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Dynamic iron dysregulation, lung function, and functional deterioration in adults aged 50 years and older with asthma: a longitudinal cohort study

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Research Article

Keywords: adults aged 50 years and older, asthma, ferritin variability, iron fragility index, lung function, FEV1, activities of daily living

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Dynamic iron dysregulation, lung function, and functional deterioration in adults aged 50 years and older with asthma: a longitudinal cohort study

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Abstract

Background: Adults aged 50 years and older with asthma may have reduced pulmonary and functional reserve. Most previous studies of iron status and respiratory health have relied on single biomarker measurements, and it remains unclear whether within-person instability in iron-related measures is associated with lung function or functional deterioration.

Methods: We conducted a longitudinal secondary analysis of participants with asthma at wave 2 of the English Longitudinal Study of Ageing, using data from waves 2, 4, 6, and 8. Dynamic iron-related exposures included ferritin coefficient of variation (CV), ferritin slope, repeated low ferritin exposure, and a composite iron fragility index (IFI). The principal fully adjusted lung-function analysis included 532 participants contributing 1,154 forced expiratory volume in 1 second (FEV1) observations. Core models adjusted for age, sex, smoking status, and body mass index; extended models additionally adjusted for C-reactive protein (CRP) and hemoglobin. Generalized estimating equations assessed repeated respiratory symptoms, and Cox models assessed time to first severe activities of daily living (ADL) deterioration as a secondary longitudinal association.

Results: In extended models, higher IFI was associated with lower overall FEV1 (beta = -0.028, 95% confidence interval [CI] -0.053 to -0.004), and ferritin CV showed the clearest association among the dynamic measures (beta = -0.352, 95% CI -0.562 to -0.142). Neither measure showed a clear interaction with follow-up time. Ferritin CV was associated with time to first severe ADL deterioration (hazard ratio [HR] = 2.25, 95% CI 1.11 to 4.60), and IFI showed a similar association (HR = 1.19, 95% CI 1.03 to 1.37). Additional adjustment for CRP and hemoglobin only modestly attenuated the lung-function

estimates. Findings were generally stable after inverse probability weighting and alternative handling of extreme ferritin CV values, whereas symptom and subgroup findings were less consistent.

Conclusions: Among adults aged 50 years and older with asthma, higher ferritin variability and IFI were associated with lower overall FEV1 and with severe ADL deterioration during the observed multiwave period. Repeated ferritin patterns may provide a different perspective from a single measurement, but their temporal interpretation, reproducibility, and clinical utility require external validation.

Keywords: adults aged 50 years and older; asthma; ferritin variability; iron fragility index; lung function; FEV1; activities of daily living

Background

Asthma in later adulthood is clinically heterogeneous. Compared with younger patients, older adults with asthma generally have lower pulmonary reserve, a greater burden of comorbidity, and a higher risk of functional decline, making the identification of markers of respiratory and functional vulnerability clinically relevant [1-3]. In addition to airway inflammation, outcomes may reflect broader systemic physiological dysregulation. Longitudinal evidence linking iron dysregulation to lung function and functional deterioration in adults with asthma remains limited.

Iron dysregulation is biologically plausible because iron homeostasis is linked to inflammation, oxidative stress, and energy metabolism [4]. Previous studies have related iron-related markers to asthma, lung function, and selected respiratory phenotypes [5], but most evidence has been cross-sectional or based on a single ferritin measurement or other static markers [6,7]. Repeated measurements may provide a different perspective by capturing within-person fluctuation and longer-term loss of physiological stability [8].

Several questions therefore remain unresolved. A single ferritin value cannot characterize temporal variability in iron metabolism, and it is unclear how dynamic iron-related measures compare with mean or current ferritin levels [8,9]. It is also uncertain whether such associations are present among adults with asthma, whether they persist after accounting for inflammation and anemia, and whether they extend from lung function to functional outcomes.

The primary objective of this study was to examine whether dynamic iron dysregulation was associated with repeated FEV1 among participants with asthma in the English Longitudinal Study of Ageing (ELSA). We focused on ferritin CV and a composite IFI and further examined respiratory symptoms, inflammation, anemia, selected subgroup patterns, and severe ADL deterioration.

Methods

Study design and participants

This longitudinal secondary analysis used waves 2, 4, 6, and 8 of ELSA [10]. Participants with asthma recorded at wave 2 formed the baseline asthma cohort. Lung-function analyses used waves 2, 4, and 6, when spirometry was available, whereas respiratory symptoms and functional outcomes were assessed through wave 8. The principal extended models for IFI, ferritin CV, and ferritin slope included 532 participants contributing 1,154 repeated FEV1 observations. Analytic sample sizes varied according to exposure, outcome, and covariate availability. Because the dynamic exposure summaries and outcome observation periods overlapped, the analyses were interpreted as longitudinal associations rather than strictly prospective prediction models.

Dynamic iron-related exposures

Repeated ferritin measurements from waves 2, 4, 6, and 8 were used to derive dynamic iron-related measures. For each participant, we calculated mean ferritin, the standard deviation of ferritin, ferritin CV as the standard deviation divided by the mean, and the cumulative number of ferritin measurements below 30 micrograms/L [11]. Ferritin CV was modeled on its original ratio scale. Ferritin slope was estimated by regressing log-transformed ferritin on follow-up time within each participant among those with at least two measurements and was expressed as change in log ferritin per year. Log transformation was used to reduce skewness and improve trajectory estimation.

The IFI combined ferritin slope, ferritin CV, and cumulative low ferritin exposure. Ferritin slope was directionally aligned so that a steeper decline represented greater fragility; the three components were standardized as z scores and summed. Higher IFI values therefore represented greater dynamic iron dysregulation. A one-unit change in IFI represented a one-point change on this summed standardized scale. The individual IFI components were also analyzed separately.

Outcomes

The primary outcome was repeated FEV1, measured in liters during nurse-visit spirometry. Secondary outcomes included repeated asthma-like symptoms and time to first severe ADL deterioration during available follow-up. For domain-specific analyses, gross motor ADL items comprised walking across a room, bathing, and getting into or out of bed, whereas fine motor

ADL items comprised eating and dressing. Because the dynamic ferritin summaries and ADL follow-up were derived from overlapping waves, the Cox analyses were treated as secondary longitudinal association analyses. Additional outcome definitions are provided in the Supplementary Methods.

Covariates

Core models adjusted for age, sex, smoking status, and body mass index (BMI). Extended models additionally included log-transformed C-reactive protein (CRP) and hemoglobin because inflammation and anemia may influence both ferritin-related measures and lung function. Comparisons between core and extended models were used to assess the degree of attenuation after accounting for these factors.

Statistical analysis

Primary analysis of repeated FEV1

Linear mixed-effects models estimated the associations of IFI, ferritin CV, ferritin slope, and repeated low ferritin exposure with repeated FEV1. Models included participant-specific random intercepts. Follow-up time was expressed in years. The main exposure term estimated the association with the overall FEV1 level, whereas the exposure-by-time interaction assessed whether the rate of change in FEV1 differed over follow-up. Core and extended covariate models were fitted as defined above.

Secondary respiratory and functional analyses

Repeated binary respiratory symptoms were analyzed using generalized estimating equations with a logit link [12,13]. Time to first severe ADL deterioration was analyzed using Cox proportional hazards models. Symptom analyses were considered exploratory. Because the dynamic exposure and ADL observation windows overlapped, the ADL hazard ratios were interpreted as longitudinal associations and not as strictly prospective risk estimates.

Explanatory and nonlinearity analyses

The degree of attenuation between core and extended models was examined to assess whether CRP and hemoglobin accounted for the principal associations. Exploratory mediation analyses evaluated whether mean log-transformed CRP statistically mediated part of the association between ferritin CV and FEV1 [14]. These analyses were not interpreted causally. Restricted

cubic splines [15] and piecewise linear models [16] were used to examine possible nonlinearity in the association between ferritin slope and FEV1.

Effect modification

Potential effect modification was examined by age, sex, smoking status, grip strength, and functional status using interaction terms and stratified models. These analyses were intended to identify potentially susceptible groups and to support interpretation of heterogeneity rather than to establish definitive subgroup effects.

Sensitivity analyses

Sensitivity analyses addressed selection bias, reverse causation, extreme ferritin CV values, and multiple testing. Inverse probability weighting (IPW) was used to address complete-case selection [17]. Reverse-causation analyses applied baseline restrictions and excluded early deterioration. Ferritin CV models were repeated after winsorization or tail trimming. The false discovery rate (FDR) was controlled within prespecified analysis families [18]. Alternative IFI constructions, time-varying and event-based analyses, all-cause mortality analyses, and directionality analyses are described in the Supplementary Methods. All tests were two-sided. Analyses were conducted in R version 4.1.3, primarily using lme4 [19], geepack [13], and lavaan [20].

Use of generative AI-assisted tools

During manuscript preparation, the authors used generative AI-assisted tools for language editing, formatting, journal-style refinement, and preparation of submission-related text. These tools were not used to generate data, perform statistical analyses, or draw scientific conclusions. All AI-assisted content was reviewed, verified, and edited by the authors, who take full responsibility for the final manuscript.

Results

Analytic sample

The principal extended models for IFI, ferritin CV, and ferritin slope included 532 participants contributing 1,154 repeated FEV1 observations (Supplementary Table S68). Compared with participants excluded from the complete-case analyses, included participants were younger, had

lower CRP, and had higher baseline FEV1; differences in ferritin and ferritin CV were modest (Supplementary Table S52).

Primary associations with lung function

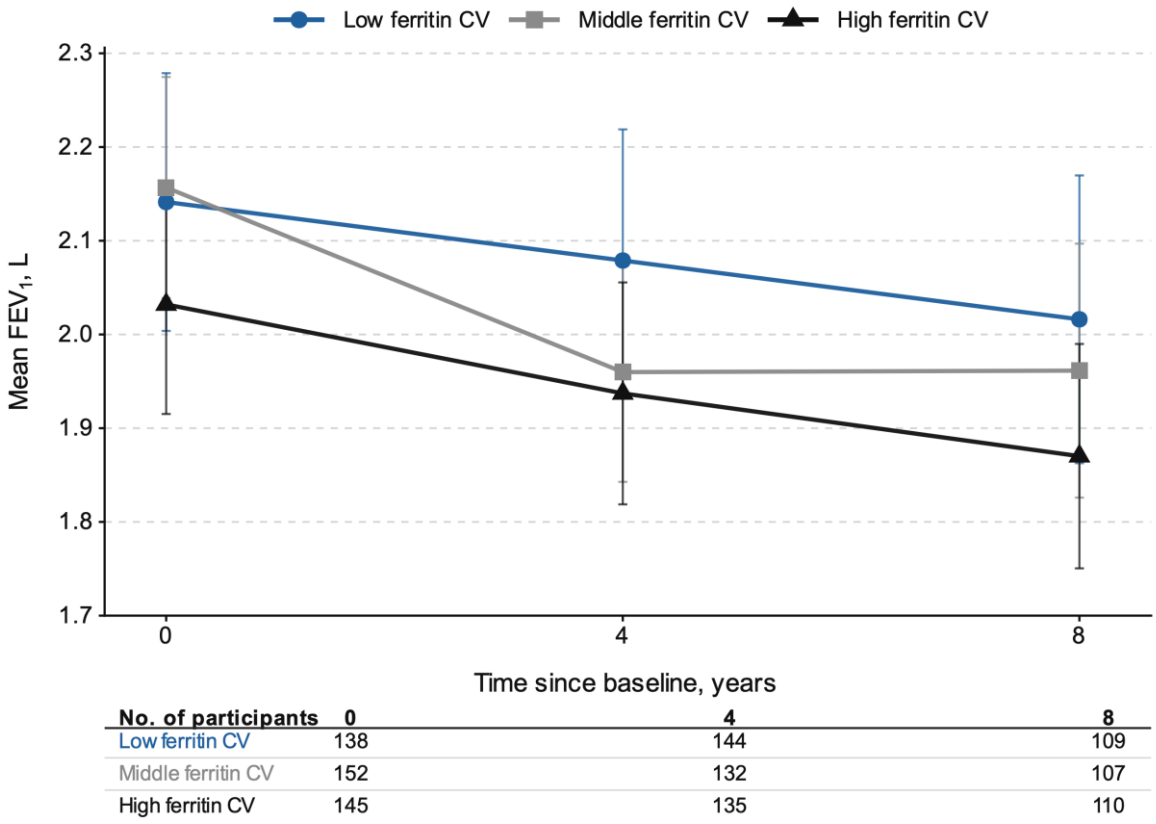
In core models, IFI was associated with lower overall FEV1 (beta = -0.033, 95% CI -0.058 to -0.008; P = 0.009), and ferritin CV showed a larger inverse association (beta = -0.374, 95% CI -0.587 to -0.160; P < 0.001). After additional adjustment for CRP and hemoglobin, the corresponding estimates were beta = -0.028 (95% CI -0.053 to -0.004; P = 0.023) for IFI and beta = -0.352 (95% CI -0.562 to -0.142; P = 0.001) for ferritin CV (Table 1). Neither exposure-by-time interaction was statistically supported, indicating differences in overall FEV1 level rather than clearly different rates of decline. Ferritin slope and repeated low ferritin exposure showed weaker and less consistent associations (Supplementary Tables S66-S67).

Table 1. Core and extended associations of the iron fragility index and ferritin variability with repeated FEV1

Exposure	Core model main effect, beta (95% CI); P value	Extended model main effect, beta (95% CI); P value	Extended exposure x time, beta (95% CI); P value
Iron fragility index (IFI)	-0.033 (-0.058 to -0.008); 0.009	-0.028 (-0.053 to -0.004); 0.023	0.001 (-0.002 to 0.004); 0.556
Ferritin variability (CV)	-0.374 (-0.587 to -0.160); <0.001	-0.352 (-0.562 to -0.142); 0.001	0.011 (-0.011 to 0.033); 0.331

Beta coefficients represent differences in FEV1 in liters per one-unit increase in each exposure on its modeled scale. Ferritin CV was modeled as a ratio, and IFI was modeled as the sum of standardized component scores. Core models adjusted for age, sex, smoking status, and body mass index. Extended models additionally adjusted for log-transformed CRP and hemoglobin. Participant-specific random intercepts accounted for repeated measurements. CI, confidence interval; CRP, C-reactive protein; CV, coefficient of variation; FEV1, forced expiratory volume in 1 second; IFI, iron fragility index.

Descriptive trajectories were separated by ferritin CV group in a direction consistent with the mixed-effects models: participants in the high-variability group had lower mean FEV1 across follow-up, without a clear indication of a steeper decline (Figure 1).



No. of participants	0	4	8
Low ferritin CV	138	144	109
Middle ferritin CV	152	132	107
High ferritin CV	145	135	110

Figure 1. Descriptive longitudinal FEV1 trajectories according to ferritin variability. Mean FEV1 values are shown for low, middle, and high ferritin coefficient of variation (CV) groups over 8 years of follow-up. Points represent means, error bars represent 95% confidence intervals, and the numbers of participants with available FEV1 measurements are shown below the plot. Participants with higher ferritin variability had lower mean FEV1 across follow-up, with no clear evidence of a faster longitudinal decline.

Associations with respiratory symptoms

Associations with respiratory symptoms were modest. No clear association was observed with the composite outcome of any asthma-like symptom (Supplementary Table S5). In item-level analyses, higher IFI was associated with greater odds of reporting an asthma attack (OR = 1.09, 95% CI 1.02 to 1.17; P = 0.012), as was each additional low-ferritin measurement (OR = 1.37, 95% CI 1.12 to 1.68; P = 0.002) (Supplementary Table S6). No consistent pattern was observed for wheeze or night waking. These findings were interpreted as exploratory.

Heterogeneity across selected subgroups

Age-stratified estimates suggested that the inverse association between ferritin CV and FEV1 was more evident among participants aged 60-69 years (beta = -0.379, 95% CI -0.650 to -0.108; P = 0.006) and those aged 70 years or older (beta = -0.311, 95% CI -0.596 to -0.026; P = 0.033),

whereas the estimate was weaker among participants aged 50-59 years. Sex-by-age analyses suggested a clearer signal among women aged 60-69 years (Supplementary Figure 1A-B).

Grip-strength and functional-status analyses were directionally consistent but imprecise. Among participants aged 60 years or older, inverse estimates were observed in both weak- and strong-grip groups. The high-instability/weak-grip phenotype had the lowest descriptive mean FEV1 in the four-group iron-muscle analysis (Supplementary Figure 1C; Supplementary Table S18). Associations were also more apparent among participants with fewer baseline ADL or instrumental ADL limitations (Supplementary Figure 1D; Supplementary Tables S14-S22).

Among participants classified as current smokers, ferritin CV remained associated with lower FEV1 (beta = -0.440, 95% CI -0.724 to -0.156; P = 0.002) (Supplementary Figure 1E). Evidence for IFI, ferritin slope, and repeated low ferritin exposure was weaker. Because formal interaction tests provided limited support, all subgroup findings should be interpreted as hypothesis-generating.

Explanatory analyses

Exploratory mediation analysis showed an overall indirect association through mean log-transformed CRP of -0.065 (95% CI -0.126 to -0.012; P = 0.022), while the direct association between ferritin CV and FEV1 remained (beta = -0.241, 95% CI -0.431 to -0.054; P = 0.010). Age-stratified mediation estimates are reported in Supplementary Tables S63-S64. Because the analysis was observational and the measurement periods overlapped, these estimates do not establish a causal inflammatory pathway.

The modest change from the core to the extended estimates suggested that CRP and hemoglobin did not fully account for the associations of IFI and ferritin CV with FEV1 (Table 1; Supplementary Tables S66-S68). In the extended models, log-transformed CRP was associated with lower FEV1, whereas hemoglobin showed no clear association.

For ferritin slope, restricted cubic splines suggested a nonlinear main effect (P = 0.015), whereas no clear nonlinearity was observed for current ferritin or ferritin CV. A data-driven piecewise analysis identified an exploratory turning point at approximately 0.0645 log-ferritin units per year: below this point, a higher slope was associated with higher FEV1, whereas above it, a

higher slope was associated with lower FEV1 (Supplementary Tables S70-S76 and S84; Supplementary Figure 2B). This threshold requires independent validation.

Associations with functional deterioration

In secondary Cox analyses over the overlapping observation window, ferritin CV was associated with time to first severe ADL deterioration (HR = 2.25, 95% CI 1.11 to 4.60; P = 0.025), and IFI showed a similar association (HR = 1.19, 95% CI 1.03 to 1.37; P = 0.019). Ferritin slope showed no clear association, and repeated low ferritin exposure was not statistically significant (Table 2). These hazard ratios describe longitudinal associations rather than strictly prospective prediction.

Table 2. Associations of dynamic iron-related measures with time to first severe ADL deterioration

Exposure	HR (95% CI)	P value
Ferritin variability (CV)	2.25 (1.11 to 4.60)	0.025
Ferritin slope	1.09 (0.32 to 3.78)	0.890
Repeated low ferritin exposure	1.22 (0.98 to 1.51)	0.077
Iron fragility index (IFI)	1.19 (1.03 to 1.37)	0.019

Hazard ratios (HRs), 95% confidence intervals (CIs), and P values are from Cox proportional hazards models adjusted for age, sex, smoking status, body mass index, log-transformed CRP, and hemoglobin. Estimates correspond to a one-unit increase in each exposure on its modeled scale. Because the exposure summaries and ADL observation period overlapped, the models were interpreted as longitudinal association analyses. ADL, activities of daily living; CI, confidence interval; CRP, C-reactive protein; CV, coefficient of variation; HR, hazard ratio; IFI, iron fragility index.

Domain-specific findings were exploratory and not uniform. Ferritin CV was associated with gross motor ADL deterioration (HR = 2.22, 95% CI 1.18 to 4.19; P = 0.014), and IFI showed a directionally similar gross-motor association (HR = 1.08, 95% CI 1.00 to 1.16; P = 0.038) (Supplementary Table S26). Formal comparisons did not show clear differences between gross and fine motor coefficients (Supplementary Table S27). In the four-group iron-muscle analysis, the high-instability/weak-grip group had the lowest descriptive ADL-free survival, but the reference choice and limited interaction support precluded a definitive joint-effect interpretation (Figure 2; Supplementary Tables S28-S31).

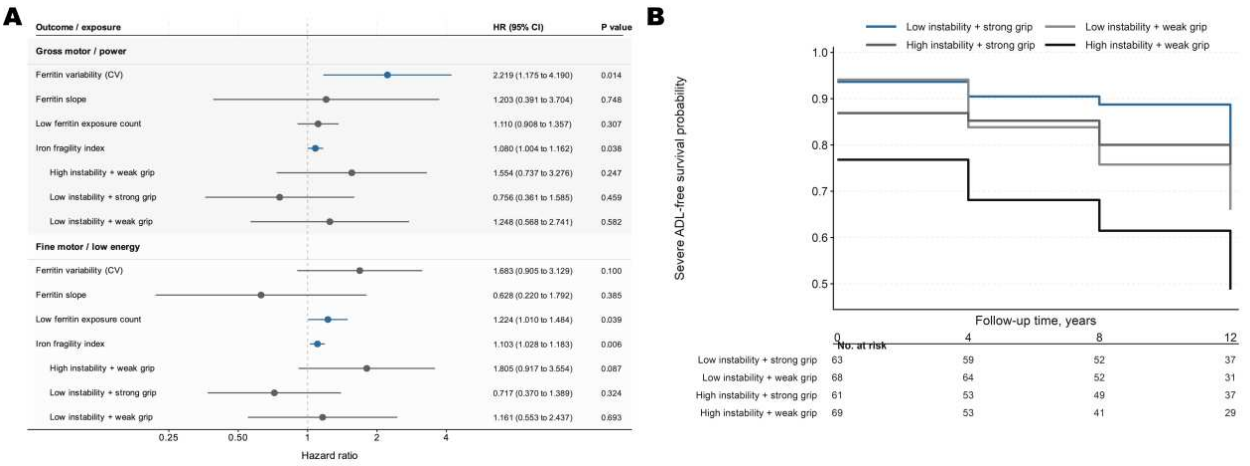


Figure 2. Exploratory functional outcomes associated with dynamic iron dysregulation in adults with asthma. (A) Associations of dynamic iron-related measures with deterioration in gross motor and fine motor ADL domains. Points represent hazard ratios (HRs), horizontal lines represent 95% confidence intervals (CIs), and the vertical dashed line denotes HR = 1. (B) Severe ADL-free survival according to combined iron-instability and grip-strength phenotype. Kaplan-Meier curves are shown with numbers at risk below the plot. The high-instability/weak-grip group had the lowest descriptive ADL-free survival. Domain and phenotype analyses were exploratory, and formal comparisons or interaction tests provided limited support. Unless otherwise indicated, models were adjusted for age, sex, smoking status, body mass index, log-transformed CRP, and hemoglobin. ADL, activities of daily living; CI, confidence interval; CRP, C-reactive protein; CV, coefficient of variation; HR, hazard ratio; IFI, iron fragility index.

Sensitivity and supplementary analyses

Selection and attrition analyses did not materially alter the principal lung-function estimates. Complete-case samples were smaller than the source repeated-measures panel, and excluded participants were generally older, had higher CRP, and had lower baseline FEV1; differences in the principal ferritin-related exposures were modest. IPW produced estimates similar to those from the complete-case IFI and ferritin CV models (Supplementary Tables S52-S54). Results were also stable after winsorization or tail trimming of ferritin CV (Supplementary Table S61), suggesting that extreme values were unlikely to account fully for the main associations.

Reverse-causation analyses yielded directionally consistent but attenuated estimates, with weaker support after restriction to participants with preserved baseline lung function (Supplementary Tables S77-S80). Event-based and time-varying analyses were less consistent: current low ferritin status was most clearly associated with incident low FEV1, whereas recent change, cumulative CV, and high-variability intervals showed weaker associations (Supplementary Tables S32-S40).

Directionality analyses did not identify a clear within-person bidirectional cross-lagged association between ferritin and FEV1 in conventional cross-lagged panel, random-intercept

cross-lagged panel, or parallel-process growth models. After family-wise FDR correction, the lung-function family retained the strongest support, whereas symptom, smoking, sex-by-age, mediation, and interaction families were less consistent. These analyses did not materially alter the principal ferritin CV and IFI estimates, although time-varying and directionality analyses were less consistent.

Discussion

In this longitudinal analysis of adults aged 50 years and older with asthma, higher ferritin CV and IFI were associated with lower overall FEV1. Secondary Cox analyses also identified associations with time to first severe ADL deterioration during the overlapping multiwave observation period. The FEV1 findings reflected differences in overall lung-function level rather than clearly different rates of decline. Ferritin CV was the clearest individual dynamic measure, and its association was stable across core, extended, IPW, and extreme-value analyses. Respiratory symptom and subgroup findings were less consistent.

These findings suggest that a single ferritin value may not fully describe the longitudinal pattern of iron-related physiology. Ferritin CV captured within-person variability and showed clearer associations with FEV1 than ferritin slope or repeated low ferritin exposure. The composite IFI produced a concordant, although smaller, association by integrating several dimensions of iron-related instability [8,9]. However, the study did not directly quantify incremental prediction or model improvement relative to baseline or mean ferritin; repeated ferritin patterns should therefore be viewed as a different perspective rather than as proven superior markers.

Inflammation may explain part, but not all, of the observed association. The exploratory CRP analysis identified a statistical indirect association, while the direct association between ferritin CV and FEV1 remained. The modest attenuation after adding CRP and hemoglobin to the core models also suggests that these factors did not fully account for the principal estimates. Because the mediation analysis was observational and temporally overlapping, it should not be interpreted as evidence of a causal biological mechanism.

The ADL findings add a functional dimension to the lung-function results [21,22], but they require cautious interpretation because exposure construction and outcome follow-up overlapped. Gross-motor estimates appeared more prominent for ferritin CV and IFI, although

formal comparisons did not establish a clear difference from fine-motor domains. The poorer descriptive ADL-free survival in the high-instability/weak-grip group is compatible with an interrelated pattern involving iron instability, respiratory reserve, and muscle vulnerability [22-24], but it does not establish biological interaction or joint causation.

Subgroup analyses suggested stronger inverse estimates among older participants, women aged 60-69 years, participants classified as current smokers, and selected grip-strength or functional-status groups. Formal interaction tests, however, provided limited support, and several families did not remain significant after FDR correction. These patterns should therefore be considered hypothesis-generating.

Strengths of this study include the use of repeated ferritin and lung-function measurements, evaluation of both individual dynamic measures and a composite index, explicit comparison of core and CRP/hemoglobin-adjusted models, and a broad set of missingness, extreme-value, nonlinearity, time-varying, directionality, and functional analyses. The stability of the ferritin CV estimate across the principal, IPW, and extreme-value analyses supports the internal robustness of this association.

Several limitations should be considered. First, the observational design precludes causal inference, and residual confounding and reverse causation remain possible. Second, the dynamic ferritin measures were constructed from observations that overlapped with repeated FEV1 assessment and ADL follow-up; neither the mixed-model coefficients nor the ADL hazard ratios should be interpreted as strictly prospective effects. Third, the study did not directly test whether dynamic measures improved prediction or model fit beyond baseline or mean ferritin. Fourth, complete-case analyses reduced sample size, and excluded participants differed in age, CRP, and baseline FEV1, although IPW produced similar estimates. Fifth, subgroup, mediation, interaction, time-varying, event-based, and phenotype analyses were exploratory, sometimes inconsistent, and subject to multiple testing. Sixth, IFI is a study-specific composite that requires independent validation, and the turning point identified for ferritin slope was data-driven. Finally, generalizability beyond the ELSA asthma cohort and adults aged 50 years and older remains uncertain.

Conclusions

Among adults aged 50 years and older with asthma, higher ferritin variability and IFI were associated with lower overall FEV1, and secondary analyses identified associations with severe ADL deterioration during the observed multiwave period. CRP and hemoglobin did not fully account for the lung-function estimates. Repeated ferritin patterns may provide a different perspective from a single measurement, but their temporal interpretation, reproducibility, and clinical utility require external validation.

List of abbreviations

ADL, activities of daily living; BMI, body mass index; CI, confidence interval; CLPM, cross-lagged panel model; CRP, C-reactive protein; CV, coefficient of variation; ELSA, English Longitudinal Study of Ageing; FDR, false discovery rate; FEV1, forced expiratory volume in 1 second; GEE, generalized estimating equations; HR, hazard ratio; IADL, instrumental activities of daily living; IFI, iron fragility index; IPW, inverse probability weighting; OR, odds ratio; RI-CLPM, random-intercept cross-lagged panel model.

Declarations

Ethics approval and consent to participate

This study was a secondary analysis of de-identified data from ELSA. ELSA received ethical approval from the London Multicentre Research Ethics Committee/National Research Ethics Service (MREC/01/2/91), and all participants provided written informed consent. The present study involved no new participant recruitment, intervention, or primary data collection and was conducted in accordance with the applicable data-access and ethical requirements.

Consent for publication

Not applicable.

Availability of data and materials

The ELSA datasets analyzed during the current study are available through the UK Data Service subject to registration and applicable data-use conditions. No participant-level ELSA data are redistributed with this article. The supplementary information contains detailed methods and

results. Additional derived analytical materials may be available from the corresponding author on reasonable request, subject to applicable ELSA data-use restrictions.

Clinical Trial Number

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

KM contributed to conceptualization, methodology, software, formal analysis, data curation, visualization, and drafting the manuscript. MX contributed to methodology, software, and formal analysis. LY contributed to software, formal analysis, and visualization. LW contributed to methodology and software. XG contributed to methodology, formal analysis, and visualization. CH supervised and administered the project. JW acquired funding. YW supervised and administered the project and acquired funding. KM had full access to the data and takes responsibility for the integrity of the data and the accuracy of the analysis. YW supervised the study and takes responsibility for the overall content. All listed authors reviewed and approved the final manuscript.

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