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Interacting and joint effects of frailty and inflammation on cardiovascular disease risk and the mediating role of inflammation in middle-aged and elderly populations

Zihan Xu[1†], Yingbai Wang[1†], Xiaolin Li[1], Xuefei Hou[1], Suru Yue[1], Jia Wang[1], Shicai Ye[2*] and Jiayuan Wu[1*]

Abstract

Background Frailty and inflammation may increase the risk of cardiovascular disease (CVD), but their interacting and joint effects on CVDs remain unclear. To explore the interaction effects of frailty and inflammation on CVDs and the role of inflammation in the relationship between frailty and CVDs to provide better understanding of the underlying pathogenesis of CVD.

Methods A total of 220,608 initially CVD-free participants were recruited from the UK Biobank database and were categorized into non-frailty, pre-frailty, and frailty groups based on Fried's criteria. The participants were also grouped according to the low-grade inflammation (INFLA) score and its components: the neutrophil-lymphocyte ratio, C-reactive protein, white blood cell count, and platelet count. Cox proportional hazards models with hazard ratios (HRs) and 95% confidence intervals (CIs) were used to assess the effects of frailty phenotypes and inflammation on CVD risk. Mediation analysis was used to quantify the role of inflammation in the association between frailty and CVDs. The potential interactions between frailty and inflammation in terms of CVD risk were also evaluated using additive and multiplicative scales.

Results During a median follow-up of 13.3 years, 48,978 participants developed CVDs. After adjusting for various confounders, participants with pre-frailty and frailty had a higher risk of CVDs than those with non-frailty (HRs: 1.20 (95% CI: 1.18–1.23) and 1.80 (95% CI: 1.69–1.91), respectively). A higher risk of CVDs was observed among participants with moderate and high INFLA scores than those with low INFLA scores (HRs: 1.09 (95% CI: 1.07–1.12) and 1.27 (95% CI: 1.24–1.30), respectively). The INFLA score and its components had limited mediating effects in the association between frailty and CVDs. Significant interactions were observed between frailty phenotypes and INFLA scores on CVDs on the multiplicative scale but not on the additive scale.

†Zihan Xu and Yingbai Wang contributed equally to this work.

*Correspondence:
Shicai Ye
caizi23@126.com
Jiayuan Wu
wujiay@gdmu.edu.cn

Full list of author information is available at the end of the article

Conclusion Inflammation may amplify the harmful effect of frailty on the incidence of CVDs. Improving frailty alone might not substantially reduce the risk of CVDs, but effectively controlling inflammation might help to reduce the negative effects of frailty on cardiovascular health.

Keywords Frailty, Inflammation, Cardiovascular diseases, Mediation analysis, Interaction

Introduction

Cardiovascular diseases (CVDs) are the most common non-communicable chronic diseases and the foremost cause of disease burden globally. One of the aims of the Sustainable Development Goals is to reduce premature mortality from non-communicable diseases by 30% worldwide by 2030 [1]. Approximately 90% of CVDs can be avoided through proactive preventive measures [2]. The American Heart Association states that interventions for risk factors are critical for the primary and secondary prevention of CVDs. Formulating effective and targeted prevention strategies to control modifiable risk factors could significantly reduce the risk of CVDs [3].

Frailty occurs primarily in the elderly and is characterized by a decline in physiological function in multiple systems. Furthermore, it involves increased susceptibility to stressors, risk of morbidity, disability, and mortality [4]. Evidence has demonstrated a bidirectional relationship between frailty and CVDs. According to longitudinal studies, frailty is an independent risk factor for CVDs and coexists in patients with CVDs [5]. Long-term frailty may be accompanied by endocrine system disorders, resulting in changes in cardiac structure and function that increase the risk of cardiovascular events [6–8]. CVDs and frailty also share common risk factors, including obesity, lack of physical activity, smoking, alcohol abuse, and unhealthy diet patterns. Considering that frailty might be a reversible syndrome, effective interventions for reversing it may reduce the risk of CVDs.

While frailty and CVDs appear to be intertwined, the underlying mechanisms linking them have not been well described. Low-grade inflammation may be a plausible link between frailty and increased risk of CVDs [9]. Inflammation is an immune surveillance response that is essential to host defense for repairing damaged tissues and removing toxic substances [10]. However, when the response becomes a state of chronic low-grade inflammation, it prolongs the presence of immune system cells, which leads to metabolic abnormalities, disrupts homeostasis, and promotes the development of various age-related chronic diseases. Recent studies have emphasized the prognostic value of various inflammatory markers, including the systemic immune-inflammation index (SII), C-reactive protein-to-albumin ratio (CAR), and Naples score, in patients with CVDs [11–15]. Moreover, studies have shown that inflammation is closely associated with frailty and plays an important role in accelerating the process of aging and frailty [16].

The Fried frailty phenotype is one of the most widely used tools for frailty measurement and was formulated based on five criteria: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, and low physical activity. However, this assessment system does not include inflammatory indexes and cannot assess the role of inflammation in frailty. Moreover, evidence has shown that the effectiveness of anti-inflammatory therapy in CVDs has been limited [17]. Thus, further exploration of the special relationships in the inflammation–frailty–CVD triad is necessary. Therefore, we conducted a longitudinal and population-based cohort study based on the UK Biobank database to explore the mediating role and interaction effect of low-grade inflammation in the context of frailty and CVD. The results could provide novel perspectives and strategies for the prevention and management of CVDs.

Methods

Data sources

Details of the UK Biobank's study design and data-collection approaches can be found on the official website (http://www.ukbiobank.ac.uk) and have been elaborated in previous studies [18]. From 2006 to 2010, the UK Biobank recruited over 500,000 individuals from the general population in England, Scotland, and Wales via postal invitations. Participants were registered with the National Health Service (NHS) and lived within 25 miles of one of the 22 assessment centers.

After providing written informed consent, the participants were asked to complete nurse-administered touch-screen questionnaires and face-to-face interviews about diet, lifestyle, and health information; to undergo comprehensive physical examinations; and to provide biological samples. The UK Biobank has been sanctioned by the North West Multi-center Research Ethics committee. This study was conducted based on UK Biobank Data Resource Application number 97,101.

All participants who participated in the UK Biobank study and provided informed consent were originally included in this study. We excluded participants with a baseline diagnoses of CVDs ($N = 151,905$). We also excluded individuals with missing data for frailty evaluation ($N = 10,243$), inflammation score calculation ($N = 46,205$), and covariates ($N = 73,418$). Ultimately, a total of 220,608 participants were included in the final analysis (Fig. 1).

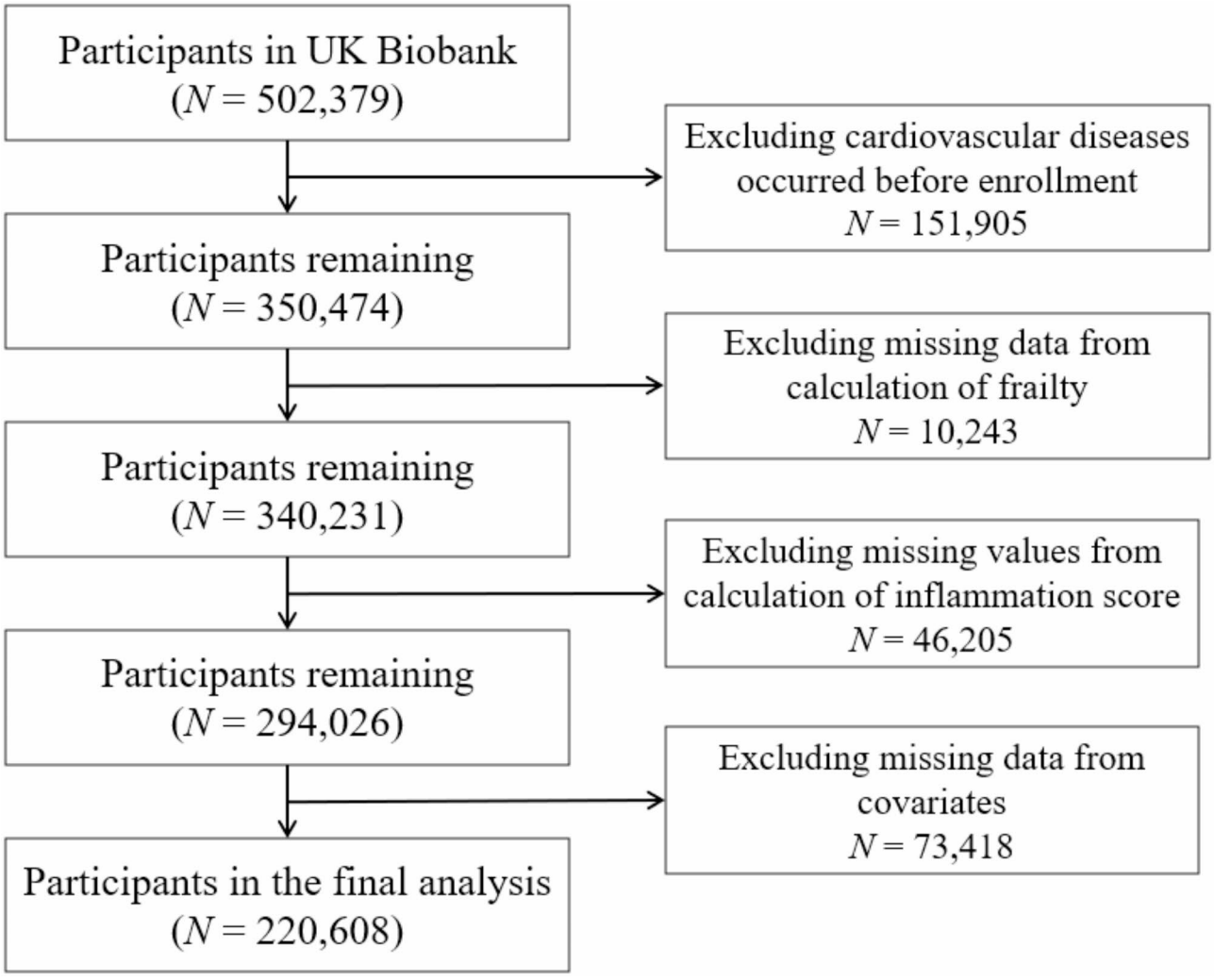

Fig. 1 Flowchart of the study design and participants

Exposure to frailty

Frailty status was evaluated using the Fried frailty phenotype, which consists of five components: weight loss, fatigue, grip strength, walking speed, and physical activity. Participants were categorized into three phenotypes: non-frailty (no frailty criteria met), pre-frailty (one to two frailty criteria met), and frailty (three or more frailty criteria met) [19, 20]. Considering the differences in specific questions and measurements between the UK Biobank and Fried criteria, we made appropriate adjustments to the definition of frailty criteria to ensure that the assessment could be performed using the available data [21]. The definition of frailty in this study is shown in Table S1.

Exposure to inflammation

We computed a low-grade inflammation (INFLA) score as an aggregated measure of low-grade inflammation, which involved four inflammatory markers: the neutrophil-lymphocyte ratio (NLR), C-reactive protein (CRP), white blood cell count (WBC), and platelet count (PC) [22]. Blood samples from the participants were typically sent to the UK Biobank central laboratory for analysis within 24 h after sampling. CRP was detected by immunoturbidimetric high-sensitivity assays on a Beckman Coulter AU5800 clinical chemistry analyzer, while the other indicators were analyzed using a Beckman Coulter LH750 hematology analyzer.

The INFLA score reassigns values to each component based on deciles. The lowest deciles (1st to 4th) were assigned values of -4 to -1, the highest deciles (7th to 10th) were scored from 1 to 4, and the 5th and 6th deciles were given a value of 0. As such, the sum of scores of the four components yields an INFLA score ranging from − 16 to 16, with higher scores indicating higher levels of low-grade inflammation.

Outcome and follow-up

The primary outcome was the incidence of CVDs. CVDs encompassed ICD-10 codes for hypertension (I10-I15), stroke (I60-I69), transient ischemic attack (G45), peripheral vascular disease (I70-I79), atrial fibrillation (I48), coronary heart disease (I20-I25), and heart failure (I50). The survival time was gauged from the date of enrollment until the first diagnosis of CVDs, death, loss to follow-up, or the end of the follow-up period in February 2023 (whichever came first).

Covariates

The covariates examined were sex, age, ethnicity, body mass index (BMI), educational level, Townsend Deprivation Index (TDI), average annual household income, smoking status, drinking consumption, dietary pattern, physical activity, diabetes, and hyperlipidemia history. BMI was calculated based on the height and weight measured at the initial assessment, with values over 25 kg/m^2 defined as overweight and those over 30 kg/m^2 defined as obesity. Educational level was divided into two groups: "college or university degree" and "other."

The TDI is a composite index of socioeconomic poverty level in residential areas that is assigned according to the participant's zip code and calculated based on the combination of unemployment rate, car-ownership rate, home-ownership rate, and household crowding [23, 24]. Average annual household income levels were categorized as low, middle, and high using thresholds of £31,000 and £100,000 per year. Smoking status was divided into three groups: "never," "previous," and "current." Alcohol consumption was divided into "daily or almost daily" and "other."

Dietary pattern scores were calculated based on the consumption of fruits, vegetables, fish, red meat, and unprocessed red meat. Each appropriate intake was awarded 1 point for a potential total score of 5 points. Physical activity was defined as the number of days per week that included at least 10 min of moderate physical activity. More than 5 days was considered indicative of regular physical activity habits.

Statistical analyses

Categorical variables were expressed as counts and proportions and were assessed using the χ^2 test. Continuous variables are presented as either means with standard deviations or medians with interquartile ranges and were evaluated using the Kruskal–Wallis test. The between-group disparities in the cumulative risk of CVDs were assessed using Kaplan–Meier curves. Cox proportional hazards models with hazard ratios (HRs) and 95% confidence intervals (CIs) were used to examine the correlations between the frailty phenotype or INFLA score and CVD risk. The proportional hazard assumption was examined by plotting Schoenfeld residuals, and no evidence of serious violation was observed.

Four different Cox regression models were sequentially developed to elucidate the association of frailty phenotypes or INFLA score categories with CVD risk to observe how the effect sizes (HRs and 95% CIs) changed when controlling various potential confounders. Model 0 involved a univariate analysis without adjustment for any covariate. Model 1 was adjusted for demographic variables (sex, age, ethnicity, BMI, education level, TDI, and average total household income), while Model 2 was adjusted for smoking status, alcohol consumption, physical exercise, and healthy diet score based on Model (1) Model 3 (the fully adjusted model) was additionally adjusted for diabetes and hyperlipidemia based on Model (2) The INFLA score was also included as a covariate in the fully adjusted model for the association between frailty phenotypes and CVDs, while frailty phenotypes were included as a confounder for the relationship between INFLA score and CVDs. The non-linear associations between INFLA scores or its components and CVD risk were tested through restricted cubic splines (RCSs) for multivariate Cox regression analyses.

Causal mediation analyses were employed to examine the potential mediating role of INFLA scores and its components in the correlation between frailty phenotypes and CVDs. We performed a counterfactual causal mediation analysis based on a Cox regression model, which has proven to be the preferred method for the analysis of mediation models with a binary mediator and a survival outcome [25]. In the mediation model, the non-frailty group was considered as the reference group. We performed a bootstrap approach using randomly selected subsamples from the data and recalculated the model 1000 times to improve the stability of the results. We also conducted causal mediation analysis to explore the mediation effect of INFLA scores and its components in the association between frailty phenotypes and CVDs.

The total effect corresponds to the effect of frailty phenotypes on CVDs after adjustment for different covariates. The direct effect is the effect of frailty phenotypes on CVDs after controlling different covariates as well as mediating variables. The indirect effect is the effect of frailty phenotypes on CVD risk through mediators after controlling for different covariates. The proportion of the mediation effect was calculated as the indirect effects divided by the total effect.

We also investigated the interactions between frailty phenotypes and INFLA scores in regard to CVDs on additive and multiplicative scales. For additive interaction, we formulated a new term with 9 combinations (3×3) based on the frailty phenotypes (non-frailty, pre-frailty, and frailty) and INFLA score levels (low, moderate, and high). Individuals with non-frailty and low INFLA

scores were considered as the reference group. The relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP), and the corresponding 95% CIs were calculated to evaluate the additive interaction. If the 95% CIs of RERI and AP contained 0, no additive interaction was found. For multiplicative interaction, a product term between frailty phenotypes and INFLA score groups was introduced [26]. A *P* value less than 0.05 in likelihood tests indicated that the multiplicative interaction was statistically significant.

Subgroup analyses were performed based on sex (male and female), age (< 60 years and > 60 years), and ethnicity (White and others) to explore the effects of frailty phenotypes or INFLA score on CVDs in different subgroups. Two sensitivity analyses were conducted to validate the robustness of the results. First, we treated death before the incidence of CVDs as a competing event and employed a competing-risk model with sub-distribution HR (SHRs) and 95% CIs as size effects. Second, we excluded participants who had been diagnosed with CVDs within the first 5 years of follow-up to minimize the potential effect of reverse causality. All statistical analyses were conducted using R software (Version 4.3.3), and statistical significance was defined using $P < 0.05$.

Results

Baseline characteristics of the study participants

Table 1 presents the baseline characteristics of the 220,608 participants. The average age was 54.0 ± 8.0 years, and 123,714 (56.1%) were females. At baseline, 3,072 (1.4%) participants had frailty, and 71,369 (32.4%) participants had pre-frailty. Participants with frailty tended to be elderly, obese, and current smokers. They also tended to be from more deprived areas and to have lower household incomes. Moreover, they were less likely to engage in regular physical exercise, had greater rates of diabetes and hyperlipidemia, and had higher INFLA scores. The baseline features of participants with different INFLA score levels are shown in Table S2. At baseline, individuals with high INFLA scores were more likely to be obese, have less education, smoke, have low household income, and spend less time exercising.

Correlation between frailty and CVD risk

During a median follow-up of 13.3 years, a total of 48,978 participants developed CVDs. As shown in Fig. 2A, the cumulative risk of CVDs was found to be highest in the frailty group, followed by the pre-frailty group ($P < 0.001$ for log-rank test). The results of Cox proportional hazards models are shown in Table 2. Frailty phenotypes were significantly associated with CVD risk even after adjusting for various potential confounding factors. In the fully adjusted model, participants with frailty and pre-frailty had an increased risk of CVDs by 80.0% (HR: 1.800, 95% CI: 1.694 to 1.911) and 20.3% (HR: 1.203, 95% CI: 1.181 to 1.226) compared with the non-frailty participants, respectively.

As shown in Table S3, a significant correlation between frailty phenotypes and CVD risk was found in all subgroups. Notably, the effect of frailty on CVD risk was more significant among females than males. Among females, in comparison with the non-frailty group, the HRs were 2.54 (95% CI: 2.36–2.73) for the frailty group and 1.38 (95% CI: 1.34–1.42) for the pre-frailty group, respectively. Regarding males, the HRs were 1.90 (95% CI: 1.71–2.11) and 1.21 (95% CI: 1.18–1.24) for the frailty and pre-frailty phenotypes when compared with the non-frailty phenotype, respectively. As shown in Table S4, consistent trends were obtained from both sensitivity analyses based on the competing risk model and those omitting participants who developed CVDs within the first five years of follow-up. As shown in Fig. 3, the effects of frailty phenotypes on CVD risk remained significant for each level of the INFLA score, and the impact of frailty phenotypes was most significant for high INFLA scores, followed by moderate INFLA scores.

Correlation between low-grade inflammation and CVD risk

Figure 2B shows the cumulative risk of CVD at different levels of INFLA scores. Individuals with high INFLA scores had the greatest risk of CVDs, followed by those with moderate INFLA scores ($P < 0.001$ for log-rank test). As shown in Fig. 2C, there was a linear association between INFLA scores and CVD risk ($P = 0.136$ for nonlinearity). As shown in Table 3, the Cox regression models showed that high and moderate INFLA scores were closely related to a higher risk of CVDs compared with low INFLA scores (HRs: 1.27 (95% CI: 1.24–1.30) and 1.09 (95% CI: 1.07–1.12) in the fully adjusted models, respectively).

Table S5 shows the results of subgroup analyses, and a consistent result was observed in each subgroup. The significant association between INFLA scores and CVD risk remained even after adjusting for competing events or excluding participants with CVDs occurrence during the first five years (Table S6). As shown in Fig. 4, the association between INFLA score and CVD risk remained significant for each frailty phenotype, and the most significant impact of the score was observed in the frailty group, followed by the pre-frailty group.

Concerning the four components of the INFLA score, higher levels of CRP, WBC, PC, and NLR were significantly associated with increased risk of CVDs ($P < 0.001$ for log-rank test, Figure S1). As shown in Figure S2, CRP, WBC, and PC had a nonlinear association with CVD risk ($P < 0.05$ for nonlinearity), while NLR had a linear relationship with CVD risk ($P = 0.061$ for nonlinearity). The results of Cox regression analyses for these

Table 1 Baseline characteristics of the study participants by frailty phenotype

Variables	Total	Non-frailty	Pre-frailty	Frailty	*P* value
N (%)	220,608 (100.0)	146,167 (66.3)	71,369 (32.4)	3072 (1.4)	
Sex, n (%)					< 0.001
Male	96,894 (43.9)	67,033 (45.9)	28,977 (40.6)	884 (28.8)	
Female	123,714 (56.1)	79,134 (54.1)	42,392 (59.4)	2188 (71.2)	
Age, years	54.0 ± 8.0	54.1 ± 7.9	53.9 ± 8.0	54.3 ± 7.9	< 0.001
Ethnicity, n (%)					< 0.001
White	210,603 (95.5)	141,290 (96.7)	66,626 (93.4)	2687 (87.5)	
Other	10,005 (4.5)	4877 (3.3)	4743 (6.6)	385 (12.5)	
BMI (kg/m^2)					< 0.001
< 25	90,105 (40.8)	65,235 (44.6)	24,210 (33.9)	660 (21.5)	
25 ~ 30	93,876 (42.6)	61,832 (42.3)	30,909 (43.3)	1135 (36.9)	
>30	36,627 (16.6)	19,100 (13.1)	16,250 (22.8)	1277 (41.6)	
Education level, n (%)					< 0.001
College or University degree	95,760 (43.4)	66,690 (45.6)	28,114 (39.4)	956 (31.1)	
Other	124,848 (56.6)	79,477 (54.4)	43,255 (60.6)	2116 (68.9)	
Smoking status, n (%)					< 0.001
Never	129,486 (58.7)	87,330 (59.7)	40,517 (56.8)	1639 (53.4)	
Previous	69,738 (31.6)	46,285 (31.7)	22,578 (31.6)	875 (28.5)	
Current	21,384 (9.7)	12,552 (8.6)	8274 (11.6)	558 (18.2)	
Alcohol consumption, n (%)					< 0.001
Alcoholics	47,711 (21.6)	34,232 (23.4)	13,127 (18.4)	352 (11.5)	
Non-alcoholics	172,897 (78.4)	111,935 (76.6)	58,242 (81.6)	2720 (88.5)	
Household income, pounds per year, n (%)					< 0.001
< 31,000	83,490 (37.8)	50,540 (34.6)	30,910 (43.3)	2040 (66.4)	
31,000 ~ 100,000	121,288 (55.0)	83,770 (57.3)	36,551 (51.2)	967 (31.5)	
> 100,000	15,830 (7.2)	11,857 (8.1)	3908 (5.5)	65 (2.1)	
Townsend deprivation index	-2.4 [-3.8, 0.0]	-2.5 [-3.9, -0.3]	-2.0 [-3.6, 0.6]	-0.7 [-3.0, 2.4]	< 0.001
Regular physical exercise, n (%)	161,185 (73.1)	112,676 (77.1)	47,402 (66.4)	1107 (36.0)	< 0.001
Health diet score	3.0 ± 1.2	3.0 ± 1.2	3.0 ± 1.2	2.7 ± 1.3	< 0.001
Diabetes	9717 (4.4)	4631 (3.2)	4629 (6.5)	457 (14.9)	< 0.001
Hyperlipidemia	30,251 (13.7)	18,451 (12.6)	11,113 (15.6)	687 (22.4)	< 0.001
NLR	2.1 [1.6, 2.7]	2.1 [1.6, 2.6]	2.1 [1.6, 2.7]	2.1 [1.6, 2.7]	0.152
CRP, mg/L	1.0 [0.5, 2.1]	1.0 [0.5, 1.9]	1.2 [0.6, 2.4]	1.9 [0.9, 3.5]	< 0.001
WBC, × 10^9/L	6.6 ± 1.6	6.5 ± 1.6	6.7 ± 1.6	7.1 ± 1.8	< 0.001
PC, × 10^9/L	251.8 ± 55.5	250.6 ± 54.5	253.6 ± 57.0	261.6 ± 61.8	< 0.001
INFLA score	0.0 [-4.0, 4.0]	-1.0 [-5.0, 4.0]	0.0 [-4.0, 5.0]	3.0 [-2.0, 7.0]	< 0.001

BMI, body mass index; NLR, Neutrophil-to-Lymphocyte ratio; CRP, C-reactive protein; PC, Platelet count; WBC, White blood cell count; INFLA score, low-grade inflammation score

four components are shown in Table 3, and the effects of CRP, WBC, PC, and NLR on CVD risk were significant in different adjustment models. In the fully adjusted model, high levels of CRP, NLR, WBC, and PC indicated the highest risk of CVDs (HRs: 1.27 (95% CI: 1.24–1.30, $P < 0.001$), 1.11 (95% CI: 1.09–1.14, $P < 0.001$), 1.14 (95% CI: 1.12–1.17, $P < 0.001$), and 1.04 (95% CI: 1.01–1.06, $P = 0.002$), respectively).

Mediation analysis

The results of the mediation analysis are shown in Table 3. When compared with the non-frailty group, the proportions mediated by the INFLA score in CVD incidence were merely 4.3% in the frailty group and 3.7% in the pre-frailty group. Similarly, when compared with the non-frailty group, CRP, NLR, WBC, and PC mediated 4.9%, 0.9%, 2.6%, and 2.6% of the CVD incidence in the frailty group and 3.9%, 0.9%, 1.9%, and 1.9% in the pre-frailty group, respectively.

Interaction effects of frailty and low-grade inflammation on CVD risk

The interaction effects of frailty phenotypes and the INFLA score on CVD risk are presented in Table 4. On the additive scale, as frailty severity and the INFLA score increased, so did the risk of CVDs. For example, when compared with participants with non-frailty and a low INFLA score, the highest CVD risk was found among

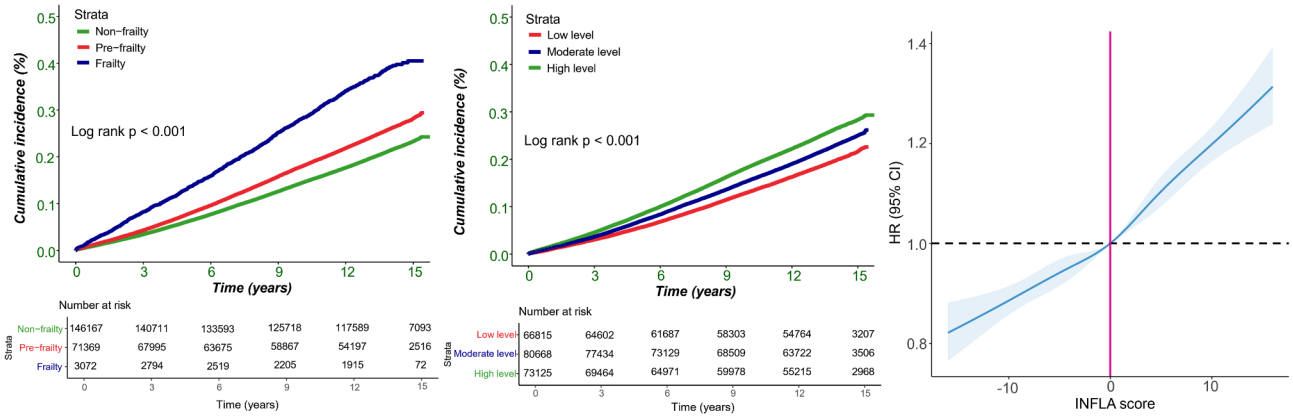

Fig. 2 Correlations between frailty or inflammation and CVD risk. (**A**) Cumulative incidence curve of CVDs stratified by frailty phenotypes. (**B**) Cumulative incidence curve of CVDs stratified by INFLA levels. (**C**) Restricted cubic spline plot of the relationship between INFLA score and CVDs risk. CVDs, cardiovascular diseases; INFLA, low-grade inflammation

Table 2 Association between frailty and cardiovascular disease risk

Models	Non-frailty	Pre-frailty		Frailty	
	HR (95% CI)	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Model 0	1 (reference)	1.26 (1.23–1.28)	< 0.001	2.08 (1.96–2.21)	< 0.001
Model 1	1 (reference)	1.25 (1.22–1.27)	< 0.001	2.02 (1.90–2.14)	< 0.001
Model 2	1 (reference)	1.22 (1.20–1.24)	< 0.001	1.89 (1.78–2.01)	< 0.001
Model 3	1 (reference)	1.20 (1.18–1.23)	< 0.001	1.80 (1.69–1.91)	< 0.001

Model 0 was a crude model without adjusting for any covariate

Model 1 was adjusted for sex, age, ethnicity, BMI, education level, TDI, and average total household income

Model 2 was additionally adjusted for smoking status, alcohol consumption, physical exercise, and healthy diet score

Model 3 was additionally adjusted for diabetes, hyperlipidemia, and INFLA score

HR, hazard ratio; CI, confidence interval

people with frailty and a high INFLA score (HR: 1.99; 95% CI: 1.84–2.18), followed by those with frailty and moderate INFLA score (HR: 1.97; 95% CI: 1.70–2.28). However, despite the upward trend, the additive interaction effect between frailty phenotypes and INFLA score on CVD risk was insignificant (Table 5).

The RERI and AP for frailty and high INFLA scores were – 0.21 (95% CI: -0.55 to 0.13) and – 0.10 (95% CI: -0.27 to 0.07), while those for frailty and moderate INFLA scores were – 0.15 (95% CI: -0.51 to 0.21) and – 0.08 (95% CI: -0.26 to 0.11), respectively. Similar results were found in the additive interaction between pre-frailty and high/moderate INFLA scores. There was no evidence of additive interaction effects between frailty phenotypes and any the components of the INFLA score on CVD risk (Table 5).

Significant multiplicative interaction was observed between frailty phenotypes and INFLA scores on CVD risk. The HRs were 1.76 (95% CI: 1.62–1.91) for the combination of frailty and high INFLA score, 1.69 (95% CI: 1.52–1.88) for the combination of frailty and moderate INFLA score, 1.31 (95% CI: 1.28–1.34) for the combination of pre-frailty and high INFLA score, and 1.13 (95% CI: 1.10–1.16) for the combination of pre-frailty and moderate INFLA score when compared with people with non-frailty and low INFLA scores. When alternative analyses were conducted with the four components of the INFLA score, consistent trends were observed (Table 4).

Discussion

In this prospective cohort study, frailty and pre-frailty were associated with 80.0% and 20.3% higher risks of CVDs as compared with non-frailty, respectively. Low-grade inflammation was also linked to a higher risk of CVDs, but its mediating effect in the frailty–CVD relationship was limited. We identified a significant multiplicative interaction between frailty and inflammation on CVD risk, suggesting that low-grade inflammation may amplify the adverse effects of frailty on CVDs. These findings provide new insights into the complex relationship between frailty, inflammation, and CVDs.

Frailty and CVDs may have a common pathophysiological foundation. A systematic review of 29 studies demonstrated that endothelial dysfunction, a known premorbid stage in the pathophysiology of CVDs, is significantly associated with frailty and serves as a key link between frailty and CVDs [27].

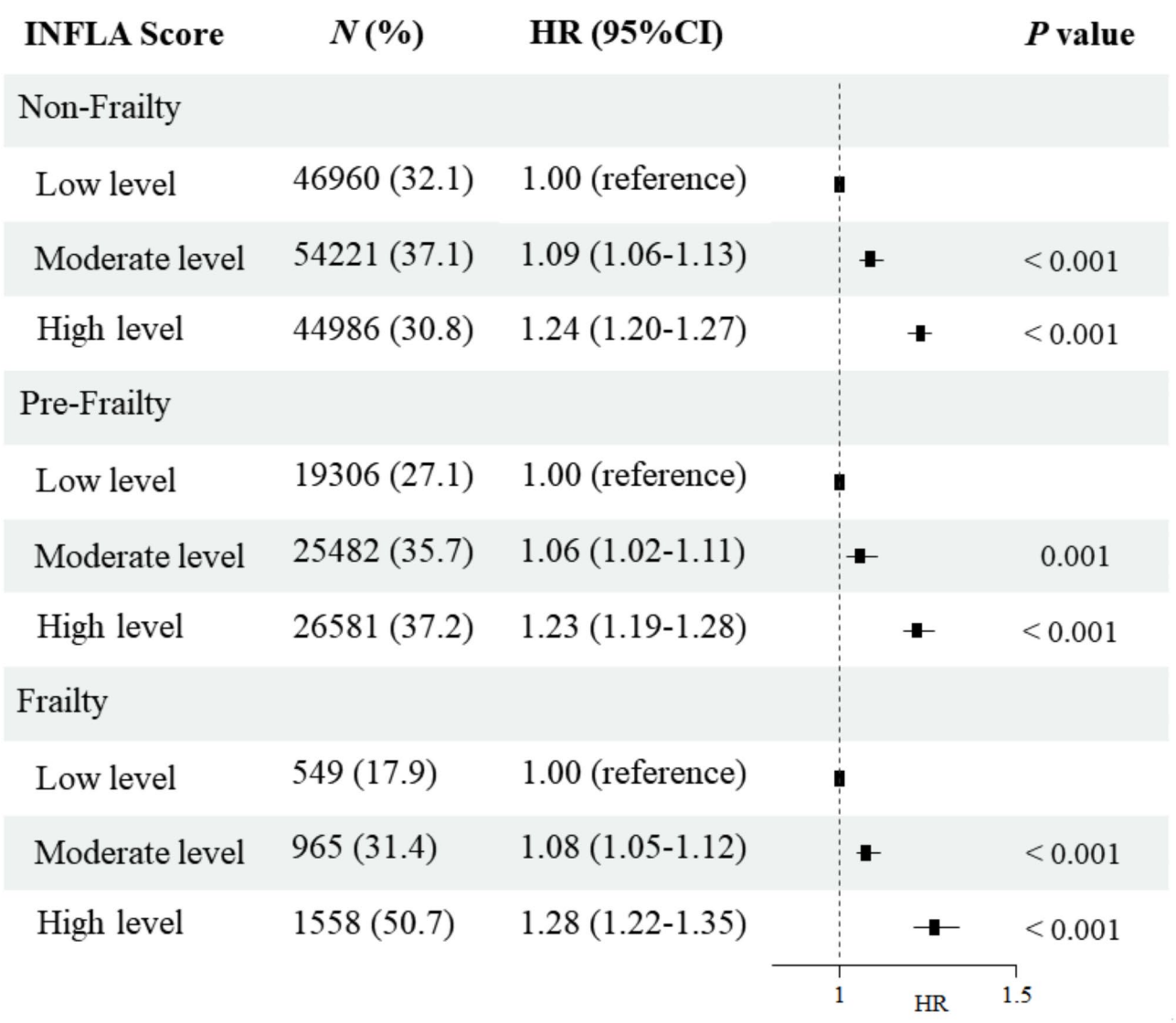

Fig. 3 The associations of INFLA scores with CVD risk stratified by frailty phenotypes. INFLA, low-grade inflammation; HR, hazard ratio; CI, confidence interval

Although previous studies have highlighted a significant association between INFLA scores and CVD risk, the underlying mechanism of low-grade inflammation in the development of CVDs is not yet fully understood. Study have shown that pro-inflammatory cytokines accelerate atherosclerosis by activating endothelial cells and promoting oxidative stress [28]. Moreover, interaction between genetic variants and unhealthy lifestyle may activate different cells that release inflammatory markers, thereby increasing the risk of CVDs [29].

The INFLA score was calculated using four inflammatory indicators: NLR, CRP, WBC, and PC. This method is not only convenient for rapid assessment of low-grade inflammation in routine medical settings, but also suitable for extensive clinical testing and large-scale public-health screening, which has broad public health significance. Studies have revealed the critical role of neutrophils in the development of CVDs, where they participate in inflammatory responses by releasing enzymes and forming neutrophil extracellular traps (NETs) and may induce atherosclerosis or myocardial infarction [30]. In contrast, lymphocytes reflect the adaptive immune systems and promote the induction of autoimmune inflammation, especially in chronic inflammatory responses. In this regard, NLR has been proposed as an inflammatory biomarker and is significantly associated with progression of atherosclerosis [31].

Elevated CRP levels reflect systemic inflammation and could be an important marker for hypertension and hypertensive heart diseases [32]. The accumulation of white blood cells in the arterial walls not only promotes plaque growth and instability, but also triggers

Table 3 Association between INFLA score and cardiovascular disease risk

Inflammatory factors	Low level	Moderate level		High level	
	HR (95% CI)	HR (95% CI)	*P* value	HR (95% CI)	*P* value
INFLA score					
Model 0	1 (reference)	1.19 (1.16–1.21)	< 0.001	1.40 (1.37–1.43)	< 0.001
Model 1	1 (reference)	1.12 (1.09–1.11)	< 0.001	1.35 (1.32–1.38)	< 0.001
Model 2	1 (reference)	1.11 (1.08–1.13)	< 0.001	1.31 (1.28–1.35)	< 0.001
Model 3	1 (reference)	1.09 (1.07–1.12)	< 0.001	1.27 (1.24–1.30)	< 0.001
Mediation proportion (%)		3.7		4.3	
CRP					
Model 0	1 (reference)	1.38 (1.35–1.41)	< 0.001	1.78 (1.74–1.82)	< 0.001
Model 1	1 (reference)	1.14 (1.12–1.17)	< 0.001	1.36 (1.30–1.37)	< 0.001
Model 2	1 (reference)	1.13 (1.11–1.16)	< 0.001	1.31 (1.28–1.34)	< 0.001
Model 3	1 (reference)	1.12 (1.10–1.15)	< 0.001	1.27 (1.24–1.30)	< 0.001
Mediation proportion (%)		3.9		4.9	
NLR					
Model 0	1 (reference)	1.03 (1.01–1.06)	0.003	1.12 (1.09–1.14)	< 0.001
Model 1	1 (reference)	1.04 (1.02–1.06)	< 0.001	1.13 (1.11–1.16)	< 0.001
Model 2	1 (reference)	1.03 (1.01–1.06)	0.003	1.12 (1.09–1.14)	< 0.001
Model 3	1 (reference)	1.03 (1.01–1.06)	0.005	1.11 (1.09–1.14)	< 0.001
Mediation proportion (%)		0.9		0.9	
WBC					
Model 0	1 (reference)	1.16 (1.13–1.18)	< 0.001	1.28 (1.26–1.31)	< 0.001
Model 1	1 (reference)	1.09 (1.06–1.11)	< 0.001	1.21 (1.19–1.24)	< 0.001
Model 2	1 (reference)	1.08 (1.06–1.11)	< 0.001	1.19 (1.17–1.22)	< 0.001
Model 3	1 (reference)	1.07 (1.05–1.09)	< 0.001	1.14 (1.12–1.17)	< 0.001
Mediation proportion (%)		1.9		2.6	
PC					
Model 0	1 (reference)	0.90 (0.88–0.92)	< 0.001	1.07 (1.04–1.11)	< 0.001
Model 1	1 (reference)	0.98 (0.96–0.99)	0.041	1.05 (1.03–1.08)	< 0.001
Model 2	1 (reference)	0.98 (0.96–0.99)	0.037	1.05 (1.02–1.07)	< 0.001
Model 3	1 (reference)	0.98 (0.96–0.99)	0.029	1.04 (1.01–1.06)	0.002
Mediation proportion (%)		0.1		0.4	

Model 0 was a crude model without adjusting for any covariate

Model 1 was adjusted for sex, age, ethnicity, BMI, education level, TDI, and average total household income

Model 2 was additionally adjusted for smoking status, alcohol consumption, physical exercise, and healthy diet score

Model 3 was additionally adjusted for diabetes, hyperlipidemia, and frailty phenotypes

HR, hazard ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; PC, platelet count; WBC, white blood cell count; INFLA score, low-grade inflammation score

myocardial infarction and stroke [33]. Platelets also contribute to the rupture of atherosclerotic plaques or thrombosis after endothelial cell erosion by releasing proinflammatory mediators, such as chemokines and cytokines, which promotes the progression of atherosclerotic diseases [34]. Therefore, low-grade inflammation assessment and inflammatory marker levels could be included in routine screening and monitoring of CVD to provide important information for the prevention and control of CVD.

Given the strong link between frailty and elevated levels of inflammatory parameters [35–37], we examined the mediating role of inflammation in the frailty–CVD association. However, we found only a weak mediating effect, indicating that the relationship between frailty and CVDs is multifaceted and cannot be fully accounted for by inflammatory processes alone. Alternative mechanisms, such as metabolic dysregulation, autonomic dysfunction, and endothelial impairment, may play a more significant role in linking frailty and CVDs, highlighting the need for further investigation into these alternative pathways [38–40].

There was a significant multiplier interaction effect between low-grade inflammation and frailty on the risk of CVDs. Individuals with high inflammation levels and frailty have a significantly increased risk of CVDs, indicating that high levels of inflammation may amplify the adverse effects of frailty on CVDs. The potential mechanism of this multiplicative interaction may lie in epigenetic changes caused by frailty, such as DNA methylation

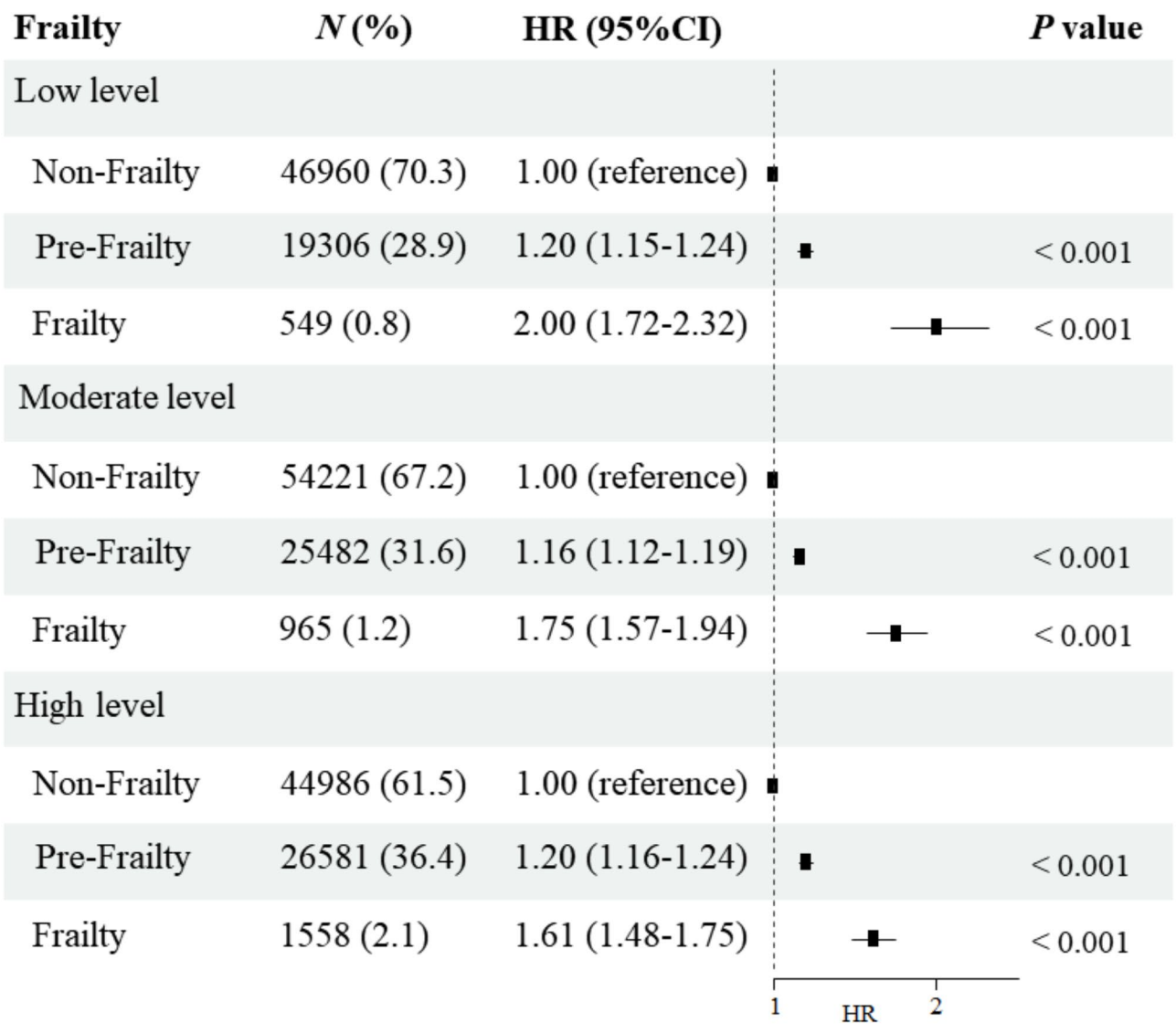

Fig. 4 The associations of frailty phenotypes with CVD risk stratified by different levels of INFLA score. INFLA, low-grade inflammation; HR, hazard ratio; CI, confidence interval

and histone modification, which could lead to overexpression of proinflammatory genes, induce chronic inflammation, and promote the development of CVDs [41].

There is already evidence that regular physical exercise is an important protective measure against CVDs. Even small amounts of regular physical activity can significantly reduce the risk, but the protective effect against CVDs diminishes once exercising is stopped [42]. For people with frailty, consistent regular physical activities and reducing sedentary time are essential to prevent CVDs [43]. Additionally, nutritional strategies, such as ensuring adequate protein intake and adhering to an anti-inflammatory diet (such as the Mediterranean diet), can support muscle preservation and metabolic health, further lowering the risk of both frailty and CVDs [44]. Given the significant interplay between frailty and inflammation on CVD risk, a comprehensive approach that combines physical activity, dietary improvements, and inflammation management may provide the most effective strategy for CVD prevention in frail individuals.

This study utilized a large prospective cohort from the UK Biobank to evaluate the mediation and interaction effects between frailty phenotype and low-grade inflammation on CVDs for the first time. Some of the strengths of this study are the rich phenotype data, long follow-up duration, comprehensive adjustments for various confounding factors, and use of multiple methods for sensitivity analyses. However, this study still has certain limitations. First, the data from the UK Biobank cohort differ from those of the general population in terms of sociodemographic and health-related factors, and this

Table 4 The interaction effects of frailty and inflammatory factors on cardiovascular disease risk

Variables	Categories	Non-frailty		Pre-frailty		Frailty	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
INFLA score	**Additive effect**						
	Low level	1 (reference)		1.19 (1.15–1.23)	< 0.001	1.91 (1.72–2.13)	< 0.001
	Moderate level	1.09 (1.06–1.13)	< 0.001	1.27 (1.22–1.31)	< 0.001	1.97 (1.70–2.28)	< 0.001
	High level	1.23 (1.20–1.27)	< 0.001	1.48 (1.43–1.53)	< 0.001	1.99 (1.84–2.18)	< 0.001
	Multiplicative effect						
	Low level	1 (reference)					
	Moderate level			1.13 (1.10–1.16)	< 0.001	1.69 (1.52–1.88)	< 0.001
	High level			1.31 (1.28–1.34)	< 0.001	1.76 (1.62–1.91)	< 0.001
CRP	**Additive effect**						
	Low level	1 (reference)		1.19 (1.15–1.24)	< 0.001	1.88 (1.67–2.12)	< 0.001
	Moderate level	1.13 (1.10–1.17)	< 0.001	1.32 (1.28–1.37)	< 0.001	2.10 (1.80–2.46)	< 0.001
	High level	1.28 (1.24–1.32)	< 0.001	1.51 (1.47–1.56)	< 0.001	2.11 (1.95–2.29)	< 0.001
	Multiplicative effect						
	Low level	1 (reference)					
	Moderate level			1.15 (1.11–1.18)	< 0.001	1.61 (1.43–1.81)	< 0.001
	High level			1.30 (1.26–1.33)	< 0.001	1.79 (1.66–1.94)	< 0.001
NLR	**Additive effect**						
	Low level	1 (reference)		1.20 (1.17–1.25)	< 0.001	1.71 (1.54–1.91)	< 0.001
	Moderate level	1.05 (1.02–1.08)	< 0.001	1.22 (1.18–1.26)	< 0.001	1.82 (1.64–2.01)	< 0.001
	High level	1.11 (1.09–1.15)	< 0.001	1.35 (1.30–1.39)	< 0.001	1.97 (1.78–2.18)	< 0.001
	Multiplicative effect						
	Low level	1 (reference)					
	Moderate level			1.12 (1.09–1.15)	< 0.001	1.57 (1.41–1.74)	< 0.001
	High level			1.24 (1.21–1.27)	< 0.001	1.66 (1.51–1.84)	< 0.001
WBC	**Additive effect**						
	Low level	1 (reference)		1.19 (1.15–1.23)	< 0.001	1.86 (1.63–2.11)	< 0.001
	Moderate level	1.07 (1.04–1.10)	< 0.001	1.27 (1.23–1.31)	< 0.001	1.88 (1.72–2.05)	< 0.001
	High level	1.15 (1.12–1.18)	< 0.001	1.36 (1.32–1.40)	< 0.001	1.93 (1.73–2.15)	< 0.001
	Multiplicative effect						
	Low level	1 (reference)					
	Moderate level			1.16 (1.13–1.19)	< 0.001	1.70 (1.56–1.85)	< 0.001
	High level			1.24 (1.21–1.27)	< 0.001	1.75 (1.57–1.95)	< 0.001
PC	**Additive effect**						
	Low level	1 (reference)		1.17 (1.14–1.21)	< 0.001	1.69 (1.51–1.89)	< 0.001
	Moderate level	0.97 (0.95-1.00)	0.045	1.15 (1.11–1.19)	< 0.001	1.70 (1.53–1.90)	< 0.001
	High level	1.02 (0.99–1.05)	0.130	1.24 (1.20–1.28)	< 0.001	1.81 (1.65–1.99)	< 0.001
	Multiplicative effect						
	Low level	1 (reference)					
	Moderate level			1.12 (1.09–1.15)	< 0.001	1.64 (1.48–1.83)	< 0.001
	High level			1.20 (1.17–1.24)	< 0.001	1.75 (1.59–1.92)	< 0.001

All results were adjusting for sex, age, ethnicity, BMI, education level, Townsend deprivation index, average total household income, smoking status, alcohol consumption, physical exercise, healthy diet score, diabetes, and hyperlipidemia

HR, hazard ratio; CI, confidence interval; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PC, platelet count; WBC, white blood cell count; INFLA score, low-grade inflammation score

condition may have led to biases in the estimates and affect the generalizability of the results. Second, the study excluded a large number of participants due to insufficient data. The missing data were not randomly lost, and it is difficult to solve this issue with imputation, so selection bias was inevitable. Third, frailty status and inflammatory markers may change over time, and further studies are needed to comprehensively evaluate the association of trajectories of frailty and inflammatory parameters changes on CVDs. Another limitation is potential volunteer bias. Participants who volunteered for these studies may differ from the general population and tend to exhibit healthier lifestyle and lower disease prevalence [45]. Finally, the mediation analysis relied on assumptions about causal relationships, but the relationship between frailty phenotype and inflammation was

Table 5 RERI and AP for additive interactions between frailty and low-grade inflammation

Inflammatory factors	Pre-frailty		Frailty	
	RERI (95% CI)	AP (95% CI)	RERI (95% CI)	AP (95% CI)
INFLA score				
Moderate level	-0.02 (-0.07 ~ 0.04)	-0.01 (-0.05 ~ 0.03)	-0.15 (-0.51 ~ 0.21)	-0.08 (-0.26 ~ 0.11)
High level	0.06 (0.00 ~ 0.12)	0.04 (0.00 ~ 0.08)	-0.21 (-0.55 ~ 0.13)	-0.10 (-0.27 ~ 0.07)
CRP				
Moderate level	0.00 (-0.06 ~ 0.06)	0.00 (-0.05 ~ 0.04)	-0.36 (-0.77 ~ 0.05)	-0.19 (-0.41 ~ 0.04)
High level	0.04 (-0.02 ~ 0.01)	0.03 (-0.01 ~ 0.07)	-0.28 (-0.65 ~ 0.10)	-0.13 (-0.31 ~ 0.05)
NLR				
Moderate level	-0.04 (-0.09 ~ 0.01)	-0.03 (-0.08 ~ 0.01)	-0.33 (-0.60~-0.05)	-0.19 (-0.36~-0.02)
High level	0.02 (-0.03 ~ 0.08)	0.02 (-0.02 ~ 0.06)	-0.28 (-0.55~-0.01)	-0.15 (-0.31 ~ 0.00)
WBC				
Moderate level	0.01 (-0.04 ~ 0.07)	0.01 (-0.04 ~ 0.05)	-0.01 (-0.33 ~ 0.32)	0.00 (-0.17 ~ 0.16)
High level	0.02 (-0.04 ~ 0.07)	0.01 (-0.03 ~ 0.05)	-0.14 (-0.43 ~ 0.14)	-0.08 (-0.23 ~ 0.08)
PC				
Moderate level	0.01 (-0.04 ~ 0.06)	0.00 (-0.04 ~ 0.05)	0.04 (-0.22 ~ 0.31)	0.02 (-0.13 ~ 0.17)
High level	0.05 (-0.01 ~ 0.10)	0.04 (0.00 ~ 0.08)	0.10 (-0.15 ~ 0.36)	0.06 (-0.08 ~ 0.19)

All results were adjusting for sex, age, ethnicity, BMI, education level, Townsend deprivation index, average total household income, smoking status, alcohol consumption, physical exercise, healthy diet score, diabetes, and hyperlipidemia

RERI, relative excess risk; AP, attributable proportion; CI, confidence interval; INFLA score, low-grade inflammation score; CRP, C-reactive protein; NLR, neutrophil-to-Lymphocyte ratio; WBC, white blood cell count; PC, platelet count

based on cross-sectional studies. Further validation in clinical trials or intervention studies is warranted before the current findings can be applied in practice.

Conclusions

In summary, this study has found a significant positive association between frailty status and CVDs, and inflammation may amplify the harmful effect of frailty on CVD incidence. Improving frailty alone might not substantially reduce the risk of CVDs, while effectively controlling inflammation might help reduce the negative effects of frailty on cardiovascular health. In the context of limited healthcare resources, interventions targeting those with pre-frailty could help to prevent CVDs. Nevertheless, more rigorous evidence-based studies are warranted to elucidate the complex relationship between frailty, inflammation, and CVDs and to provide more evidence to support public strategies for CVD prevention and control.

Abbreviations

CVD Cardiovascular disease
INFLA Low-grade inflammation
HR Hazard ratios
CI Confidence intervals
NHS National Health Service
NLR Neutrophil-lymphocyte ratio
CRP C-reactive protein
WBC White blood cell count
PC Platelet count
BMI Body mass index
TDI Townsend Deprivation Index
RCS Restricted cubic spline
RERI Relative excess risk due to interaction
AP Attributable proportion due to interaction
SHR Sub-distribution HR
NETs Neutrophil extracellular traps
SASP Senescence-associated secretory phenotype

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-025-04567-1 .

Additional File 1: **Table S1**. Frailty definition in UK Biobank. **Table S2.** Baseline characteristics of the study participants based on INFLA score levels. **Table S3.** Subgroup analyses of the association between frailty phenotypes and cardiovascular disease risk. **Table S4.** Sensitivity analyses for the association between frailty phenotypes and cardiovascular disease risk. **Table S5.** Subgroup analyses of the association between INFLA score and cardiovascular disease risk. **Table S6.** Sensitivity analyses for the association between INFLA score and cardiovascular disease risk. **Figure S1**. Cumulative incidence curve of various inflammatory indexes and cardiovascular disease risk. **Figure S2.** RCS of various inflammatory indexes and cardiovascular disease risk.

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Author contributions

Literature search: XLL, XFH, SRY; Study design: XFH, SRY and JW; Data collection: ZHX, YBW and XLL; Data analysis: XFH, SRY and JW; Model construction: ZHX, YBW and JYW; Manuscript writing: ZHX, YBW, SCY, JYW. All authors read and approved the final manuscript.

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Data availability

The UK Biobank data are available on application to the UK Biobank (www.ukbiobank.ac.uk/). This research has been conducted using the UK Biobank Resource under Application Number 97101.

Declarations

Ethics approval and consent to participate
The UK Biobank was approved by the North West Multi-center Research Ethics committee (11/NW/0382). All participants provided written and informed consent for data collection, analysis, and record linkage.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Clinical Research Service Center, Affiliated Hospital of Guangdong Medical University, Zhanjiang, Guangdong 524001, China
[2]Department of Gastroenterology, Affiliated Hospital of Guangdong Medical University, Zhanjiang, Guangdong 524001, China

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