1 (no problems) to 5 (extreme problems), with higher domain scores indicating greater impairment. Domain responses are combined into an index value representing overall health status.

ILD-specific well-being was evaluated using the K-BILD, which comprises three domains—psychological well-being, breathlessness and activity limitation, and chest symptoms, therefore yielding both domain-specific scores and a total score ranging from 0 to 100, with higher scores indicating better ILD-specific health state. Cough-related symptom burden was assessed using the LCQ, which evaluates the physical, psychological, and social impact of cough. Domain scores range from 1 to 7 and the total score from 3 to 21, with higher scores indicating less cough-related impairment. Functional vulnerability and physiological reserve were quantified using the CFS, scored from 1 (very fit) to 9 (terminally ill), with higher scores indicating greater frailty.

Statistical Analysis

All analyses were performed in R (version 4.3). Statistical significance was defined as a two-sided p value <0.05; p values between 0.05 and 0.10 were considered borderline or hypothesis-generating. Baseline characteristics and PROMs were summarised separately for women and men. Continuous variables are presented as means ± standard deviations and categorical variables as frequencies and percentages. Baseline comparisons used Welch's two-sample t-tests for continuous variables and χ^2 tests for categorical variables. EQ-5D-5L domain scores were analysed descriptively on their ordinal scale (1–5), with anxiety/depression additionally evaluated using a dichotomised threshold (domain score ≥2).

Longitudinal trajectories were analysed using linear mixed-effects models with restricted maximum likelihood estimation, with separate models fitted for each outcome. Models included a random intercept for patient identifier to account for repeated measurements. Time (months since baseline) was modelled as a continuous variable, sex as a fixed effect, and sex-specific differences in trajectories were assessed using a time × sex interaction term. Fixed-effect estimates are reported with standard errors, degrees of freedom, 95% confidence intervals, and p values. Model assumptions were assessed by inspection of residual and scaled residual plots.

Sex-stratified correlation analyses examined cross-domain relationships across EQ-5D-5L, K-BILD, and LCQ domains using Pearson correlation coefficients. Differences in correlation strength between women and men were evaluated descriptively. Analyses used all available data under the missing-at-random assumption of mixed-effects models; no imputation was performed. Patients required at least two observations for longitudinal analyses. Directionally consistent but non-significant findings were interpreted cautiously as exploratory.

4. Results

4.1 Description of the Study Cohort

Overall, 369 eurILDreg patients contributed 2,007 documented study visits, including 129 women (35.0%) and 240 men (65.0%). Men were slightly older at baseline (67.3 ± 12.3 years; range 23–90) than women (65.6 ± 11.7 years; range 27–87). Women a higher mean number of visits per patient (6.1 ± 4.7 vs. 5.0 ± 3.5) and longer median follow-up duration (4.5 vs. 2.0 years).

Disease distribution differed by sex. IPF was more common in men (37.5% vs. 18.3%), whereas SARD-ILD was more frequent in women (24.4% vs. 14.6%). Non-IPF idiopathic interstitial pneumonias occurred at similar rates (12.2% vs. 12.9%), while granulomatous ILDs were slightly more frequent in women (22.1% vs. 17.5%). Detailed cohort characteristics are presented in Table 1.

4.2 EQ-5D-5L

At baseline, EQ-5D-5L index scores were comparable between women and men (p = 0.337), but domain-level profiles (1 = no problems, 5 = extreme problems) showed sex-related differences in burden composition. Mobility (1.72 vs 1.69) and self-care (1.35 vs 1.30) were similar, whereas women reported higher mean burden in usual activities (2.04 vs 1.90), pain/discomfort (2.27 vs 2.07), and anxiety/depression (1.88 vs 1.64).

As shown in Fig.1, in the fully adjusted mixed-effects model (REML −106.3), there was no overall time trend (time_months 0.0013, SE 0.0013, t = 0.9762, df = 349.1638, p = 0.3297; 95% CI −0.0013 to 0.0038) and no baseline sex difference (male 0.0249, SE 0.0334, t = 0.7461, df = 276.6102, p = 0.4562; 95% CI −0.0408 to 0.0907). The time × sex interaction suggested a non-significant tendency toward a more negative slope in men (−0.0029, SE 0.0016, t = −1.7541, df = 352.9840, p = 0.0803; 95% CI −0.0061 to 0.0003). Lower EQ-5D index scores were independently associated with impaired oxygenation at rest (−0.1312, SE 0.03951, df = 445.2, t = −3.320, p = 0.000976) and current smoking (−0.1353, SE 0.06395, df = 247.0, t = −2.116, p = 0.035330), whereas ILD subtype, FVC % predicted, DLCO % predicted, and former smoking were not significant. The proportion with anxiety/depression ≥2 was borderline higher in women (χ^2 = 3.71, p = 0.054, Fig.2).

4.3 K-BILD

At baseline, ILD-specific health state assessed by K-BILD was comparable between women and men, with no clinically meaningful sex differences in overall level or domain-specific burden. Mean K-BILD Total scores were 66.4 ± 19.9 in women and 68.2 ± 18.6 in men, reflecting only a small numerical difference at study entry. Score ranges were very wide in both sexes (women 15.6–100; men 20.0–100), indicating pronounced inter-individual heterogeneity that substantially exceeded any between-sex contrast. Distributional characteristics were similar, with mildly left-skewed and slightly platykurtic profiles in both groups, consistent with a broad spread of perceived disease burden rather than clustering at extreme values.

Across K-BILD domains, mean scores and distributional features overlapped extensively between sexes (Fig.3). Activity limitation scores showed marked within-sex variability but no systematic sex separation (55.1 ± 28.0 in women vs 57.5 ± 29.0 in men; medians 56.3 vs 58.3; full range 0–100 in both groups). Psychological HRQoL was nearly identical between women (66.2 ± 21.6) and men (67.6 ± 18.9), with identical medians (69.1) and wide score ranges (women 9.5–100; men 14.3–100). Chest symptom scores were numerically higher in men (74.2 ± 21.4 in women vs 77.5 ± 20.4 in men), but distributions overlapped substantially. Formal testing supported these descriptive findings: a Welch two-sample t-test for the psychological domain showed no significant sex difference (t = −0.61, p = 0.545), with a mean difference of −1.39 points (95% CI −5.89 to 3.12), excluding both statistically and clinically relevant baseline disparities.

Across longitudinal follow-up, mean K-BILD Total scores in women and men remained broadly similar, with small, fluctuating between-sex differences that were negligible relative to pronounced within-sex variability (Fig.4). Early follow-up showed near stability (time point 2: 65.36 ± 18.76 vs 67.76 ± 20.02), followed by modest decline and convergence (time point 3: 63.24 ± 20.79 vs 62.92 ± 20.80) and subsequent stabilisation (time point 4: 63.98 ± 17.47 vs 62.83 ± 21.78). Later time points showed numerical increases in both sexes, but sample sizes were small. Across early and mid follow-up, distributions frequently spanned more than 80 points, underscoring inter-individual heterogeneity that dominated any average sex effect.

In the fully adjusted linear mixed-effects model, overall ILD-specific values remained largely stable after accounting for clinical and physiological covariates. The estimated cohort-level baseline K-BILD Total score was 65.6 points (95% CI 62.3–68.9). Time was not significantly associated with K-BILD Total in the reference group (women), with an estimated change of −0.081 points per month (SE 0.097; t = −0.840; df = 359.172; 95% CI −0.272 to 0.109; p = 0.401). Men had numerically higher baseline scores than women (+3.03 points; SE 2.74; t = 1.10; df = 257.777; 95% CI −2.37 to 8.43; p = 0.271), a difference well within the range of inter-individual variability.

The only sex-related signal was observed in the time × sex interaction, which showed a negative trend (−0.243 points/month; SE 0.125; t = −1.94; df = 366.964; 95% CI −0.489 to 0.003; p = 0.053). This suggests a steeper decline over time in men than in women, with model-estimated slopes of −0.324 points/month for men and −0.081 points/month for women. Although the confidence interval crossed zero and the effect narrowly missed conventional statistical significance, the direction and magnitude indicate a borderline, hypothesis-generating signal toward a steeper longitudinal decline in men rather than definitive evidence of sex-specific divergence.

No ILD subtype was independently associated with K-BILD Total in the adjusted model, including PPF (p = 0.273), SARD–ILD (p = 0.684), CPFE (p = 0.820), granulomatous ILD (p = 0.977), or other ILDs (p = 0.330). Each 1% decrease in FVC % predicted was associated with a −0.214-point change in K-BILD Total (95% CI 0.096–0.332; p < 0.001), and each 1% decrease in DLCO % predicted with a −0.213-point change (95% CI 0.065–0.362; p = 0.005). Age, long-term oxygen therapy, and smoking status were not independently associated after adjustment. Random-effects estimates demonstrated substantial between-patient heterogeneity (variance 179.2; SD 13.39) relative to residual variance (151.3; SD 12.30), indicating that individual differences in HRQoL far outweighed average longitudinal changes captured by fixed effects.

4.4. Leicester Cough Questionnaire

At baseline, cough-related symptom burden assessed by the LCQ was comparable between women and men (Fig.5). Mean LCQ total scores were 7.2 ± 3.0 in women and 7.0 ± 3.0 in men, indicating a similar overall cough burden in both sexes. Domain-specific scores overlapped extensively across physical, psychological, and social domains. Psychological scores were numerically slightly higher in women (2.6 ± 1.0) than in men (2.5 ± 1.0), but this difference was not statistically significant ($p = 0.478$), excluding a clinically relevant baseline sex disparity.

In the unadjusted linear mixed-effects model (lcq_total ~ time × sex; 885 observations), LCQ total scores showed a small but statistically significant improvement over time (Fig.6). The estimated monthly change was +0.0336 points (SE 0.0124; $t = 2.71$; df = 643.7; $p = 0.0069$; 95% CI 0.009 to 0.058). There was no significant baseline sex difference (male vs female −0.440; SE 0.335; $t = -1.31$; df = 456.8; $p = 0.1896$; 95% CI −1.10 to 0.22) and no evidence of sex-specific longitudinal change (time×sex 0.0009; SE 0.0163; $t = 0.056$; df = 644.7; $p = 0.955$). Between-patient variability was substantial (random-intercept variance 6.11; SD 2.47; residual variance 4.15; SD 2.04), indicating that individual differences in cough burden far exceeded average temporal change.

After adjustment for age, ILD subtype, lung function, gas exchange, and smoking status, the time effect was attenuated and no longer significant (time +0.0252 points/month; SE 0.0155; $t = 1.63$; df = 367.6; $p = 0.1046$; 95% CI −0.005 to 0.056). The sex main effect remained non-significant (male vs female −0.731; SE 0.452; $t = -1.62$; df = 269.4; $p = 0.1070$; 95% CI −1.62 to 0.16), and there was no sex-specific divergence in trajectories (time×sex 0.0149; SE 0.0202; $t = 0.736$; df = 374.1; $p = 0.462$).

4.5. Sex-stratified correlations between HRQoL domains across instruments

Sex-stratified correlation analyses revealed consistent differences in the internal organisation of HRQoL domains across instruments, despite similar absolute HRQoL levels. These differences were structural rather than quantitative and reflected how psychological and symptom-related domains were integrated within the overall HRQoL framework in women and men.

In women, global health status as measured by the EQ-5D index showed a stronger association with ILD-specific psychological HRQoL than in men (EQ-5D × K-BILD Psychological: $r = 0.452$ in women vs $r = 0.380$ in men; difference +0.073), indicating a closer alignment between overall perceived health and disease-specific psychological burden. Although modest in magnitude, this pattern suggests tighter psychological integration of global and ILD-specific HRQoL in women. The association between ILD-specific psychological HRQoL and cough-related psychological burden was virtually identical between sexes (K-BILD Psychological × LCQ Psychological: $r = -0.486$ in women vs $r = -0.491$ in men; difference +0.005), indicating comparable linkage between psychological disease burden and psychological cough impact in both groups (Fig.7).

Further sex-specific differences emerged when examining generic emotional distress. Women exhibited a stronger negative association between EQ-5D anxiety/depression and ILD-specific psychological HRQoL (EQ-5D Anxiety/Depression × K-BILD Psychological: $r = -0.555$ in women vs $r = -0.486$ in men; difference −0.069), suggesting that generic psychological distress translated more directly into disease-specific psychological impairment in women.

In contrast, men demonstrated a tighter coupling between physical and psychological cough domains (LCQ Psychological × LCQ Physical: $r = 0.635$ in men vs $r = 0.560$ in women; difference −0.075), indicating that psychological cough burden in men was more closely anchored to physical cough severity. Women, by comparison, showed greater dissociation between physical cough symptoms and their psychological impact.

Taken together, these findings indicated sex-specific differences in HRQoL architecture rather than differences in symptom severity or longitudinal decline. Women exhibited stronger cross-instrument psychological coupling, whereas men showed tighter symptom-driven integration of physical and psychological cough domains.

4.6. Frailty

At baseline and across all observations, frailty burden was essentially identical between women and men, with identical mean CFS values in both groups (mean 3.24), comparable dispersion (SD 1.24 in women vs 1.38 in men), indicating no descriptive sex difference in overall frailty level.

In the unadjusted linear mixed-effects model, the estimated baseline CFS in women was 3.1007 (SE 0.1281; t = 24.2113; df = 359.6577; p < 0.0001; 95% CI 2.8488–3.3525). Frailty increased significantly over time, with an estimated monthly increase of +0.0221 points in women (SE 0.0052; t = 4.2520; df = 373.1018; p < 0.0001; 95% CI 0.0119–0.0323), demonstrating progressive worsening of frailty, as shown in Fig.8a-c. There was no evidence of a baseline sex difference (male vs female estimate −0.0045; SE 0.1589; t = −0.0285; df = 359.4656; p = 0.9773; 95% CI −0.3170 to 0.3079) and no indication of sex-specific differences in frailty progression, as reflected by a non-significant time × sex interaction (estimate 0.0027; SE 0.0068; t = 0.3913; df = 376.4087; p = 0.6958; 95% CI −0.0108 to 0.0161). The implied monthly slopes were +0.0221 points for women and +0.0248 points for men, with the difference not statistically significant.

In the fully adjusted mixed-effects model, longitudinal frailty progression remained statistically significant. CFS increased by +0.0172 points per month (SE 0.0065; t = 2.6554; df = 246.7040; p = 0.0084; 95% CI 0.0044–0.0299), confirming ongoing worsening of frailty over time after adjustment for clinical and physiological covariates. Consistent with the unadjusted analysis, there was no evidence of a baseline sex difference (male vs female estimate 0.0974; SE 0.1652; t = 0.5894; df = 259.7357; p = 0.5561; 95% CI −0.2279 to 0.4226) and no sex-specific divergence in frailty trajectories, as the time × sex interaction remained non-significant (estimate 0.0078; SE 0.0085; t = 0.9190; df = 263.0189; p = 0.3589; 95% CI −0.0089 to 0.0244).

5. Discussion

In this multicentre longitudinal ILD cohort, sex differences were not reflected in the overall level or longitudinal trajectories of patient-reported outcomes but in the structure of disease burden. Women and men had comparable global PROM scores and similar rates of change over time, yet the internal organization and integration of symptom and psychological domains differed consistently by sex.

Across instruments, global summary scores suggested little to no sex difference. EQ-5D-5L index values, K-BILD Total, LCQ Total, and frailty levels were statistically comparable between women and men at baseline and longitudinally. However, this apparent equivalence concealed systematic divergence at the domain level. Within identical EQ-5D index states, women consistently reported greater limitations in usual activities, higher pain/discomfort, and higher anxiety/depression severity, while mobility and self-care were essentially identical. The borderline excess prevalence of anxiety/depression in women further reinforces this pattern. This dissociation highlights a critical limitation of relying on global indices alone: two patients with the same summary score may experience, and require management for, very different types of burden depending on sex. Importantly, women did not rate their overall health as worse, but carried a more symptom- and emotion-weighted burden within equivalent global health states.

The most original contribution of this study lies in demonstrating that PROM domains are wired differently in women and men. Absolute psychological burden was similar across sexes, but its embedding within this system diverged. In women, global health status and generic psychological distress were more tightly coupled to psychological well-being, indicating a denser psychological integration whereby emotional distress is more globally incorporated into disease experience. In contrast, men exhibited a more symptom-driven architecture: psychological cough burden was more closely aligned with physical cough severity, suggesting that psychological impact follows somatic symptom load more directly. These findings move the field beyond simplistic narratives such as “women report more anxiety” or “men have worse disease,” toward a systems-level understanding of how symptoms, emotions, and disease meaning are integrated differently by sex. Sex modifies how domains relate to one another, not merely how high individual scores are.

At the cohort level, longitudinal trajectories were largely stable after adjustment for physiology and clinical covariates. EQ-5D-5L and LCQ showed no sex-specific longitudinal divergence, and the apparent LCQ improvement in unadjusted analyses disappeared after adjustment. For K-BILD, a borderline sex signal emerged: men showed a steeper estimated decline in Total score than women. Although this effect narrowly missed statistical significance and must not be overstated, its direction is coherent with the architectural findings. If men's well-being is more tightly anchored to physical symptom load and physiology, it may become more vulnerable as disease progresses. This observation should therefore be interpreted as hypothesis-generating and warrants further targeted validation in independent cohorts.

These results extend a growing body of work showing that sex meaningfully influence the course and lived experience of ILD. The concept of a sex-specific symptom–physiology mismatch has been touched upon in prior work but not systematically quantified. Earlier studies have reported greater emotional burden, breathlessness, or cough-related impairment in women despite comparable physiological status [10, 11]. In IPF cohorts, women have been reported to experience greater breathlessness than men at comparable disease stages, and chronic cough studies consistently indicate reduced HRQoL in women at similar cough severity [23, 24]. Our findings refine this interpretation by showing that sex differences persist even when global PROM scores are comparable and become most apparent at the level of domain composition and cross-domain coupling, rather than mean levels alone, also suggesting that previously reported "worse HRQoL in women" may often reflect differences in how burden is integrated and expressed, rather than uniformly greater disease impact.

Sex differences in cough-related burden and its impact on HRQoL are also documented outside the ILD context. Studies in chronic and post-infectious cough have repeatedly shown that women report greater HRQoL impairment from similar levels of cough severity, with stronger effects on psychosocial and physical domains, including embarrassment, social isolation and stress incontinence [25–27]. More recent registry data indicate that female sex is associated with worse cough-related HRQoL as symptoms deteriorate, and that sex must be considered in cough research and clinical practice [12, 24].

Frailty adds an important contrast. Very few studies have examined how frailty translates into HRQoL by sex; existing reviews emphasise that sex shapes ILD epidemiology, exposure patterns, trial enrolment and outcomes [11]. Although functional vulnerability increased significantly over time, baseline levels and progression rates were identical between sexes. The dissociation between sex-neutral frailty trajectories and sex-specific PROM architecture supports the interpretation that observed differences are experiential and structural rather than driven by differential physical decline or vulnerability. Together with stable global PROMs, this pattern is consistent with response-shift and adaptive recalibration mechanisms, whereby patients reweight symptoms, emotions, and expectations over time. Our data suggest that sex modifies how this adaptation occurs.

Several limitations warrant consideration, including the observational design, potential residual confounding, binary sex classification, and limited power for some network analyses. Nonetheless, this study is, to our knowledge, the first to interrogate sex differences across longitudinal trajectories, cross-domain architecture, symptom–physiology mismatch, and functional vulnerability within a harmonised, multicentre, real-world ILD cohort using a multidimensional patient-centred outcome framework.

In sum, sex differences in ILD are not differences in disease severity, but differences in how disease burden is organised, integrated, and experienced. Recognising sex as a modifier of outcome architecture is essential for accurate interpretation of PROMs and for the development of genuinely person-centred, sex-sensitive ILD care.

6. Conclusions

In ILD, sex shapes how symptoms and psychological burden are organized and experienced rather than overall disease severity. Women carry a higher symptom- and emotion-weighted burden, while men's outcomes correspond more closely to physical impairment and functional limitation. Domain- and network-level analyses show systematic sex-specific differences in disease perception and symptom integration, positioning sex as an active determinant of patient-reported outcome architecture. Clinically, these findings support sex-informed interpretation of outcomes and the development of tailored interventions addressing distinct experiential profiles. Future research should incorporate PROM-based phenotyping, functional assessment, and sex-sensitive endpoints to advance precision, person-centred care and to clarify how sex-specific outcome structures influence progression and treatment response in ILD.

7. Acknowledgments

We gratefully acknowledge RARE-ILD consortium and German Center for Lung Research, as well as all participating patients and physicians who contributed data to the registry and supported the continuation of this effort.

8. Statement of Ethics

Ethics Approval and Consent to Participate: Both eurIPFreg and eurILDreg have been reviewed and approved from institutional review boards in Germany (e.g., Ethics Committee of Justus-Liebig-University of Giessen; 111/08), France, Italy, Austria, Spain, the Czech Republic, Hungary and the UK. The research was conducted strictly according to the principles of the Declaration of Helsinki. Patients were included in the registry upon signing the informed consent. The eurIPFreg and eurIPFbank are listed in ClinicalTrials.gov (NCT02951416). The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of Justus-Liebig University of Giessen (protocol code 111/08 and 4 September 2008 as date of approval). Informed consent was obtained from all subjects involved in the study.

9. Conflicts of Interest Statement

The authors declare no conflicts of interest.

10. Funding Sources

The European IPF Registry (eurIPFreg) was established with support from the European Commission (FP7) and later expanded to the European ILD Registry (eurILDreg) to encompass a broader spectrum of ILDs. Ongoing support has been provided by local institutions, foundations (Lung Fibrosis Foundation Waldhof-Elgershausen, German Lung Foundation, Robert Pfitzer Foundation), and limited industry contributions (Roche, Boehringer Ingelheim). Funding for eurILDreg projects has come from the RARE-ILD consortium through the European Joint Program on Rare Diseases. Governance is overseen by the eurIPFreg Steering Committee, with Prof. Andreas Guenther as registry coordinator.

The funding sources had no role in the study design; data collection, analysis, or interpretation; manuscript conception, writing, or revision; or in the decision to submit the manuscript for publication.

11. Authors Contributions

Conceptualization, data curation, writing—original draft: E.K., H.M., S.T., A.G.; Methodology, writing—original draft: A.G., E.K., S.T.; Investigation, writing—original draft, writing—review and editing: H.M., A.C.W., P.M., T.V., B.C., J.B., C.V., M.M.M.; Formal analysis, data curation: H.M., A.C.W., E.K., A.G.; Resources, project administration, writing—original draft, writing—review and editing: B.C., J.B., C.V., M.M.M., A.G..; Investigation: A.T..; Data curation, visualization, writing—original draft: A.G.; Methodology: E.K.; Conceptualization: S.T.; Writing—original draft, writing—review and editing, E.K., H.M., S.T., A.C.W., P.M., T.V., B.C., J.B., C.V., M.M.M., A.G. Supervision: E.K. Conceptualization, data curation, methodology, validation, writing—original draft, writing—review and editing, project administration: E.K., A.G. Additionally, all authors contributed to: Drafting the work or revising it critically for important intellectual content AND Final approval of the version to be published; AND Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have read and agreed to the published version of the manuscript.

12. **Data Availability Statement**

Data supporting reported results are openly available at eurILDreg—Portal für Medizinische Datenmodelle (http://medical-data-models.org/46015, DOI 10.21961/mdm:46015.

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Figure legends

Figure 1: Spaghetti Plot of Longitudinal EQ-5D-5L Index Trajectories, stratified by sex. Longitudinal trajectories of EQ-5D-5L index values stratified by sex, showing index scores over follow-up in women and men with ILD. Abbreviation: EQ-5D-5L- EuroQol 5-Dimension 5-Level Questionnaire.

Figure 2: Spaghetti Plot of Longitudinal EQ-5D-5L Anxiety/Depression Trajectories, stratified by sex. Longitudinal trajectories of EQ-5D-5L anxiety values stratified by sex, showing scores over follow-up in women and men with ILD. Abbreviation: EQ-5D-5L- EuroQol 5-Dimension 5-Level Questionnaire.

Figure 3. Baseline distribution of K-BILD total and domain scores by sex. Violin plots depict the distribution of K-BILD Total and domain scores (Psychological, Breathlessness & Activities, Chest Symptoms) in women and men at baseline. Higher scores indicate better ILD-specific health status. Abbreviation: K-BILD- King's Brief Interstitial Lung Disease Questionnaire

Figure 4. Longitudinal trajectories of K-BILD total and domain scores stratified by sex. Longitudinal trajectories of K-BILD total and domain scores stratified by sex are shown; mean values of trajectories with

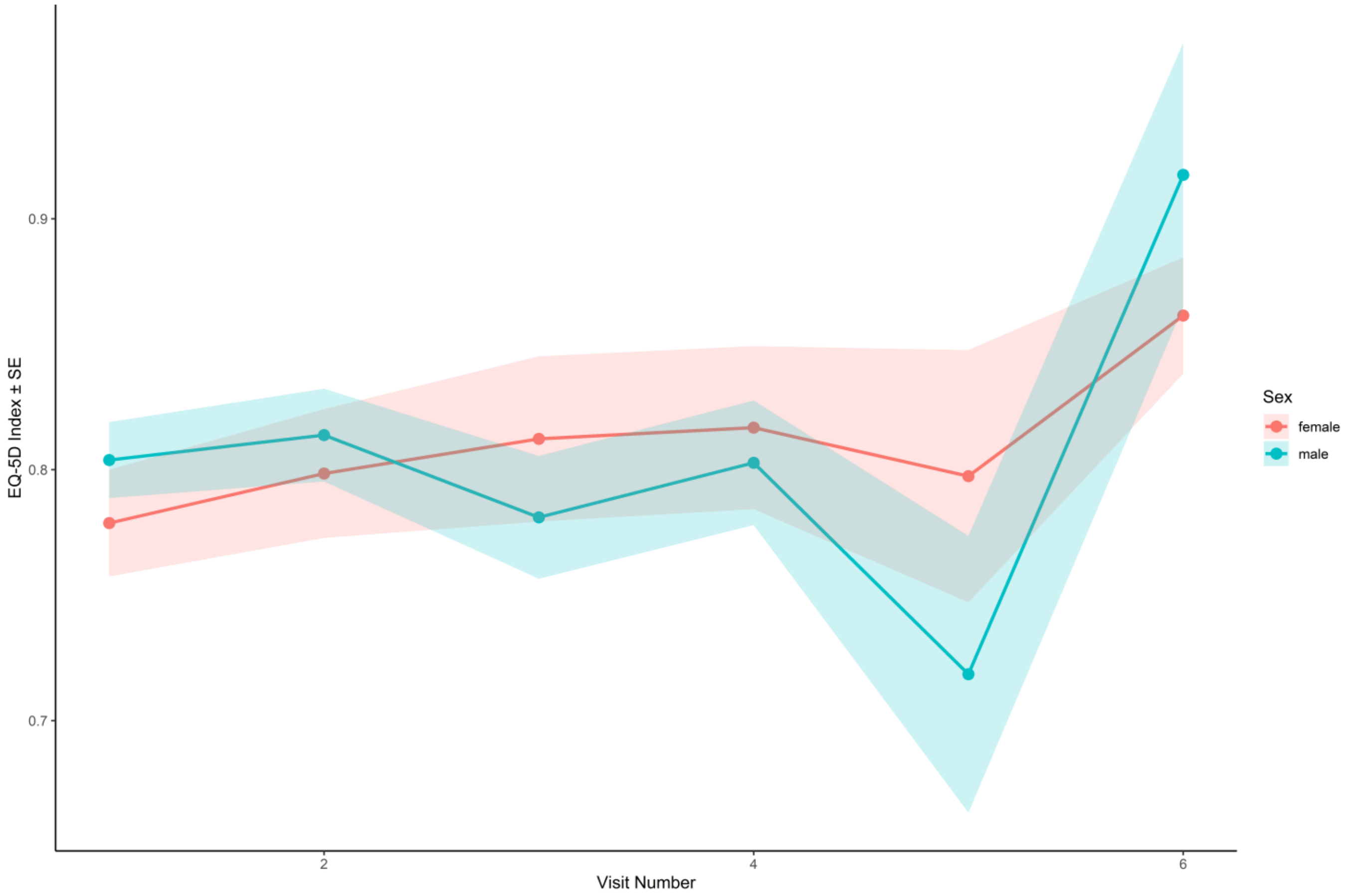
dispersion illustrate change over time in K-BILD Total and domain scores for women and men. Abbreviation: K-BILD- King's Brief Interstitial Lung Disease Questionnaire.

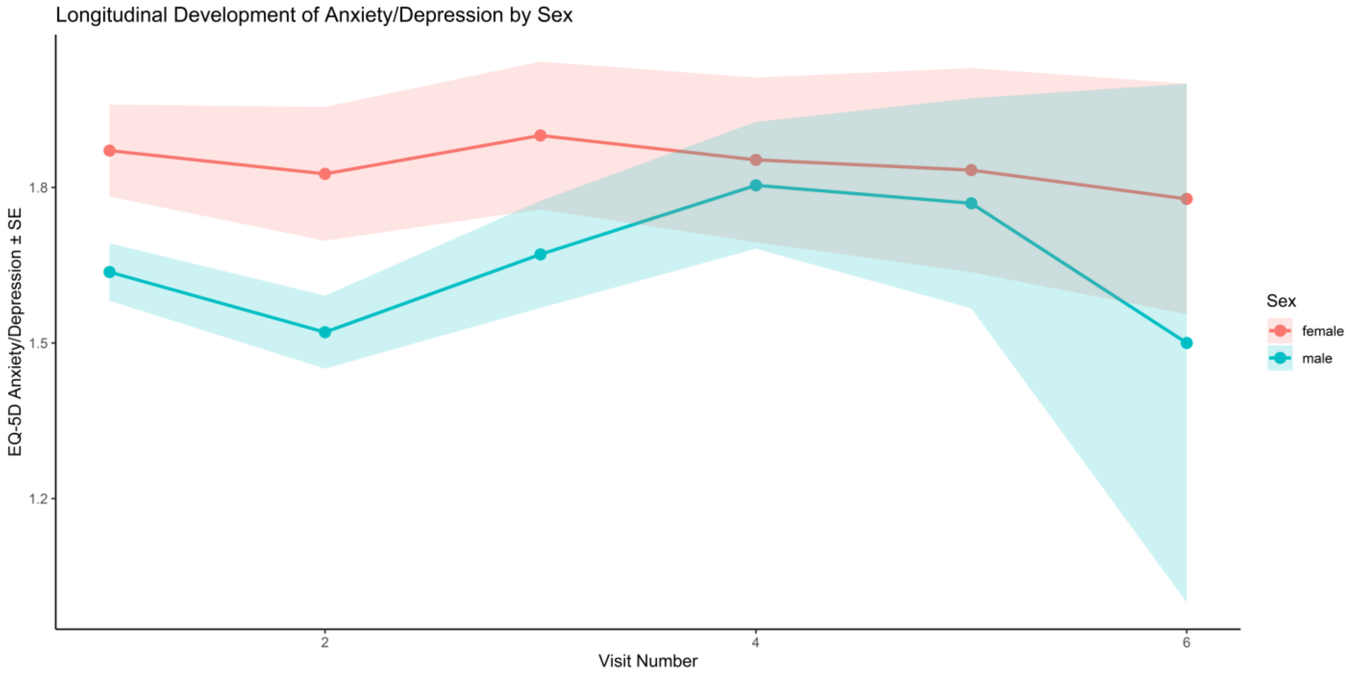
Figure 5. Distribution of LCQ total and domain-specific scores in women and men. Violin plots show the distribution of LCQ Total and domain scores (Physical, Psychological, Social) in women and men at baseline. Higher scores indicate lower cough-related impairment. Abbreviation: LCQ- Leicester Cough Questionnaire.

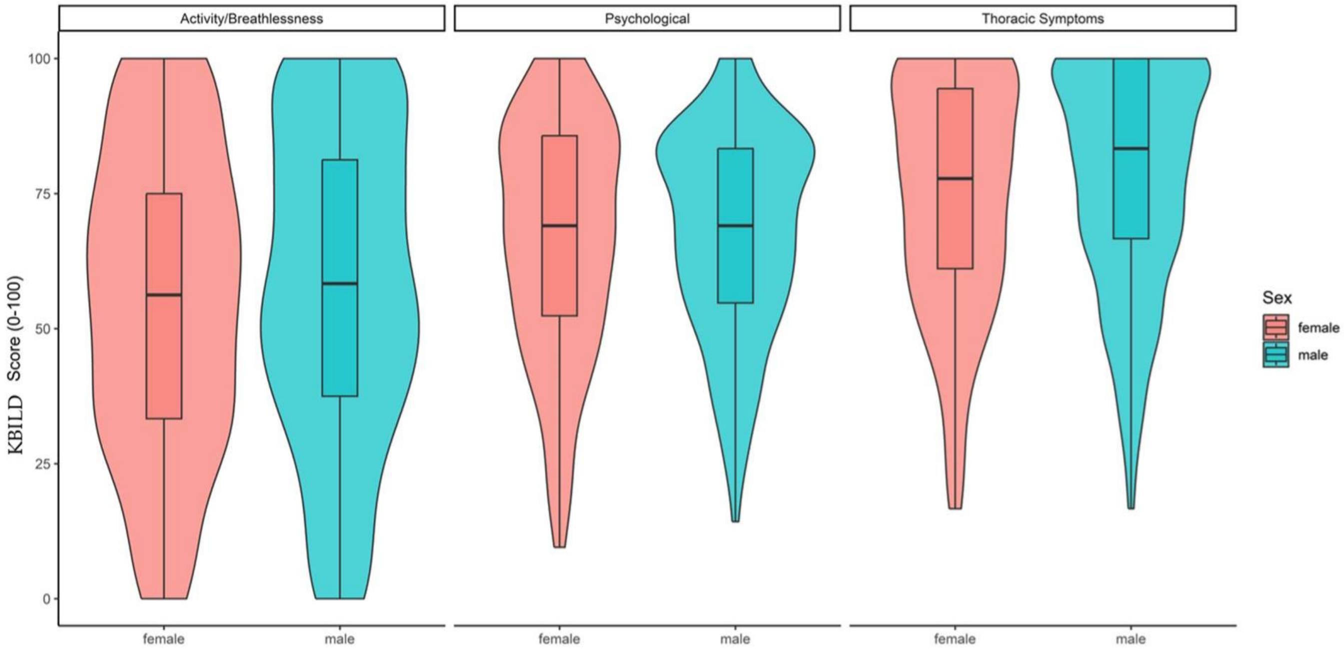
Figure 6: Longitudinal trajectories of LCQ total and domain scores stratified by sex. Mean trajectories with dispersion depict change over time in LCQ Total and domain scores in women and men across follow-up. Abbreviation: LCQ- Leicester Cough Questionnaire.

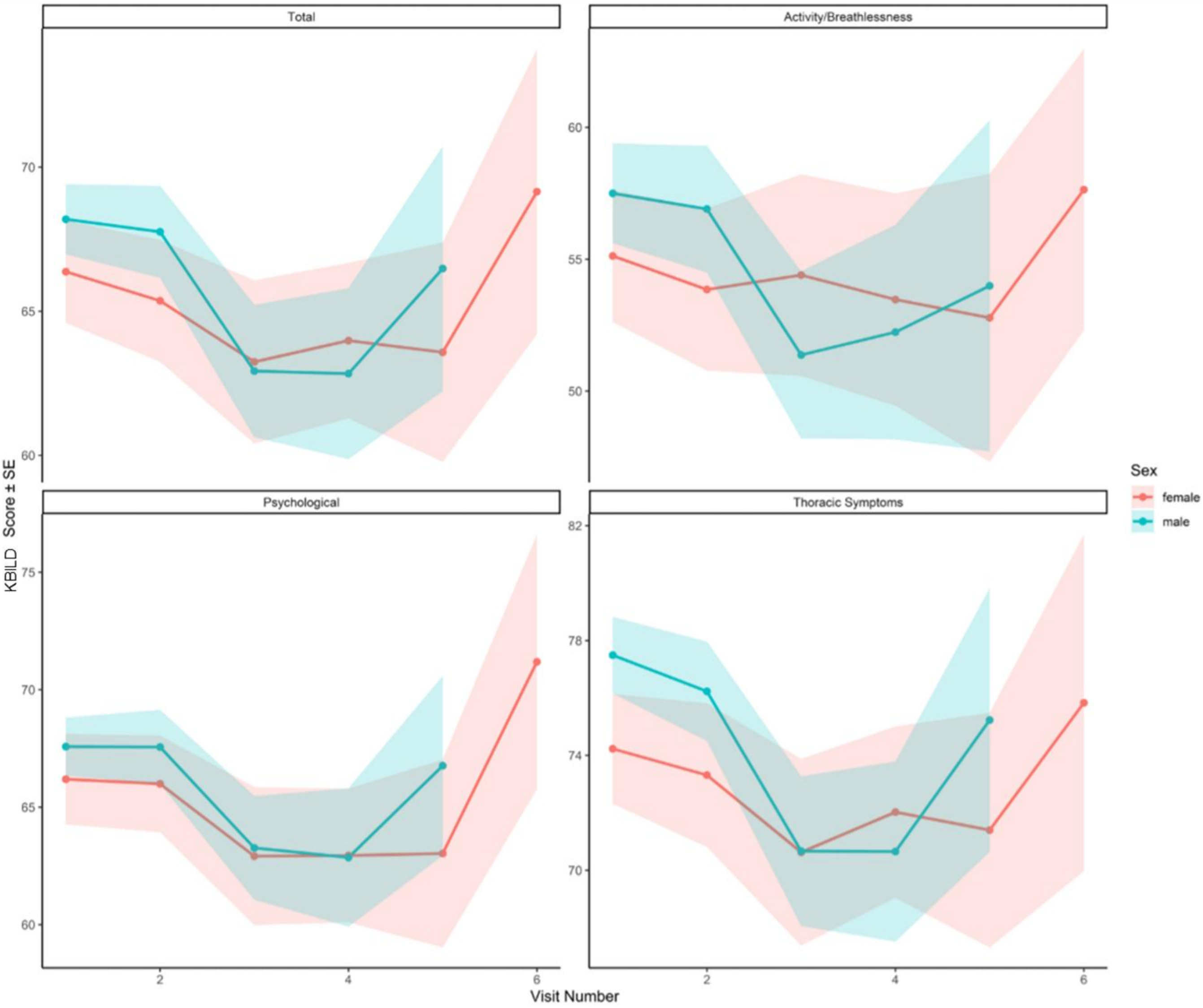
Figure 7. Sex-stratified correlations between PROMs domains across all study instruments. Heatmaps display within-sex Pearson correlation coefficients between domains of EQ-5D-5L, K-BILD, and LCQ in women and men with ILD. Colour intensity reflects correlation strength, illustrating the cross-domain structure of patient-reported outcomes by sex. Abbreviations: LCQ- Leicester Cough Questionnaire, K-BILD- King's Brief Interstitial Lung Disease Questionnaire, EQ-5D-5L- EuroQol 5-Dimension 5-Level Questionnaire.

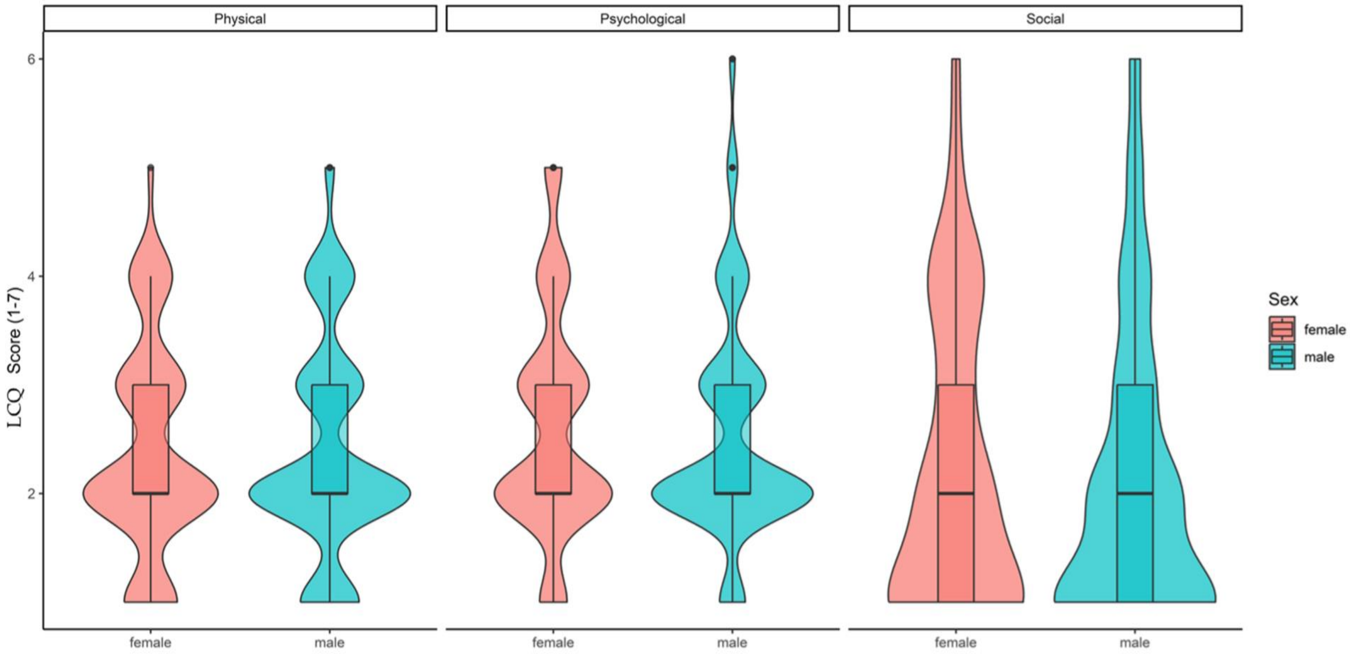
Figure 8a-c. **Frailty trajectories and model diagnostics.** (a) Sex-stratified longitudinal trajectories of Clinical Frailty Scale (CFS) scores across follow-up.
(b) Normal Q–Q plot of scaled residuals from the mixed-effects frailty model.
(c) Scale–location plot assessing homoscedasticity of residuals from the frailty model. Abbreviations: CFS- Clinical Frailty Scale; Q–Q, quantile–quantile.

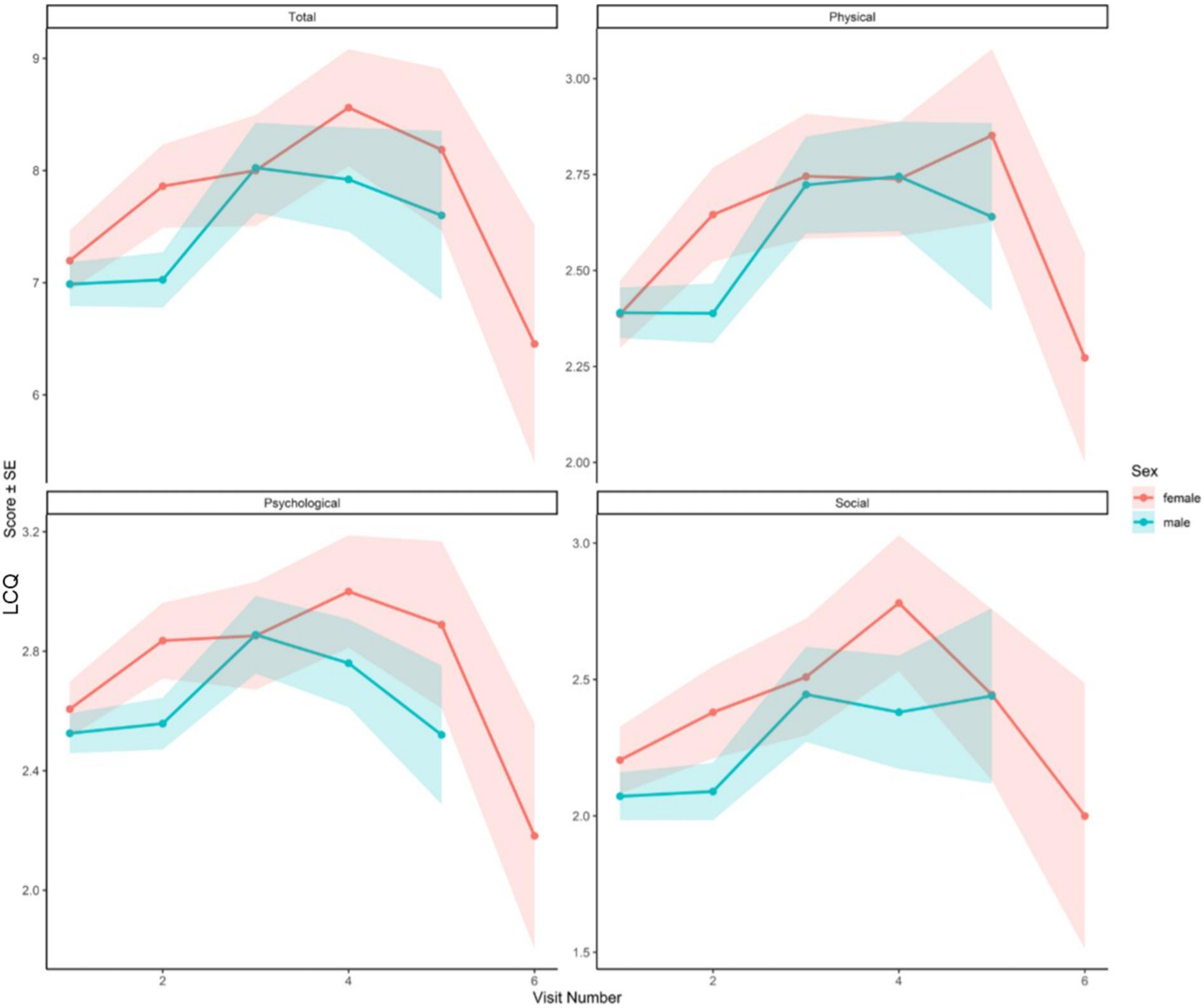

EQ-5D Index ± SE
0.9
0.8
0.7
2
4
6
Visit Number
Sex
female
male

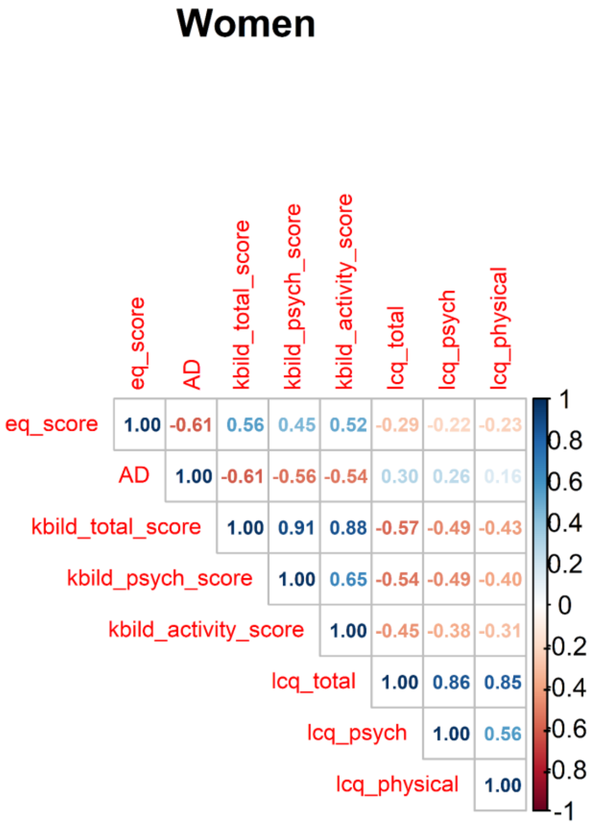

Longitudinal Development of Anxiety/Depression by Sex
EQ-5D Anxiety/Depression ± SE
1.8
1.5
1.2
2
4
6
Visit Number
Sex
female
male


Activity/Breathlessness
Psychological
Thoracic Symptoms
KBILD Score (0-100)
100
75
50
25
0
female
male
female
male
female
male
Sex
female
male

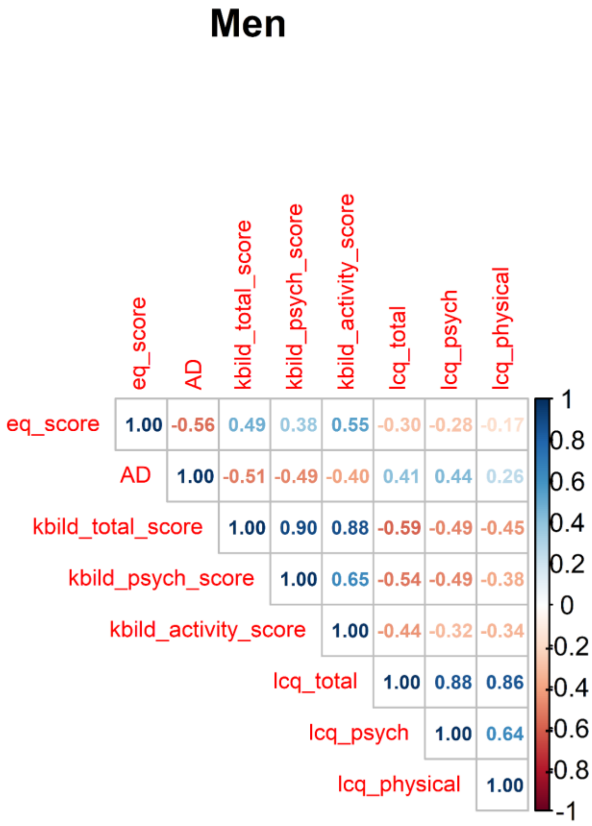

Total
Activity/Breathlessness
Psychological
Thoracic Symptoms
KBILD Score ± SE
Visit Number
70
65
60
60
55
50
75
70
65
60
82
78
74
70
2
4
6
2
4
6
Sex
female
male


Physical
Psychological
Social
LCQ Score (1-7)
6
4
2
female
male
female
male
female
male
Sex
female
male


Total
Physical
Psychological
Social
9
8
7
6
3.00
2.75
2.50
2.25
2.00
3.2
2.8
2.4
2.0
3.0
2.5
2.0
1.5
2
4
6
Visit Number
LCQ
Score ± SE
Sex
female
male



	eq_score	AD	kbild_total_score	kbild_psych_score	kbild_activity_score	lcq_total	lcq_psych	lcq_physical
eq_score	1.00	-0.61	0.56	0.45	0.52	-0.29	-0.22	-0.23
AD		1.00	-0.61	-0.56	-0.54	0.30	0.26	0.16
kbild_total_score			1.00	0.91	0.88	-0.57	-0.49	-0.43
kbild_psych_score				1.00	0.65	-0.54	-0.49	-0.40
kbild_activity_score					1.00	-0.45	-0.38	-0.31
lcq_total						1.00	0.86	0.85
lcq_psych							1.00	0.56
lcq_physical								1.00



	eq_score	AD	kbild_total_score	kbild_psych_score	kbild_activity_score	lcq_total	lcq_psych	lcq_physical
eq_score	1.00	-0.56	0.49	0.38	0.55	-0.30	-0.28	-0.17
AD		1.00	-0.51	-0.49	-0.40	0.41	0.44	0.26
kbild_total_score			1.00	0.90	0.88	-0.59	-0.49	-0.45
kbild_psych_score				1.00	0.65	-0.54	-0.49	-0.38
kbild_activity_score					1.00	-0.44	-0.32	-0.34
lcq_total						1.00	0.88	0.86
lcq_psych							1.00	0.64
lcq_physical								1.00

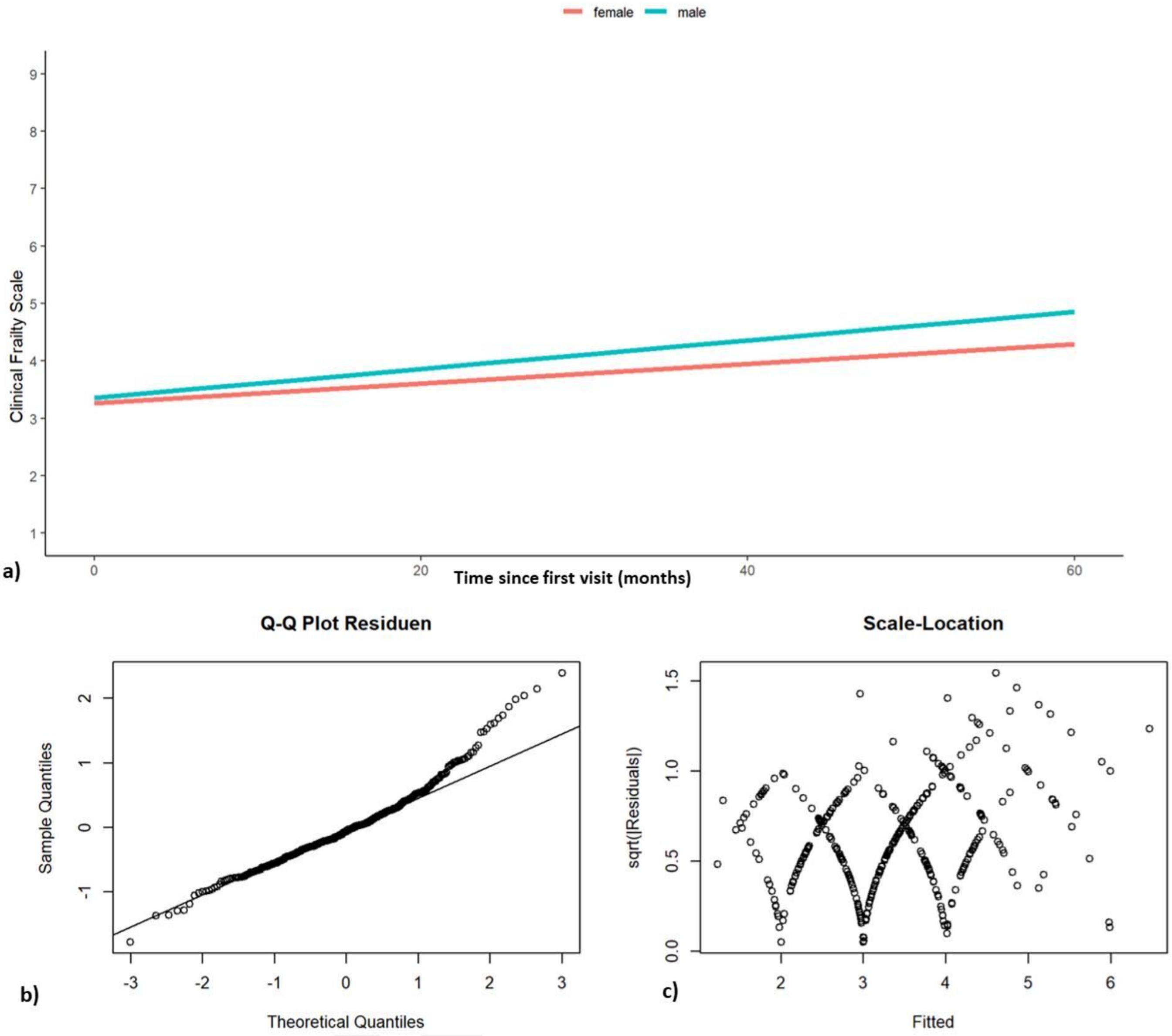

female
male
Clinical Frailty Scale
9
8
7
6
5
4
3
2
1
0
20
40
60
Time since first visit (months)
a)
Q-Q Plot Residuen
Sample Quantiles
2
1
0
-1
-3
-2
-1
0
1
2
3
Theoretical Quantiles
b)
Scale-Location
sqrt(|Residuals|)
1.5
1.0
0.5
0.0
2
3
4
5
6
Fitted
c)

Table 1. Baseline Characteristics, Disease Distribution, Follow-up, and Outcomes Stratified by Sex

Characteristic	Female (n = 129)	Male (n = 240)
Study population (n=369) **documented visits (2,007)**	129 (34.7%)	240 (64.5%)
Age at baseline, years Mean (SD)	65.6 (11.7)	67.3 (12.3)
Age Range	27–87	23–90
Smoking status, n (%)		
Current smoker	5 (4.5%)	15 (7.0%)
Ex-smoker	54 (49.1%)	145 (67.4%)
Never smoker	51 (46.4%)	55 (25.6%)
Missing data	19	25
Pack-years, mean (SD)	18.5 (16.3)	27.7 (21.0)
ILD diagnosis, n (%)		
IIP (non-IPF)	16 (12.2%)	31 (12.9%)
– NSIP (subset of IIP)	7 (5.3%)	16 (6.7%)
IPF	24 (18.3%)	90 (37.5%)
SARD-ILD	32 (24.4%)	35 (14.6%)
– SSc–ILD	18 (13.7%)	4 (1.7%)
– RA–ILD	13 (9.9%)	42 (17.5%)
– PMDM / antisynthetase syndrome	4 (3.1%)	6 (2.5%)
– Sjögren- ILD	4 (3.1%)	0 (0.0%)
Granulomatous ILD (sarcoidosis, HP)	29 (22.1%)	42 (17.5%)
Unclassifiable ILD	24 (18.3%)	37 (15.4%)
Drug-induced ILD	1 (0.8%)	1 (0.4%)
ILA	3 (2.3%)	4 (1.7%)
–CPFE	5 (3.8)	31 (12.9)
– PPF	17 (13.2%)	28 (11.7%)
Visits per patient, mean (SD), range	6.1 (4.7) 1-18	5.0 (3.5) 1-20
Follow-up duration, months Median (IQR) range	4.5 (1.7–12.0) 1-31.3	2.0 (0.3–5.4) 1.0 to 37.9
Clinical outcomes at 2025-12-01		
Alive (ongoing)	124 (96.1%)	221 (92.1%)
Lung transplantation	3 (2.3%)	16 (6.7%)
Death	2 (1.6%)	3 (1.2%)

Abbreviations: CPFE – Combined pulmonary fibrosis and emphysema; HP – Hypersensitivity pneumonitis; IIP – Idiopathic interstitial pneumonia; ILA – Interstitial lung abnormality; ILD – Interstitial lung disease; IPF – Idiopathic pulmonary fibrosis; IQR – Interquartile range; NSIP – Nonspecific interstitial pneumonia; PM/DM – Polymyositis/Dermatomyositis; PPF – Progressive pulmonary fibrosis; RA – Rheumatoid arthritis; SARD – Systemic autoimmune rheumatic disease; SD – Standard deviation; SSc – Systemic sclerosis; *n* – number.