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Frailty and the Incidence of Major Ocular Diseases: A Prospective Cohort Study Integrating Proteomic Mediation Analysis

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Abstract

Background

The long-term association between frailty phenotype and major vision-threatening ocular diseases (age-related macular degeneration (AMD), diabetic retinopathy (DR), glaucoma, and cataract), as well as the underlying molecular mechanisms, remain unclear.

Methods

Cox proportional hazards models were used to assess the association between frailty status (classified as non-frail, prefrail, or frail) and the risk of four ocular diseases. Olink proteomics identified plasma proteins signatures associated with frailty status and ocular diseases. Mediation analysis assessed the overall and stage-specific (prefrail vs. frail) proteins as potential mediators.

Results

During a median follow-up of 15.7 years, prefrailty and frailty were associated with significantly elevated risks of AMD (Prefrail: HR = 1.17; Frail: HR = 1.49), DR (Prefrail: HR = 1.96; Frail: HR = 3.91), glaucoma (Prefrail: HR = 1.13; Frail: HR = 1.61), and cataract (Prefrail: HR = 1.16; Frail: HR = 1.49) (all $P < 0.001$). Proteomic profiling revealed 1,068 and 1,387 proteins associated with prefrailty and frailty, respectively, enriched in immune-inflammatory pathways (e.g., leukocyte migration). Similarly, proteins associated with all four ocular diseases were enriched in inflammatory and cell adhesion pathways. Mediation analysis further demonstrated that a spectrum of plasma proteins partially explained these associations, with a stage-specific escalation in the proportion of harmful mediators observed in DR.

Conclusions

These findings establish a significant link between frailty and common ocular diseases, unveiling a mediating role of systemic inflammatory and extracellular matrix proteins, with a progressive, stage-specific pattern in DR. These results highlight frailty as both a marker of shared pathways in systemic and ocular aging, and a potential integrated biomarker for interventions aimed at preventing vision loss.

1. Introduction

Age-related macular degeneration (AMD), diabetic retinopathy (DR), glaucoma, and cataract are major causes of vision loss and blindness in middle-aged and older adults globally, contributing to a significant personal and public health burden[1]. While traditional risk factors such as advanced age[2, 3], genetic susceptibility[4], smoking[5], hypertension[6], and diabetes[7] are well recognized, growing evidence suggests

that systemic physiological decline may play a critical role in the development and progression of these ocular diseases[8].

Frailty is a geriatric syndrome characterized by reduced multisystem physiological reserve, manifesting as diminished resilience to minor stressors[9]. It not only predicts higher risks of falls, hospitalization, and mortality but is also regarded as a robust marker of biological aging[10]. The core mechanisms underlying frailty involve chronic low-grade inflammation, oxidative stress, and immune dysregulation[11], which have also been implicated in various ocular pathological processes, such as retinal degeneration[12], microvascular damage[13], and lens opacification[14]. This mechanistic overlap suggests that frailty and ocular diseases may share common biological underpinnings.

While cross-sectional and disease-specific studies have reported links between frailty and various ophthalmic parameters or disease risks[15–17], large-scale prospective studies systematically evaluating the relationship between frailty and multiple sight-threatening diseases remain scarce. Moreover, the biological pathways linking systemic frailty to ocular pathology are not well defined. High-throughput plasma proteomics offers a powerful approach to uncover shared molecular signatures, offering insights into biomarkers and potential therapeutic targets for these age-related conditions.

To address these gaps, we conducted a prospective cohort study using data from the UK Biobank to investigate the associations between the frailty phenotype and the incidence of four major ocular diseases (AMD, DR, glaucoma, and cataract). We further evaluated potential effect modifications by age, sex, and BMI. By integrating large-scale plasma proteomic profiling, we aimed to identify circulating protein signatures associated with both frailty and ocular diseases, and to assess their potential mediating roles in the observed epidemiological links. Our findings are expected to provide novel insights into the biological connections between systemic frailty and ocular health.

2. Materials and methods

2.1 Study design and population

The UKB is a large, multicenter (covering England, Scotland, and Wales) prospective cohort study that enrolled over 500,000 participants aged 40 to 69 years between 2006 and 2010[18]. Each participant completed touchscreen questionnaires, verbal interviews, physical examinations, and provided biological samples. Ethical approval was granted by the North West Multi-Centre Research Ethics Committee (Ref: 11/NW/0382), and all participants provided written informed consent. The present study is a part of the UKB project (Application ID: 540454).

As shown in **Figure S1**, 502,128 participants were initially included. Individuals with missing data on frailty phenotype assessment (N = 41,000) and those diagnosed with AMD, DR, glaucoma, or cataract at baseline were excluded. A total of 456,849 participants were retained for the primary analysis. For the

proteomics sub-analysis, an additional 41,118 individuals without available proteomic data were excluded, resulting in a final sample size of 411,18 participants.

2.2 Assessment of exposure: frailty phenotype

Given that the measurements collected by UKB differed from those in the Cardiovascular Health Study on which Fried's original definition of frailty phenotype was based[19], this study adopted the modified version proposed by Peter *et al.* to assess frailty status, adapted to the UKB data structure[20]. The frailty phenotype was determined based on the following five criteria: unintentional weight loss, exhaustion, low physical activity, slow walking speed, and weak grip strength (see **Supplementary Table S1** for details). Participants were categorized into three groups according to the number of criteria met: non-frail (0 criteria), prefrail (1–2 criteria), or frail (≥ 3 criteria)[21]. For analytical purposes requiring a continuous measure, the total number of fulfilled criteria (range 0–5) was also used as a continuous score, directly derived from the same five-item phenotype. Individuals with missing data on any of the five frailty indicators were excluded from the analysis.

2.3 Assessment of outcome

Participants free of target ocular diseases at baseline were followed up from recruitment until the first occurrence of an ocular event, death, loss to follow-up, or the end of follow-up, whichever occurred first.

Incident cases of age-related macular degeneration (AMD), diabetic retinopathy (DR), glaucoma, and cataract were identified through a comprehensive case ascertainment strategy. This strategy integrated three primary data sources within the UK Biobank: (1) hospital inpatient records coded with the International Classification of Diseases, Ninth or Tenth Revisions (ICD-9/ICD-10); (2) touchscreen questionnaire items related to eye problems and age at diagnosis; and (3) self-reported medical conditions. The specific diagnostic codes and data fields used to define each disease are provided in **Supplementary Table S2.**

2.4 OLINK proteomics

During the baseline period (2006–2010), UKB randomly collected 54,306 plasma samples, which were sent to the Olink Bioscience Analytical Service Center in Sweden. Quantitative detection of proteins in four functional panels (Cardiometabolic, Inflammation, Neurology, and Oncology) was performed using the Olink Explore 3072 platform. Detailed procedures for sample selection, processing, data normalization, and strict quality control measures have been fully disclosed in the official document UKB (https://biobank.ndph.ox.ac.uk/ukb/ukb/docs/Olink_proteomics_data.pdf), and the related methods have also been described in detail in previous studies[22]. After excluding proteins with a missing rate exceeding 20%, a total of 2,916 high-quality plasma proteins were finally included in this study. All protein expression levels were log2-transformed and standardized for subsequent analyses. The full names and abbreviations of each protein are provided in **Supplementary Table S3**.

2.5 Covariates

This study included potential confounding factors associated with frailty status and ocular disease risk: (1) Sociodemographic factors: age (continuous), sex (categorical, male or female), race and ethnicity (White/Caucasian, Black/African American, or Other); (2) Socioeconomic status indicators: educational level (College and above/Below college), household income (less than £31,000/more than £31,000), and the Townsend Deprivation Index (TDI, continuous). The TDI was calculated based on national census data, incorporating indicators such as unemployment, overcrowding, and home and car ownership, with higher values indicating more severe socioeconomic deprivation[23]; (3) Anthropometric indicators: BMI (kg/m², categorical), which was divided into normal weight (< 25), overweight (25-29.9), and obesity (≥ 30); (4) Health behavior indicators: smoking status (categorical, never, former, or current smoker), alcohol intake frequency (categorical, Daily or almost daily/Three or four times a week/Once or twice a week/One to three times a month/Special occasions only/Never), and metabolic equivalent task (MET) physical activity level (min/wk, categorical, low, moderate, or high). Among the above variables, age was calculated based on birth dates, while sex, race and ethnicity, educational level, smoking, and alcohol intake were self-reported at baseline. BMI was obtained from baseline physical measurements, and MET was assessed using the International Physical Activity Questionnaire. The TDI was matched to regional-level statistical data based on the residential postcode of participants.

2.6 Statistical analysis

First, the baseline characteristics of participants were described by frailty status (non-frail, prefrail, and frail). Continuous variables were presented as mean ± standard deviation, and intergroup comparisons were performed using the weighted t-test or Kruskal-Wallis H test. Categorical variables were expressed as frequencies and percentages, and the chi-square test was used for intergroup comparisons. For covariates with a missing rate below 20%, multiple imputation was used to fill in the missing values[24].

Cox proportional hazards models were applied to evaluate the association between frailty phenotype and the incidence risk of four ocular diseases, with hazard ratios (HRs) and their 95% confidence intervals (CIs) calculated. Three sequentially adjusted models were established: Model 1 was unadjusted for any covariates; Model 2 was adjusted for age, sex, and race and ethnicity; Model 3 was further adjusted for educational level, household income, TDI, BMI, smoking status, alcohol intake frequency, and MET based on Model 2.

To further explore the effect modification, stratified interaction analyses were performed by age (< 60 years vs. ≥60 years), sex (female vs. male), and BMI (< 25 kg/m² vs. 25.0-29.9 kg/m² vs. ≥30 kg/m²). Sensitivity analyses included: (1) excluding participants without proteomic data; (2) excluding individuals who developed new-onset ocular diseases within two years of follow-up to reduce the possibility of reverse causality.

In the proteomic analysis, linear regression models were first used to assess the association between frailty phenotype and the level of plasma protein, with the non-frail group serving as the reference. Meanwhile, Cox regression models were used to screen proteins associated with the incidence risk of four ocular diseases. For the three comparisons of frailty phenotype in Model 3 (prefrail vs. non-frail, frail

vs. non-frail, and trend test), the Benjamini-Hochberg (BH) method was used to calculate the false discovery rate (FDR), respectively. An FDR < 0.05 was considered statistically significant.

Furthermore, pathway enrichment analysis was performed on the significantly associated proteins using the Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) databases to explore biological pathways and functions related to frailty phenotype or four ocular diseases.

Mediation analysis was conducted using the “mediation” package in R software. In these models, frailty was operationalized as the continuous score (range 0–5) representing the count of fulfilled frailty criteria, which was used to evaluate the mediating effects of specific plasma proteins on its association with the incidence risk of ocular diseases. A total of 5,000 bootstraps were employed as a validated method to estimate the bias-corrected confidence intervals. All mediation analyses were adjusted for all covariates in Model 3, and the mediation proportion and *P* value were reported in the results.

To examine whether the mediating effects of plasma proteins differed across the spectrum of frailty, we conducted a stratified analysis based on each protein’s prior association with frailty status. Specifically, significant mediating proteins were stratified into two groups: those that were more strongly associated with the prefrail state and those more strongly associated with the frail state. This approach allowed us to separately assess the mediation patterns in earlier versus more advanced stages of frailty. The distributions of mediation proportions between these two groups were compared using the Wilcoxon rank-sum test.

All statistical analyses were performed using R software (version 4.3.2, http://www.r-project.org). A two-tailed *P* value < 0.05 was considered statistically significant.

3. Results

3.1 Baseline characteristics of the study population

In this study with a median follow-up of 15.7 years (interquartile range: 14.8–16.5 years) among 456,849 UKB participants, 170,530 prefrail cases and 15,725 frail cases were documented. The mean age of the study population was 56.4 ± 8.1 years, with females accounting for 53.9% (N = 246,341). The baseline characteristics stratified by frailty phenotype are detailed in Table 1.

Overall, compared with non-frail participants, frail individuals tended to be older, predominantly female, have a higher proportion of non-White ethnicity, lower educational level, lower household income, and higher TDI scores. They also had a higher prevalence of obesity, current smoking, lower alcohol intake frequency, and low physical activity levels.

Table 1
Baseline characteristics of participants by frailty phenotype*.

Variable	Total (N = 456,849)	Non-frail (N = 270,594)	Prefrail (N = 170,530)	Frail (N = 15,725)	*P* value
Age, y (SD)	56.4 (8.1)	56.2 (8.1)	56.6 (8.1)	57.8 (7.6)	< 0.001
Sex, n (%)					< 0.001
Female	246,341 (53.9)	139,577 (51.6)	96,904 (56.8)	9,860 (62.7)	
Male	210,508 (46.1)	131,017 (48.4)	73,626 (43.2)	5,865 (37.3)	
Race and ethnicity, n (%)					< 0.001
White/Caucasian	434,439 (95.1)	261,586 (96.7)	158,984 (93.2)	13,869 (88.2)	
Black/African American	6,698 (1.5)	2,716 (1.0)	3,474 (2.0)	508 (3.2)	
Other	15,712 (3.4)	6,292 (2.3)	8,072 (4.7)	1,348 (8.6)	
Educational level, n (%)					< 0.001
College and above	53,549 (11.7)	34,711 (12.8)	17,722 (10.4)	1,116 (7.1)	
Below college	403,300 (88.3)	235,883 (87.2)	152,808 (89.6)	14,609 (92.9)	
Household income					< 0.001
Less than £31,000	221,390 (48.5)	115,870 (42.8)	93,485 (54.8)	12,035 (76.5)	
Greater than £31,000	235,459 (51.5)	154,724 (57.2)	77,045 (45.2)	3,690 (23.5)	
TDI (SD)	-1.4 (3.1)	-1.7 (2.9)	-1.0 (3.2)	0.6 (3.6)	< 0.001
BMI, kg/m² (SD)					< 0.001
< 25.0	151,734 (33.2)	103,457 (38.2)	45,635 (26.8)	2,642 (16.8)	
25.0-29.9	194,661 (42.6)	118,792 (43.9)	71,113 (41.7)	4,756 (30.2)	

Variable	Total (N = 456,849)	Non-frail (N = 270,594)	Prefrail (N = 170,530)	Frail (N = 15,725)	*P* value
≥ 30	110,454 (24.2)	48,345 (17.9)	53,782 (31.5)	8,327 (53.0)	
Smoking status, n (%)					< 0.001
Never	250,117 (54.7)	152,941 (56.5)	90,016 (52.8)	7,160 (45.5)	
Former	159,005 (34.8)	93,507 (34.6)	60,071 (35.2)	5,427 (34.5)	
Current	47,727 (10.4)	24,146 (8.9)	20,443 (12.0)	3,138 (20.0)	
Alcohol intake frequency, n (%)					< 0.001
Daily or almost daily	94,701 (20.7)	62,739 (23.2)	30,296 (17.8)	1,666 (10.6)	
Three or four times a week	107,108 (23.4)	71,108 (26.3)	34,300 (20.1)	1,700 (10.8)	
Once or twice a week	118,444 (25.9)	70,855 (26.2)	44,388 (26.0)	3,201 (20.4)	
One to three times a month	50,803 (11.1)	27,858 (10.3)	21,055 (12.3)	1,890 (12.0)	
Special occasions only	50,964 (11.2)	23,481 (8.7)	23,732 (13.9)	3,751 (23.9)	
Never	34,829 (7.6)	14,553 (5.4)	16,759 (9.8)	3,517 (22.4)	
MET, min/wk, n (%)					< 0.001
Low	84,125 (18.4)	40,982 (15.1)	36,500 (21.4)	6,643 (42.2)	
Moderate	188,209 (41.2)	113,168 (41.8)	69,480 (40.7)	5,561 (35.4)	
High	184,515 (40.4)	116,444 (43.0)	64,550 (37.9)	3,521 (22.4)	

* Data were presented as frequency (%), or mean (standard deviation). Abbreviations: BMI, body mass index; TDI, Townsend deprivation index; MET, metabolic equivalent task.

3.2 Association between frailty phenotype and common ocular diseases

Cox proportional hazards model analysis showed that the frailty phenotype was significantly and positively correlated with the incidence risk of the four major ocular diseases, and this association

remained robust after sequential adjustment for confounding factors (Table 2). In the fully adjusted model (Model 3), compared with non-frail participants, prefrail participants had a significantly increased risk of developing AMD (HR = 1.17, 95%CI = 1.12–1.22, $P < 0.001$), DR (HR = 1.96, 95%CI = 1.82–2.11, $P < 0.001$), glaucoma (HR = 1.13, 95%CI = 1.08–1.18, $P < 0.001$), and cataract (HR = 1.16, 95%CI = 1.13–1.19, $P < 0.001$). The risks were further exacerbated in frail individuals: AMD (HR = 1.49, 95%CI = 1.35–1.63), DR (HR = 3.91, 95%CI = 3.50–4.38), glaucoma (HR = 1.61, 95%CI = 1.46–1.77), and cataract (HR = 1.49, 95%CI = 1.40–1.57), with all P values < 0.001.

In addition, there was a significant positive relationship between frailty status and the incidence risk of the four ocular diseases, with all P values for trend < 0.001. Consistent with this trend, when frailty was analyzed as the continuous score (range 0–5) as described in the Methods, per unit increase was associated with significantly elevated risks for all four diseases.

Table 2
Association between frailty phenotype and common ocular diseases.

	Model 1		Model 2		Model 3	
	HR (95%CI)	***P***	**HR (95%CI)**	***P***	**HR (95%CI)**	***P***
AMD						
Non-frail	Reference		Reference		Reference	
Prefrail	1.30 (1.25, 1.36)	**< 0.001**	1.21 (1.16, 1.26)	**< 0.001**	1.17 (1.12, 1.22)	**< 0.001**
Frail	1.94 (1.78, 2.12)	**< 0.001**	1.64 (1.50, 1.80)	**< 0.001**	1.49 (1.35, 1.63)	**< 0.001**
P for trend	**< 0.001**		**< 0.001**		**< 0.001**	
Per unit	1.23 (1.21, 1.26)	**< 0.001**	1.17 (1.14, 1.19)	**< 0.001**	1.14 (1.11, 1.16)	**< 0.001**
DR						
Non-frail	Reference		Reference		Reference	
Prefrail	2.72 (2.53, 2.92)	**< 0.001**	2.65 (2.46, 2.85)	**< 0.001**	1.96 (1.82, 2.11)	**< 0.001**
Frail	8.87 (8.00, 9.82)	**< 0.001**	8.15 (7.34, 9.05)	**< 0.001**	3.91 (3.50, 4.38)	**< 0.001**
P for trend	**< 0.001**		**< 0.001**		**< 0.001**	
Per unit	1.92 (1.87, 1.97)	**< 0.001**	1.88 (1.83, 1.93)	**< 0.001**	1.53 (1.48, 1.57)	**< 0.001**
Glaucoma						
Non-frail	Reference		Reference		Reference	
Prefrail	1.19 (1.14, 1.24)	**< 0.001**	1.14 (1.09, 1.19)	**< 0.001**	1.13 (1.08, 1.18)	**< 0.001**
Frail	1.87 (1.71, 2.05)	**< 0.001**	1.67 (1.53, 1.83)	**< 0.001**	1.61 (1.46, 1.77)	**< 0.001**
P for trend	**< 0.001**		**< 0.001**		**< 0.001**	
Per unit	1.19 (1.17, 1.22)	**< 0.001**	1.15 (1.13, 1.18)	**< 0.001**	1.14 (1.12, 1.17)	**< 0.001**
Cataract						
Non-frail	Reference		Reference		Reference	

	Model 1		Model 2		Model 3	
	HR (95%CI)	***P***	**HR (95%CI)**	***P***	**HR (95%CI)**	***P***
Prefrail	1.31 (1.28, 1.35)	**< 0.001**	1.22 (1.19, 1.25)	**< 0.001**	1.16 (1.13, 1.19)	**< 0.001**
Frail	2.03 (1.92, 2.14)	**< 0.001**	1.71 (1.62, 1.81)	**< 0.001**	1.49 (1.40, 1.57)	**< 0.001**
P for trend	**< 0.001**		**< 0.001**		**< 0.001**	
Per unit	1.25 (1.23, 1.26)	**< 0.001**	1.18 (1.17, 1.20)	**< 0.001**	1.13 (1.12, 1.15)	**< 0.001**

Data are presented as HR (95%CI). Model 1: Non-adjusted. Model 2: Adjusted for age, sex, and race and ethnicity. Model 3: Adjusted for age, sex, race and ethnicity, educational level, income, Townsend deprivation index, body mass index, smoking status, alcohol intake frequency, and metabolic equivalent task.

3.3 Subgroup and sensitivity analyses

Results of the stratified interaction analysis showed that among the three stratification factors (age, sex, and BMI), only age had a significant modifying effect on the association between frailty phenotype and DR (*P* for interaction = 0.003) as well as glaucoma (*P* for interaction = 0.024). Particularly, the risk increments of DR and glaucoma associated with frailty were much greater in participants aged ≥ 60 years than in those aged < 60 years. In contrast, sex and BMI had no significant modifying effect on the association between frailty and the four ocular diseases (**Figure S2**).

Sensitivity analysis results indicated that the primary findings remained consistent even after excluding participants with follow-up duration less than two years or those without proteomic data, demonstrating good robustness of the study results (**Supplementary Table S4**).

3.4 Proteomic signature for frailty phenotype

In the subsample of 41,118 participants with available proteomic data (baseline characteristics shown in **Supplementary Table S5**), linear regression models identified 1,068 and 1,387 proteins significantly associated with prefrailty and frailty, respectively (FDR < 0.05, **Figs. 1A-B, Supplementary Table S6**).

GO enrichment analysis revealed that proteins associated with both prefrailty and frailty were significantly enriched in biological processes (BP) such as leukocyte migration, myeloid leukocyte migration, monocyte chemotaxis, and response to lipopolysaccharide (Figs. 1C-D, **Supplementary Table S7**). Prefrail-associated proteins showed prominent enrichment positive regulation of cell adhesion, leukocyte chemotaxis, and positive regulation of cytokine production, while frail-associated proteins were notably enriched in complement activation, extracellular matrix organization, and neutrophil activation.

At the cellular component (CC) level, common enrichments included the external side of plasma membrane, vesicle lumen, and collagen-containing extracellular matrix (ECM). For molecular function (MF), glycosaminoglycan binding and chemokine receptor binding were shared, whereas scavenger receptor activity, integrin binding, serine-type peptidase activity, indicating enhanced extracellular matrix degradation, and cell-matrix interactions were more specific to frailty.

KEGG pathway analysis further revealed involvement of frailty-associated proteins in inflammatory aging-related pathways such as the PPAR signaling pathway, EGFR tyrosine kinase inhibitor resistance, and antigen processing and presentation (Figs. 1C-D, **Supplementary Table S7**).

3.5 Proteomic signature of the four common ocular diseases

Cox regression analysis identified 333, 1,062, 214, and 260 proteins associated with the risk of AMD, DR, glaucoma, and cataract, respectively (Fig. 2A, **Supplementary Table S8**). After FDR correction, 8, 887, 1, and 18 proteins remained significant for each disease, respectively (**Figure S3, Supplementary Table S9**). Enrichment analysis showed that all four ocular diseases shared significant enrichment in inflammation-related BP terms such as cell-matrix adhesion, leukocyte migration, and positive regulation of chemotaxis (Fig. 2B, **Supplementary Table S10**). The integrin-mediated signaling pathway was uniquely enriched in DR and glaucoma. At the CC level proteins were commonly localized to structures like collagen-containing extracellular matrix, with the strongest enrichment signals observed for DR. Cytokine receptor binding was a shared MF term across all diseases. KEGG analysis revealed significant enrichment of the ECM-receptor interaction and cytokine-cytokine receptor interaction pathways in AMD, DR, and cataract.

3.6 Mediation analysis of proteins in the associations between frailty phenotype and common ocular diseases

Further mediation analysis identified proteins that exerted a significant mediating effect on the association between frailty and ocular diseases: 168 proteins for AMD, 749 proteins for DR, and 198 proteins for cataract, with the maximum mediation proportions reaching 10.04%, 32.36%, and 9.62%, respectively (**Supplementary Table S11**). Venn diagram intersection analysis was used to screen out mediating proteins that were simultaneously associated with frailty status and disease risk. These proteins were further divided into prefrail-specific and frail-specific groups according to their association strength with the prefrail or frail stage (Figs. 3A-C, **Supplementary Table S12**). Box plot results showed that in DR, prefrail-specific proteins were predominantly associated with positive pathogenic effects (72.7%, 16/22). The proportion of positive pathogenic effects further increased to 83.7% (123/147) in frail-specific proteins, with a statistically significant difference between the two groups (P = 0.0052). These findings suggest that the mediating effect of pathogenic proteins is continuously enhanced with the progression of frailty in DR (Figs. 3D-F).

In AMD, all prefrail-specific proteins showed positive pathogenic effects (100%, 5/5). In the frail-specific group, the proportion of negative protective proteins increased to 36.8% (7/19). Although the majority still exerted positive pathogenic effects (63.2%, 12/19), the difference between the two groups was not statistically significant (P = 0.84). There was no significant stage-specific difference in the mediating effect of proteins in cataract (P = 0.58).

Discussion

This large-scale prospective cohort study established that frailty is independently associated with an increased incidence of major ocular diseases, showing a graded risk relationship. This association remained robust after full adjustment for demographic, socioeconomic, and lifestyle factors, and was further verified by sensitivity analyses. High-throughput proteomic analysis further indicated that this association is partly mediated by circulating proteins involved in immune-inflammatory and extracellular matrix pathways. The mediating role of these proteins exhibited disease-specific patterns, including a progression-dependent effect in DR.

Our findings are consistent with the research trends regarding the relationship between frailty and visual dysfunction in recent years. Existing cross-sectional or retrospective studies have indicated that frailty is closely correlated with multiple ophthalmic structural parameters (e.g., lens density, retinal nerve fiber layer thickness, corneal endothelial cell density)[25, 26], and is significantly associated with visual function decline[27] and visual field defect[28]. Small-sample cohort studies combined with Mendelian randomization analyses have further supported that frailty has a causal effect on ocular diseases, potentially serving as one of the upstream driving factors of ocular aging[16]. In addition, the frailty index has been confirmed to be associated with an elevated risk of DR[29], while frail individuals exhibit a faster decline in retinal capillary density, suggesting impaired microvascular function[15]. Another study found that individuals with high frailty severity combined with high genetic risk had a significantly higher risk of irreversible ocular diseases than those with low genetic risk and no frailty[30]. Several recent prospective studies have also shown that frailty trajectory is associated with an increased risk of AMD, implying that early intervention for frailty may reduce the burden of ocular diseases in the elderly population[17, 31]. However, previous studies mostly focused on a single ocular disease or adopted a cross-sectional design, lacking systematic comparison among multiple ocular diseases and in-depth exploration from macro-phenotype to molecular mechanisms. In contrast, the large sample size, long-term follow-up, and multi-dimensional analysis of this study provide more reliable epidemiological evidence for the association between frailty and ocular diseases.

Subgroup analysis showed that age had a modifying effect on the association between frailty and DR as well as glaucoma. The risk increment of disease onset induced by frailty was more significant in participants aged ≥ 60 years. This may be attributed to the inherent decline in physiological reserve and cumulative tissue damage in the elderly population, which makes them more likely to exceed the compensatory threshold when facing systemic stress, thus accelerating the progression of

microvascular and neurodegenerative lesions. Especially for DR, hyperglycemia itself can induce chronic inflammation and endothelial dysfunction. Superimposed with the systemic homeostasis imbalance represented by frailty, it may further exacerbate retinal microcirculation damage. The above findings emphasize that routine frailty screening should be implemented in middle-aged and elderly populations in clinical practice, particularly the identification of the prefrailty stage, which is conducive to early warning and targeted intervention of ocular diseases. As advocated by Dinarvand *et al.*, integrating frailty assessment into routine ophthalmic diagnosis and treatment processes may promote interdisciplinary collaboration and improve the quality of comprehensive management for elderly patients[32].

Our proteomic analyses provide direct molecular evidence linking systemic frailty to ocular disease risk, centered on the mechanism of inflammaging. Proteins associated with both prefrailty and frailty were enriched in immune activation pathways (e.g., leukocyte migration, complement activation), mirroring the chronic low-grade inflammation recognized as a core mechanism of frailty[33, 34]. Notably, the transition from prefrailty (enriched in positive regulation of cell adhesion and cytokine production) to frailty (enriched in complement activation and extracellular matrix organization) suggests a progression from early immune mobilization to sustained inflammation and tissue remodeling.

Crucially, these systemic inflammatory and tissue-remodeling pathways were mirrored at the ocular level. Proteins associated with AMD, DR, glaucoma, and cataract were commonly enriched in processes such as leukocyte migration and cell-matrix adhesion, reinforcing chronic inflammation as a shared pathological basis. This is consistent with established evidence implicating specific inflammatory pathways in these diseases, such as complement activation in AMD[35]. Furthermore, the specific enrichment of the integrin-mediated signaling pathway in DR and glaucoma highlights a disease-specific emphasis on cell-matrix interactions and vascular or neuronal barrier integrity, which is supported by prior identification of integrins like ITGA5 and ITGAM in DR pathology[36, 37].

Collectively, these findings support a model wherein the systemic inflammatory and tissue-remodeling state captured by the frailty phenotype, particularly its progression from prefrailty to frailty, creates a permissive environment that exacerbates shared pathogenic pathways, thereby elevating the risk for multiple ocular diseases.

The mediation analysis revealed a distinct disease- and stage-specific pattern in how plasma proteins link frailty to ocular diseases. This was most pronounced in DR, which exhibited both the highest overall mediation proportion and a significant increase in the proportion of proteins with detrimental mediating effects from the prefrail to the frail stage ($P = 0.0052$). This suggests a dynamic, cumulative pathogenic burden where progressive frailty activates or upregulates an increasing number of disease-promoting proteins, thereby amplifying DR risk. In contrast, the mediating effects for AMD and cataract showed different patterns. Although mediation was present in AMD, no significant stage-specific difference was observed. For cataract, the direction of mediation was largely balanced. This indicates that the core drivers of these diseases, such as strong genetic determinants in AMD[38] or localized aging processes in

cataract[39], may dominate their etiology. Frailty likely exerts its influence by exacerbating a shared inflammatory milieu, resulting in a more static mediation profile.

These findings underscore the selective impact of frailty on ocular disease pathways. For DR, monitoring the progression of frailty is crucial for assessing dynamically increasing risk. For AMD and cataract, clinical focus might remain primarily on disease-specific risk factors, with frailty management serving as a complementary systemic approach.

The main strengths of this study lie in the large sample size of the UKB and the long median follow-up duration of 15.7 years, which ensure the statistical power and reliability of the study results. In addition, the abundant phenotypic data and high-quality proteomic resources facilitate relatively comprehensive adjustment of confounding factors and in-depth analysis of biological mechanisms. Finally, the combination of Cox proportional hazards models, proteomic analysis, mediation analysis, and stage-specific exploration enables an in-depth investigation of the association and mechanisms between frailty and ocular diseases.

This study also has certain limitations. First, the study population was predominantly of European ancestry, which may limit the generalization of the results to other ethnic groups. Second, although a series of potential confounding factors were adjusted, observational studies cannot completely eliminate residual confounding bias due to their inherent nature. Third, proteomic data were derived from a single baseline plasma sample, failing to capture the dynamic changes in protein expression, which may affect the accuracy of mediating effect estimation. Fourth, the diagnosis of ocular diseases was based on ICD codes, questionnaire data, and self-reported information, which carries a certain risk of misclassification bias. Finally, the Olink platform covers approximately 3,000 proteins. Although it includes multiple functional modules, it does not cover the entire plasma proteome, and future studies need to combine broader-spectrum technologies for further verification.

Conclusion

In conclusion, our study establishes a clear link between the systemic frailty phenotype and an increased risk of major ocular diseases—AMD, DR, glaucoma, and cataract. This association is partially mediated by plasma proteins involved in systemic inflammation and tissue remodeling, with a distinct, stage-specific pattern evident in DR. These results position frailty as a valuable, integrative clinical indicator for identifying individuals at high risk of vision loss and advocate for its assessment to be incorporated into the holistic management of aging populations.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

Ziyu Wang and Zhimin Deng contributed to the conceptualization and design of the study. Ning Tao collected, screened, and curated the data, performed the visual analysis and formal analysis, and was the primary contributor to the writing of the manuscript. Jiayu Wang, Xuan Xiao, and Cheng Pei assisted in data interpretation and critically revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data used in this study can be accessed through the links provided in the article. Further queries can be directed to the corresponding author.

References

1. Blindness GBD, Vision Impairment C, Vision Loss Expert Group of the Global Burden of Disease S. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of

avoidable blindness in relation to VISION 2020: the Right to Sight: an analysis for the Global Burden of Disease Study. Lancet Glob Health. 2021;9(2):e144–60.

2. Wang K, Xie Y, Lin Y, et al. Unveiling the link: aging and its impact on ocular diseases. Exp Eye Res. 2025;259:110551.
3. You L, Lin Y, Zheng Y, et al. The Impact of Aging on Ocular Diseases: Unveiling Complex Interactions. Aging Dis. 2024;16(5):2803–30.
4. Seddon JM. Genetic and environmental underpinnings to age-related ocular diseases. Invest Ophthalmol Vis Sci. 2013;54(14):ORSF28–30.
5. Kai JY, Zhou M, Li DL, et al. Smoking, dietary factors and major age-related eye disorders: an umbrella review of systematic reviews and meta-analyses. Br J Ophthalmol. 2023;108(1):51–7.
6. Cheung CY, Biousse V, Keane PA, et al. Hypertensive eye disease. Nat Rev Dis Primers. 2022;8(1):14.
7. Wright WS, Eshaq RS, Lee M, et al. Retinal Physiology and Circulation: Effect of Diabetes. Compr Physiol. 2020;10(3):933–74.
8. Takefuji Y. Frailty and eye diseases: a review of the literature. Eye (Lond). 2024;38(4):648.
9. Chen X, Mao G, Leng SX. Frailty syndrome: an overview. Clin Interv Aging. 2014;9:433–41.
10. Yang ZC, Lin H, Jiang GH, et al. Frailty Is a Risk Factor for Falls in the Older Adults: A Systematic Review and Meta-Analysis. J Nutr Health Aging. 2023;27(6):487–595.
11. Salvioli S, Basile MS, Bencivenga L, et al. Biomarkers of aging in frailty and age-associated disorders: State of the art and future perspective. Ageing Res Rev. 2023;91:102044.
12. Pfeiffer RL, Marc RE, Jones BW. Persistent remodeling and neurodegeneration in late-stage retinal degeneration. Prog Retin Eye Res. 2020;74:100771.
13. Mauricio D, Gratacos M, Franch-Nadal J. Diabetic microvascular disease in non-classical beds: the hidden impact beyond the retina, the kidney, and the peripheral nerves. Cardiovasc Diabetol. 2023;22(1):314.
14. Ma Z, Liu J, Li J, et al. Klotho ameliorates the onset and progression of cataract via suppressing oxidative stress and inflammation in the lens in streptozotocin-induced diabetic rats. Int Immunopharmacol. 2020;85:106582.
15. Zhong P, Liu R, Zhu Z, et al. Frailty and risk of microvascular disease in adults with prediabetes. Diabetes Metab Syndr. 2024;18(1):102942.
16. Zhong Y, Qin Y. Frailty-Driven Risk Stratification in Age-Related Ophthalmic Diseases: Thresholds, Precision Screening, and Mendelian Randomization Insights. Transl Vis Sci Technol. 2025;14(12):17.
17. Peng Y, Zhang Y, Kam KW, et al. Dynamic frailty trajectories and risk of age-related macular degeneration: a prospective cohort study in UK Biobank. Geroscience; 2026.
18. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12(3):e1001779.
19. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol Biol Sci Med Sci. 2001;56(3):M146–56.

20. Hanlon P, Nicholl BI, Jani BD, et al. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. Lancet Public Health. 2018;3(7):e323–32.
21. Ma T, He L, Luo Y, et al. Frailty, an Independent Risk Factor in Progression Trajectory of Cardiometabolic Multimorbidity: A Prospective Study of UK Biobank. J Gerontol Biol Sci Med Sci. 2023;78(11):2127–35.
22. Sun BB, Chiou J, Traylor M, et al. Plasma proteomic associations with genetics and health in the UK Biobank. Nature. 2023;622(7982):329–38.
23. Health, Deprivation P, Townsend P, Phillimore. A Beattie Health and Deprivation Published by Croom Helm 212pp pound19.95 0-7099-4351-2 [Formula: see text]. Nurs Stand. 1988;2(17):34.
24. Deng Z, Wei Y, Dai F, et al. Association between parity and female mortality: the mediative role of depressive symptoms. Hum Reprod. 2024;39(10):2341–52.
25. Pathai S, Shiels PG, Weiss HA, et al. Ocular parameters of biological ageing in HIV-infected individuals in South Africa: relationship with chronological age and systemic biomarkers of ageing. Mech Ageing Dev. 2013;134(9):400–6.
26. Pathai S, Gilbert CE, Lawn SD, et al. Assessment of candidate ocular biomarkers of ageing in a South African adult population: relationship with chronological age and systemic biomarkers. Mech Ageing Dev. 2013;134(7–8):338–45.
27. Klein BE, Klein R, Knudtson MD, Lee KE. Relationship of measures of frailty to visual function: the Beaver Dam Eye Study. Trans Am Ophthalmol Soc. 2003;101:191-6; discussion 6–9.
28. Bernstein IA, Fisher AC, Singh K, Wang SY. The Association Between Frailty and Visual Field Loss in US Adults. Am J Ophthalmol. 2024;257:38–45.
29. Xuehao C, Dejia W, Xiaorong L. Integration of Immunometabolic Composite Indices and Machine Learning for Diabetic Retinopathy Risk Stratification: Insights from NHANES 2011–2020. Ophthalmol Sci. 2025;5(6):100854.
30. Xu Z, Lin R, Wang X, et al. Association of Physical Frailty and Genetic Predisposition with Risk of Irreversible Eye Diseases. Ophthalmol Sci. 2026;6(1):100910.
31. Zhu X, Huang Y, Liang L et al. Frailty and the Risk of Age-Related Macular Degeneration: A Prospective Cohort and Mendelian Randomization Study. J Gerontol Biol Sci Med Sci 2025;80(3).
32. Dinarvand D, Panthakey J, Hassan A, Ahmed MH. Frailty and Visual Impairment in Elderly Individuals: Improving Outcomes and Modulating Cognitive Decline Through Collaborative Care Between Geriatricians and Ophthalmologists. Diseases 2024;12(11).
33. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol. 2018;15(9):505–22.
34. Wilson D, Jackson T, Sapey E, Lord JM. Frailty and sarcopenia: The potential role of an aged immune system. Ageing Res Rev. 2017;36:1–10.

35. Whitmore SS, Sohn EH, Chirco KR, et al. Complement activation and choriocapillaris loss in early AMD: implications for pathophysiology and therapy. Prog Retin Eye Res. 2015;45:1–29.
36. Povedano E, Rejas-Gonzalez R, Montero-Calle A, et al. Electrochemical immunosensing for rapid glaucoma disease diagnosis through simultaneous determination of SPP1 and GAS6 proteins in ocular fluids. Talanta. 2026;296:128438.
37. Rejas-Gonzalez R, Montero-Calle A, Valverde A et al. Proteomics Analyses of Small Extracellular Vesicles of Aqueous Humor: Identification and Validation of GAS6 and SPP1 as Glaucoma Markers. Int J Mol Sci 2024;25(13).
38. Toomey CB, Johnson LV, Bowes Rickman C. Complement factor H in AMD: Bridging genetic associations and pathobiology. Prog Retin Eye Res. 2018;62:38–57.
39. Cvekl A, Vijg J. Aging of the eye: Lessons from cataracts and age-related macular degeneration. Ageing Res Rev. 2024;99:102407.

Figures

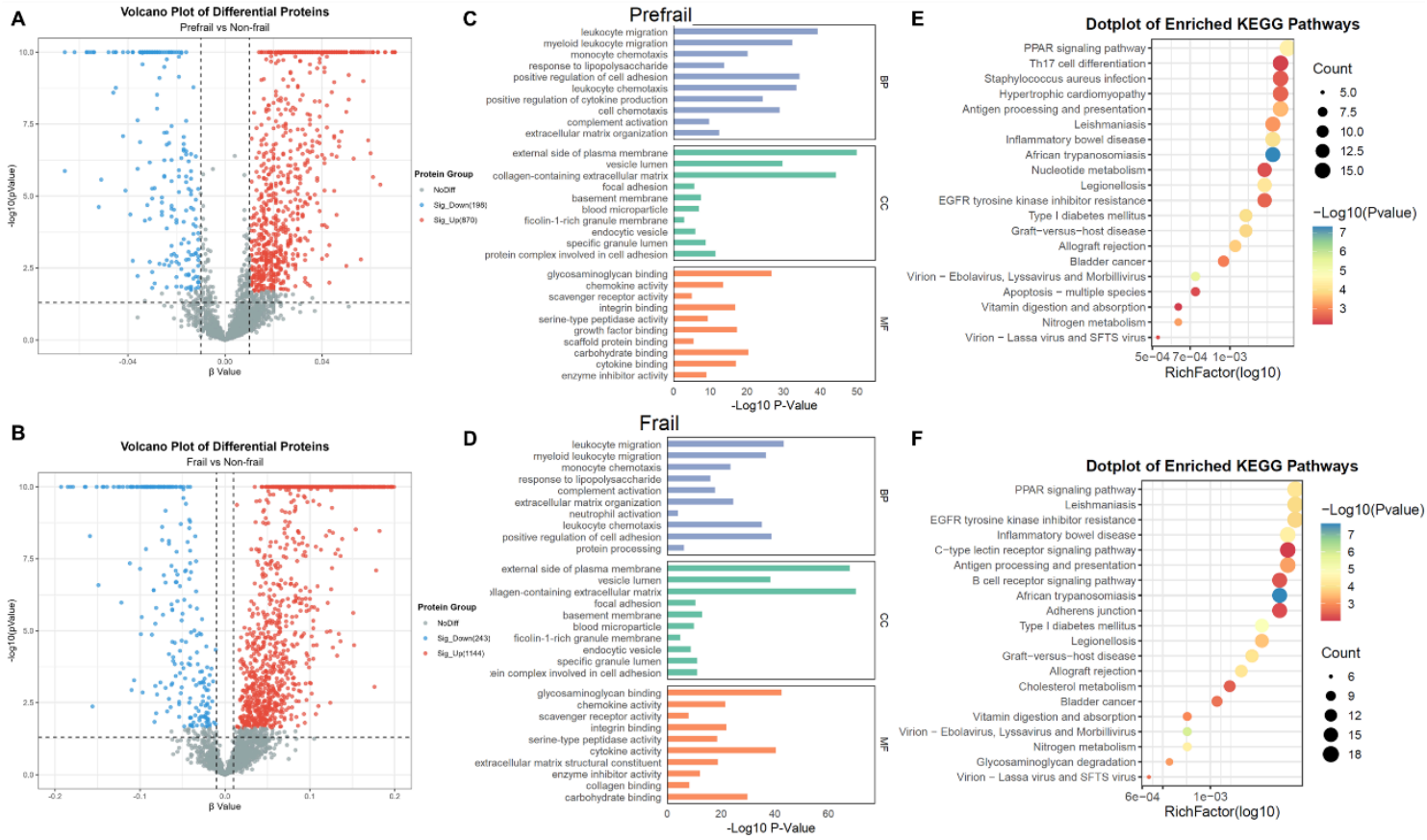


Figure 1

Enrichment analyses of frailty phenotype-associated proteins.

(A-B) Volcano plots showing the associations between 2,916 plasma proteins and the risk of prefrail (A) and frail (B) status. Significantly associated proteins were labeled with a false discovery rate (FDR) <

0.05 as the threshold: red dots indicate significantly upregulated proteins (Sig_Up), blue dots indicate significantly downregulated proteins (Sig_Down), and gray dots indicate no significant difference (NoDiff). (C-D) Gene Ontology (GO) enrichment analyses of prefrail (C) and frail (D) associated proteins, covering three dimensions including biological process (BP), cellular component (CC), and molecular function (MF). Bar charts display the top 10 significantly enriched pathways. (E-F) The most significantly enriched signaling pathways of prefrail (E) and frail (F) associated proteins identified by Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis.

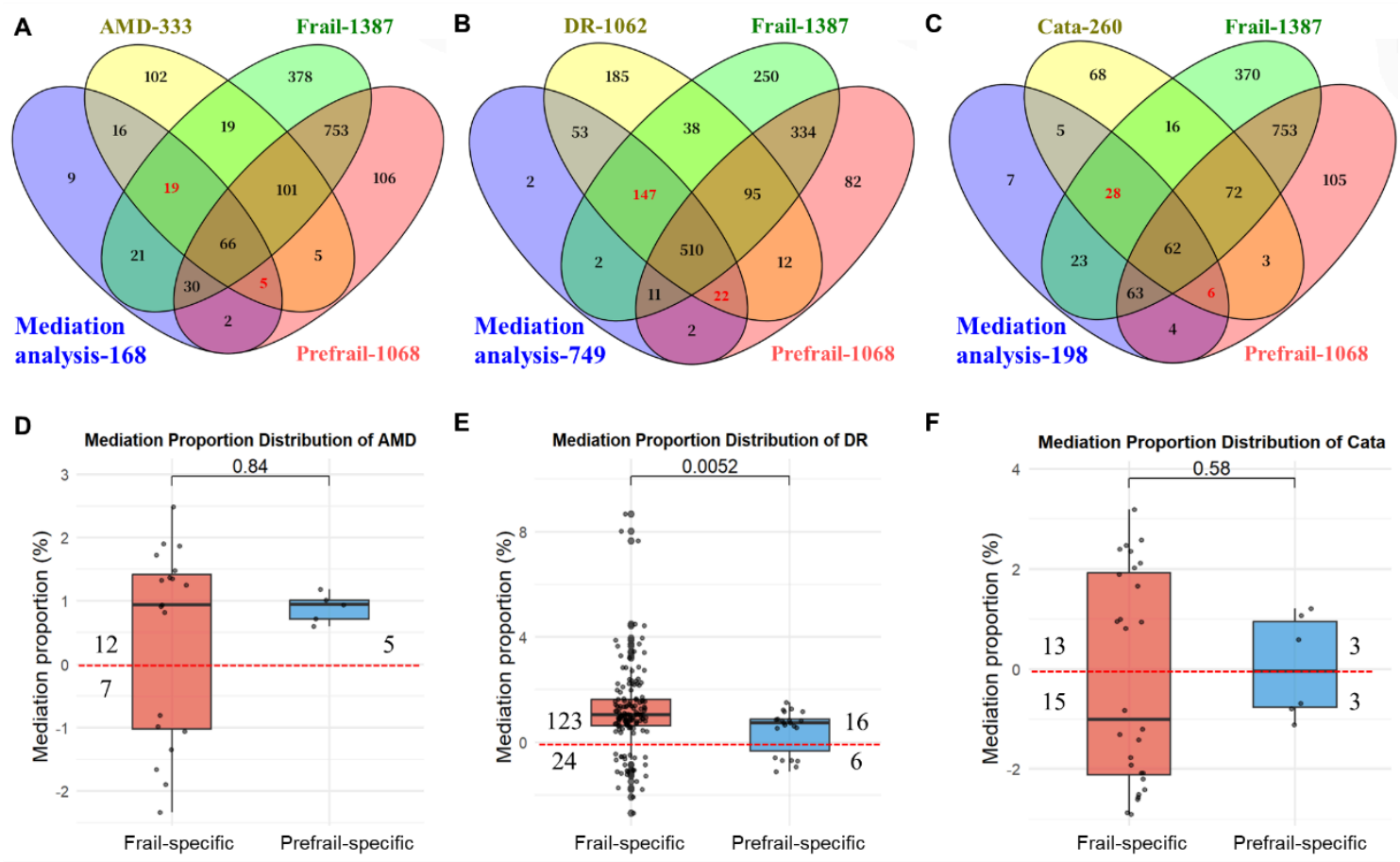


Figure 2

Screening of frailty phenotype specific mediating proteins and stage-specific analysis of their mediating effects.

(A-C) Venn diagrams showing the intersections of disease-associated proteins, frailty (prefrail and frail) associated proteins, and significant mediating proteins in AMD (A), DR (B), and CATA (C), which were used to screen out prefrail-specific and frail-specific core mediating proteins for each disease. (D-F) Box plots presenting the distribution of mediation proportions of the two types of specific proteins in AMD (D), DR (E), and CATA (F). The red dashed line represents the reference line with a mediation proportion of 0. The numbers above and below the dashed line indicate the counts of proteins exerting positive pathogenic and negative protective effects, respectively. Statistical differences were assessed

using the Wilcoxon rank-sum test. AMD, Age-related macular degeneration; DR：Diabetic retinopathy; GLA, Glaucoma; CATA：Cataract

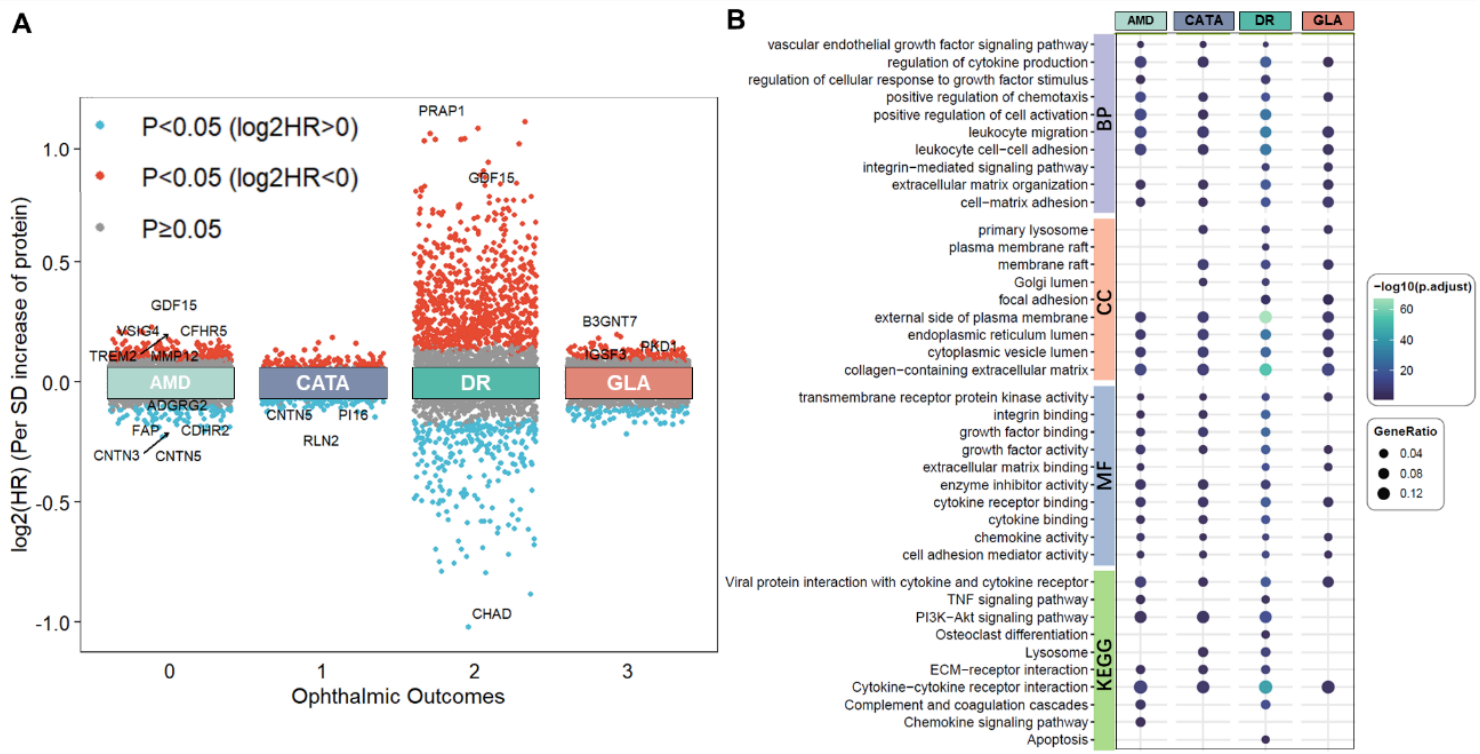


Figure 3

Bioinformatic analyses of proteins associated with four common ocular diseases.

(A) Combined volcano plots depicting the associations between 2,916 plasma proteins and the incidence risk of AMD, DR, glaucoma, and cataract. Several key proteins are labeled at the top. (B) Validated enriched pathways of proteins associated with AMD, glaucoma, and cataract identified by KEGG pathway analysis. AMD, Age-related macular degeneration; DR：Diabetic retinopathy; GLA, Glaucoma; CATA：Cataract; Kyoto Encyclopedia of Genes and Genomes (KEGG)

Supplementary Files

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