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Frailty Index as a Predictor of Migraine Risk Across the Life Course: A Multi-Level Study from Global Spatial Patterns to Individual Longitudinal Associations

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Abstract: Frailty and migraine are significant health burdens, yet their life-course relationship remains poorly defined. Identifying predictors of migraine risk, particularly in aging populations, is crucial for developing targeted preventive strategies. This multi-level study leveraged data from the Global Burden of Disease Study (GBD, 1990–2017), the US National Health and Nutrition Examination Survey (NHANES, 1999–2004), and the China Health and Retirement Longitudinal Study (CHARLS, 2011–2018). We employed spatial and cross-sectional analyses to identify the global patterns and individual-level associations, and conducted a longitudinal cohort analysis to assess cumulative migraine risk by frailty index (FI) category. Age–FI interaction effects were examined using a Linear Generalized Additive Model (LinearGAM), and longitudinal associations were evaluated with CausalForest analysis. A significant negative correlation was observed in adults aged ≥ 70 years, with age acting as an important effect modifier. The association between FI and migraine showed considerable heterogeneity across age groups. Even after full adjustment, frail individuals had significantly higher migraine prevalence. Longitudinal assessment confirmed a substantially elevated cumulative risk of migraine in frail participants. Machine learning analysis further identified a sharp increase in migraine risk once FI exceeded the exploratory threshold of 0.6. Frailty influences migraine through complex mechanisms, with age serving as a critical effect modifier. The FI is a potential, scalable predictor of migraine risk. Incorporating frailty assessment could refine prevention strategies, particularly in younger populations where migraine incidence is rising.

Keywords: frailty index; migraine; age; multi-level study; machine learning

1. Introduction

Migraine is a major global health challenge, affecting over one billion individuals worldwide and ranking as the second leading cause of disability-adjusted life years among neurological disorders [1,2]. Its impact includes debilitating neurological symptoms, impaired quality of life, and substantial socioeconomic costs driven by reduced productivity [3,4]. Although risk factors such as genetic background and sex are well established, they explain only part of individual susceptibility [5,6]. Existing risk models also fail to account for the pronounced heterogeneity in migraine's life-course trajectory, particularly its age-related variations, suggesting that dynamic, systemic biological factors are at play [7].

The frailty index (FI) represents a promising approach to these limitations. Grounded in the cumulative deficit model, the FI quantifies health deficits across multiple physiological domains, yielding a continuous measure of

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biological vulnerability [8]. Unlike traditional risk factors that examine isolated variables, the FI synthesizes multiple health indicators into a single, interpretable metric. This integrative approach predicts diverse health outcomes including cardiovascular events, cognitive decline, and mortality with superior accuracy compared with conventional biomarkers [9,10]. The FI captures the complex erosion of physiological reserve and adaptive capacity that characterizes biological aging. This systems-level perspective aligns naturally with migraine's multifactorial etiology, in which genetic susceptibility, environmental triggers, and systemic health converge to determine disease expression.

Compelling biological mechanisms support a frailty migraine connection. Frailty and migraine share overlapping pathophysiological pathways [11]. The "inflammaging" phenomenon characteristic of frailty, marked by elevated proinflammatory cytokines, parallels the neuroinflammatory cascade driving migraine and central sensitization [12]. The relationship is likely bidirectional: frailty may increase migraine susceptibility through diminished resilience to triggers, whereas chronic migraine could accelerate frailty via reduced physical activity, nutritional compromise, and psychological burden, with potential age-dependent variations.

Critical knowledge gaps impede clinical translation of frailty assessment for migraine prevention. No large-scale studies have validated the FI's predictive performance for migraine outcomes or characterized age as a potential effect modifier. Understanding whether the frailty-migraine association varies across life stages is essential for age-tailored prevention strategies. This study addresses these gaps using global epidemiological data, cross-sectional surveying and longitudinal cohort studies (GBD, NHANES and CHARLS). By employing spatial analysis, cross-sectional associations, longitudinal risk assessment, and machine learning-based effect evaluation, we provide insight into the frailty-migraine relationship across geographic, demographic, and temporal dimensions. Our findings establish the FI as a potential, scalable predictor of migraine risk and elucidate critical age-dependent effect modification. This work advances migraine prevention from reactive treatment toward proactive, personalized risk stratification, with the potential to transform outcomes for individuals affected by this debilitating condition globally.

2. Methods

2.1. Data Sources and Study Populations

All data sources are listed in Table S1. First, the integrated data from 1990 to 2017 were utilized to examine the global spatial distribution and temporal trends of migraine incidence and prevalence among individuals aged ≥ 70 years in relation to the Global Burden of Disease-Frailty Index (GBD-FI) [13]. Analyses encompassed 204 countries and territories, with all data obtained from the GBD database via the GHDx query tool (http://ghdx.healthdata.org/gbd-results-tool, accessed on 15 July 2025) [14]. The GBD-FI comprises 36 indicators (Table S2) to estimate population-level frailty, providing insights into the association between frailty and migraine.

Using the National Health and Nutrition Examination Survey (NHANES, 1999–2004), we assessed the relationship between migraine and a 39-item FI in the U.S. adult population. Detailed FI indicators are summarized in Table S3. NHANES employed a complex multistage sampling design to ensure national representativeness. Of 31,126 participants, we excluded those ages < 20 years (n = 15,794), with missing migraine data (n = 12), missing covariates (n = 4054), or insufficient FI indicators (n = 6251), yielding 5015 eligible participants [15]. Migraine was defined by self-reported severe headache or migraine in the past three months [16]. The FI incorporated 39 health deficits across demographic, functional, comorbid, and lifestyle domains. FI scores range from 0 to 1, with cut-offs for frailty (FI ≥ 0.25), pre-frailty (0.1 < FI < 0.25), and robustness (FI ≤ 0.1) [17,18].

Data from the China Health and Retirement Longitudinal Study (CHARLS) were used to analyze a nationally representative sample of adults aged ≥ 45 years. Detailed FI indicators are summarized in Table S4 [19]. The 2011 baseline survey included 17,708 participants. We excluded those with missing demographics (n = 213), loss to follow-up (n = 5540), missing covariates (n = 2404), age < 45 (n = 311), baseline migraine (n = 522), extreme BMI values (n = 2651), and >10% missing FI indicators (n = 68). Furthermore, we excluded individuals with missing follow-up waves covariates (n = 2147), resulting in a final sample of 3852 [20,21]. Migraine was identified based on self-reported concurrent headache and stomach pain [22]. A 32-item FI was constructed, using the same cut-offs.

2.2. Baseline Characteristics

All NHANES analyses applied appropriate survey weights. Baseline characteristics were summarized using the gtsummary package in R [23]. Normally distributed variables are presented as Mean ± SD; non-normally distributed variables as Median (IQR); and categorical variables as unweighted counts with weighted percentages. For categorical variables, a weighted chi-square test was used, and the detailed results are all shown in Table S5.

For CHARLS, all categorical variables across waves 1–4 were converted into factor variables to ensure correct level representation in statistical summaries. Specific categorical variables included gender, marital status, educational level, household registration type (hukou), smoking status, alcohol consumption, lipid levels, blood pressure, diabetes status, FI_group, and migraine status. As BMI was not collected in wave 4, it was excluded from analyses pertaining to that wave. Descriptive variables specified for the overall population included age, gender, marital status, education, hukou type, smoking and drinking status, lipid levels, blood pressure, diabetes, FI, and migraine status [24].

A baseline table (Table S6) summarizes characteristics overall and by FI group, providing a comprehensive overview of CHARLS waves 1–4 and facilitating comparisons across frailty groups.

2.3. Covariates Depiction

In NHANES, confounders were controlled through comprehensive covariate adjustment. Demographic factors included age (20–39, 40–59, ≥60 years); socioeconomic indicators (household income/poverty ratio: <1.30, 1.30–3.49, ≥3.50); BMI (<25, 25–30, >30 kg/m²); race/ethnicity (non-Hispanic White, Mexican American, non-Hispanic Black, other Hispanic, other); education (college$^+$, high school/GED, <high school); marital status (married/partnered, lone/widowed/divorced/single); lifestyle behaviors (smoking status: never/former/current; alcohol: ≥12 standard drinks/year); physical activity (moderate activity ≥ 10 min/month); and clinical variables (hypertension: BP ≥ 140/90 mmHg or medication use; diabetes: self-reported diagnosis/insulin/oral hypoglycemics). Variables were derived from the 1999–2004 NHANES dataset [25–28].

In CHARLS, covariates included age, gender, education level, marital status, hukou, BMI, smoking, drinking, dyslipidemia, hypertension, and diabetes. Education was categorized as college or above, secondary school, or primary school and below. Marital status was classified as married/cohabiting or other [18]. Hukou was grouped as rural or urban. BMI was divided into three categories: underweight/normal (BMI < 24), overweight (24 ≤ BMI < 28), and obese (BMI ≥ 28). Smoking was classified as current, former, or never; drinking as current, former, or never. Histories of dyslipidemia, hypertension, and diabetes were determined by self-reported prior diagnosis or current medication use. All covariates were collected via standardized household interviews across waves 1–4.

2.4. Statical Analysis

2.4.1. Definition and Regional Division of Co-Occurrence Characteristics of GBD-FI and Migraine

To explore the co-occurrence patterns between FI and migraine for incidence and prevalence, and their spatial heterogeneity across countries, we classified both FI and migraine metrics into quartiles: low (<25%), medium-low (25–50%), medium-high (50–75%), and high (>75%) [29]. Countries or territories were grouped based on alignment of these quartiles. Units with identical quartile levels for FI and a migraine metric were classified as concordant, collectively forming a concordant region. Where the FI quartile exceeded that of the migraine metric, units were designated FI-dominant; conversely, units with higher migraine quartiles than FI were designated migraine-dominant. This classification delineated three geographic zones reflecting distinct co-occurrence patterns of frailty and migraine.

2.4.2. Age-Related Trends and Correlation Analysis in FI and Migraine

We analyzed age-specific FI and migraine indicators for groups aged 70–74 to 95+ years. A dual-axis chart compares trends, using stacked bars for migraine metrics and FI with overlaid lines to show changes with age. Age-specific incidence and prevalence of migraine among those aged ≥ 70 were analyzed. Based on age-stratified estimates from 1990, we calculated the estimated annual percentage change (EAPC) for migraine incidence and prevalence across countries using linear regression on time-series data, and estimated regression coefficients with confidence intervals. Pearson correlation assessed associations between FI and migraine incidence and prevalence.

2.4.3. Cross-Sectional Analysis and Propensity Score Matching (PSM)

We first performed univariable logistic regression to screen covariates associated with migraine, followed by multivariable logistic regression to estimate independent associations, using maximum likelihood for parameter estimation.

We then generated estimates and plotted the adjusted association between FI and migraine prevalence as an RCS curve of odds ratios with 95% confidence intervals (CIs) [30]. To aid interpretability, FI was analyzed per 0.1-unit increment. Subgroup analyses were conducted by fitting separate logistic models for each subpopulation, adjusting for age, BMI, and PIR. The results are presented as a forest plot [31].

This study employed PSM [32] to compare migraine prevalence between the frailty group (FI ≥ 0.25) and the non-frailty group (FI < 0.25). Propensity scores were estimated via logistic regression using sex, race, age group, BMI group, PIR group, education level, marital status, smoking status, alcohol consumption, physical activity, hypertension, and diabetes. After nearest-neighbor matching (caliper = 0.20), we confirmed covariate balance via diagnostics and compared migraine prevalence using a conditional logistic regression model to account for the matched-pair nature of the data, including the unique pair identifiers as a stratification variable to robustly estimate frailty-associated risk.

2.4.4. Longitudinal Cohort Analysis of Cumulative Risk Curves

The time from baseline (wave 1) to each follow-up (wave 2–4) was calculated in months. Migraine at each wave defined event status and time-to-event. Participants reporting migraine at any follow-up were coded as event (status = 1), while those without events across all waves were censored (status = 0). Time-to-event was the wave when migraine was first reported. A Cox proportional hazards model assessed the risk of migraine onset [33]. Survival analyses were performed using the survival and survminer packages [34]. Survival curves were stratified by baseline frailty level, and cumulative hazard was estimated [35]. Log-rank test evaluated differences between FI groups. Cumulative hazard curves were visualized with ggsurvplot to illustrate disparities in migraine risk by frailty status.

2.4.5. Advanced Machine Learning

Analyses used Python 3.12.9. For NHANES and CHARLS, we employed pygam [36] 0.9.1 and econml [37] 0.16.0, respectively.

For NHANES, a Linear Generalized Additive Model (LinearGAM) modeled relationships between features and migraine. Model quality was evaluated via residual sum of squares (RSS). To prevent overfitting, we applied curvature penalties to the smoothing functions and used five-fold cross-validation to enhance generalizability. The strength of nonlinear feature effects was assessed via chi-square tests, identifying FI and age as the most influential predictors. For CHARLS, we used a CausalForest to estimate the Conditional Average Treatment Effect (CATE) of FI on migraine. This ensemble extends Random Forest with Causal Trees that split nodes to maximize heterogeneity in treatment effects. Double sample splitting was incorporated to mitigate selection bias.

2.5. Data Availability

The data used in this study are from the GBD database, NHANES database and CHARLS database. These are publicly available by accessing their respective websites. Access to the data do not require approval from an institutional review board because of the openness.

3. Results

3.1. Spatial Distribution Patterns and Associations between FI and Migraine

The global FI was categorized into four tiers for visualization. Europe comprised most high-FI regions, whereas China and North America were predominantly medium-high (Figure 1A). By contrast, migraine incidence was highest across much of Africa, Asia, and Russia. Migraine prevalence remained elevated in Africa but was low to medium in Europe and North America (Figure 1B). Co-dominance of FI and migraine incidence was observed in Russia, parts of South America and Africa; FI and migraine prevalence were co-dominant in North America, parts of South America and Africa (Figure 1C). FI-dominant, migraine-dominant, and co-dominant regions are detailed in Tables S7 and S8.

Spatial analysis indicated overlapping distributions of frailty and migraine for both incidence and prevalence. Quartile-based patterns were broadly similar, with 51 out of 204 countries/territories falling into the same quartile for both measures. For incidence (Figure 2A), more countries were migraine-dominant (80/204) than frailty-dominant (73/204). For prevalence (Figure 2A), frailty-dominance was slightly more common (78/204) than migraine-dominance (75/204). In the global population aged ≥ 70, migraine incidence and prevalence decreased as FI increased (Figure 2B**)**. Age-stratified analyses (Figure 2C) showed that FI rose consistently with age, while migraine incidence plateaued between ages 70–84 and declined after 85; migraine prevalence declined steadily with age. In correlation analyses among adults aged ≥ 70, FI was inversely associated with the EAPC of both migraine incidence and prevalence, reaching statistical significance for incidence ($r = -0.15$, $p = 0.029$), but not for prevalence ($r = -0.10$, $p = 0.142$).

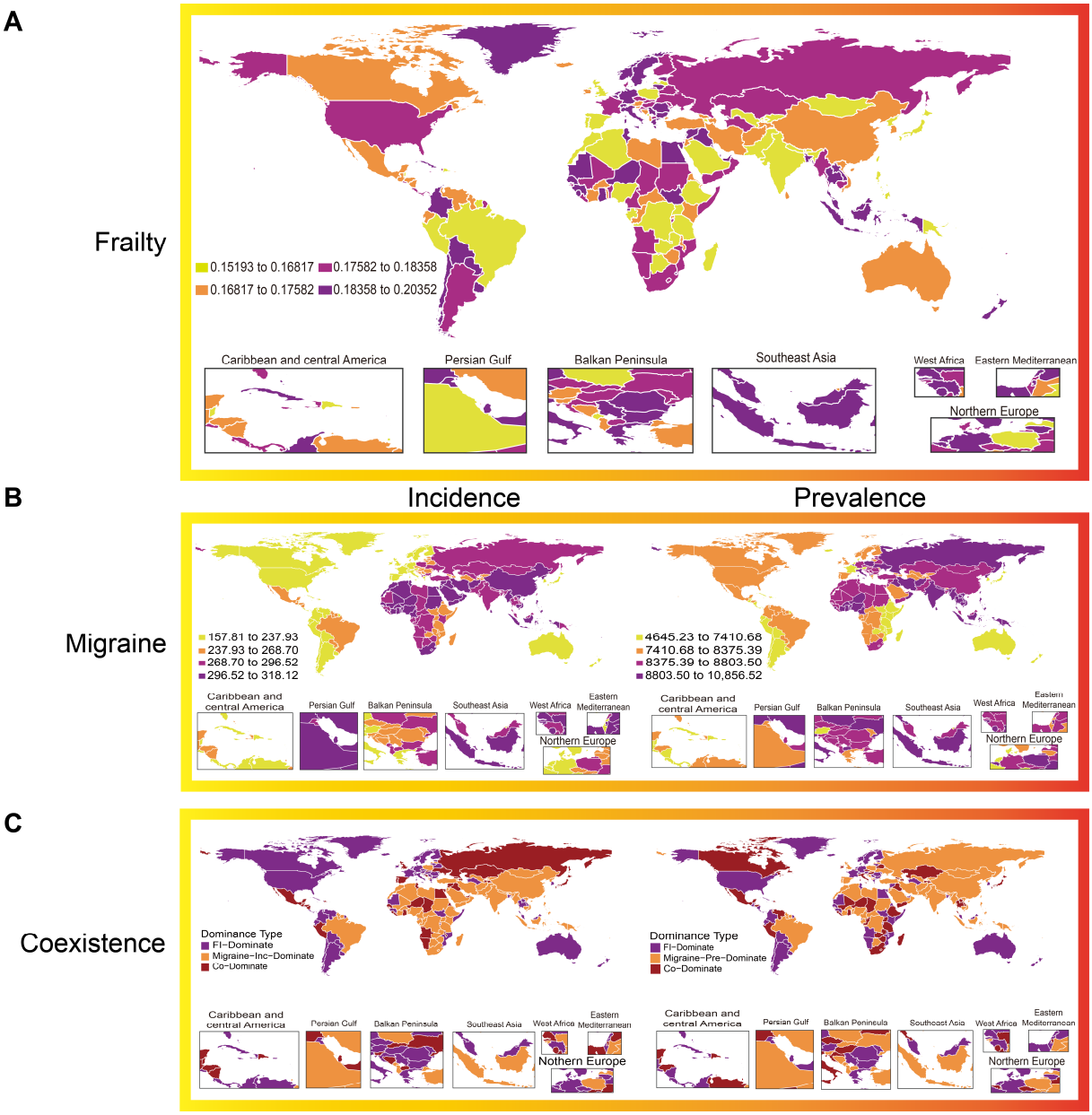

Figure 1. Global geographical distribution of the frailty index, migraine incidence and prevalence, and dominance patterns. (**A**) Countries and regions were categorized into frailty index (FI) quartiles to illustrate population-level frailty (0–25%: yellow; 25–50%: orange; 50–75%: magenta; 75–100%: purple). (**B**) The left panel presents incidence and the right panel presents prevalence, each categorized into quartiles. (**C**) Purple, orange, and red denote FI-dominant, migraine-dominant, and co-dominant countries, respectively.

3.2. Cross-Sectional Analysis and Propensity Score Matching in American Individuals

The detailed inclusion and exclusion process for the NHANES database is illustrated in Figure 3A, resulting in a final eligible sample of 5015 participants. The adjusted RCS model revealed a significant, monotonic dose-response relationship between FI and migraine (p-overall < 0.0001), which was notably nonlinear (p-nonlinear = 0.0129) (Figure 3B). Subgroup analyses and interaction tests examined this association across demographics and health behaviors, with detailed results provided in Table S9.

In univariate analysis, most variables were associated with migraine risk, with pre-frail and robust status showing protective effects relative to the frail group (Figure 3C). After full adjustment in the multivariate model, the association between FI categories and migraine remained significant and strengthened (Figure 3D). Compared with the frail group, the robust group had a 76% lower migraine risk (OR = 0.24, 95% CI: 0.19–0.31, $p < 0.01$), and the pre-frail group had a 55% lower risk (OR = 0.45, 95% CI: 0.37–0.55, $p < 0.01$). Other significant predictors included female sex (OR = 1.75, 95% CI: 1.47–2.09), age 40–59 years (OR = 2.03, 95% CI: 1.49–2.78), and

cohabiting (OR = 1.71, 95% CI: 1.16–2.52), which increased migraine risk, whereas college education or above was protective (OR = 0.66, 95% CI: 0.51–0.85). Complete univariate and multivariate results are provided in Table S10.

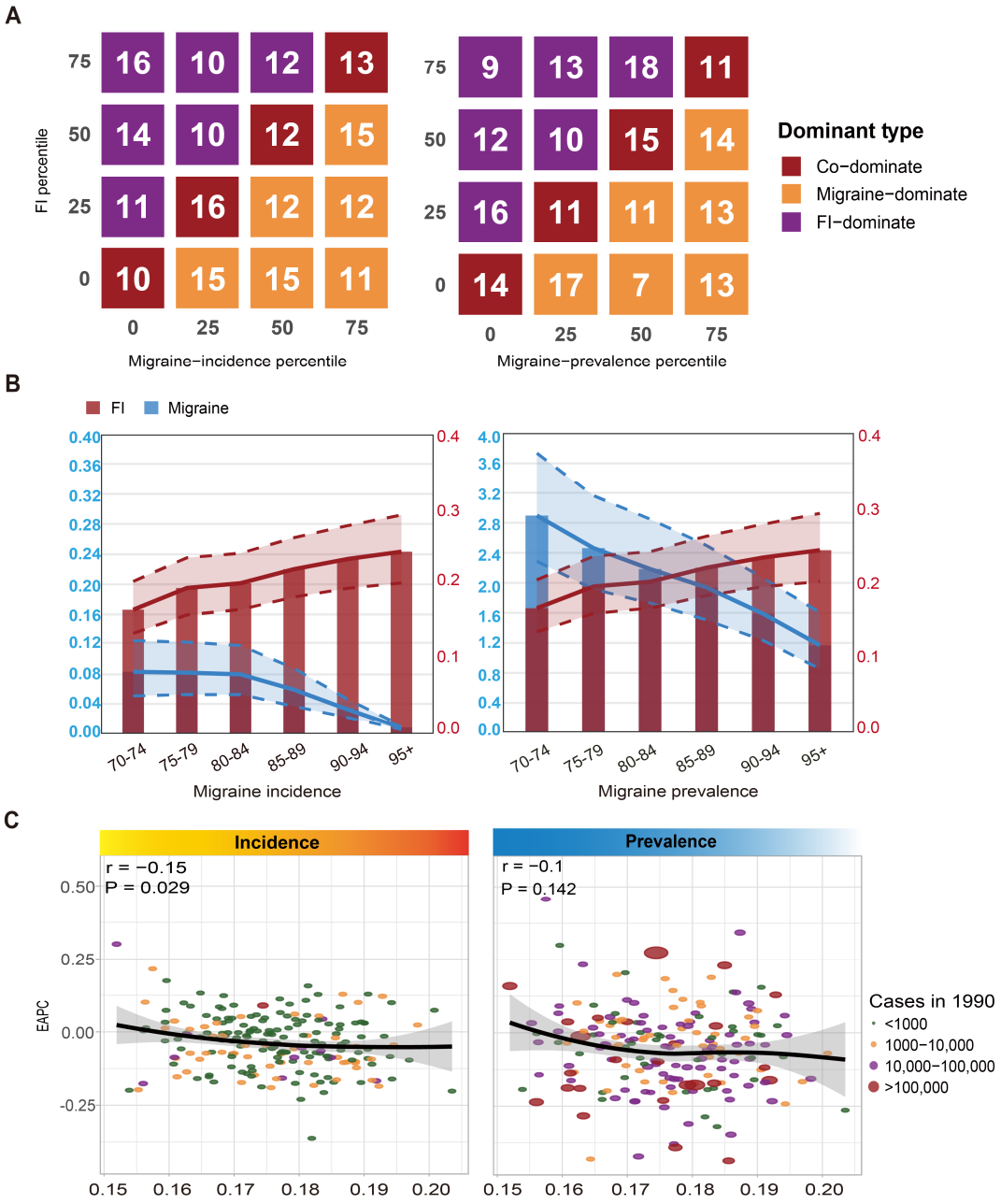

Figure 2. Association of FI with the comorbid presentation of migraine. (**A**) Country counts per quartile in the FI-Migraine coexistence matrix. Countries were classified by their FI and migraine incidence and prevalence quartiles. The left panel shows FI quartile patterns in relation to incidence; the right panel shows corresponding patterns for prevalence. (**B**) Temporal trends of FI and migraine metrics (incidence and prevalence) among adults aged ≥ 70 years in the global aging population. The red polyline and bars depict the trajectory and magnitude of FI, respectively, while the blue polyline and corresponding bars depict the trajectory and magnitude of migraine metrics. (**C**) The relationship between the 2017 FI and the 1990–2017 estimated annual percentage change (EAPC) in absolute migraine incidence and prevalence among adults aged ≥ 70 years.

Before matching, the treatment and control groups showed substantial divergence in propensity score distributions, with limited overlap (Figure 3E,F). After matching, the distributions aligned closely, particularly in the medium-to-high score range (0.6–0.9), indicating effective balance (Figure 3G,H). Covariate influence was further mitigated, as reflected by the reduced "distance" between groups. In the matched sample, migraine prevalence was significantly higher in the FI group (27%) than in controls (16.5%) (Figure 3I). In addition, conditional logistic regression analysis of the matched pairs revealed that the frail group had a significantly increased risk of migraine (Conditional OR = 1.835, 95% CI: 1.485–2.266, $p < 0.001$).

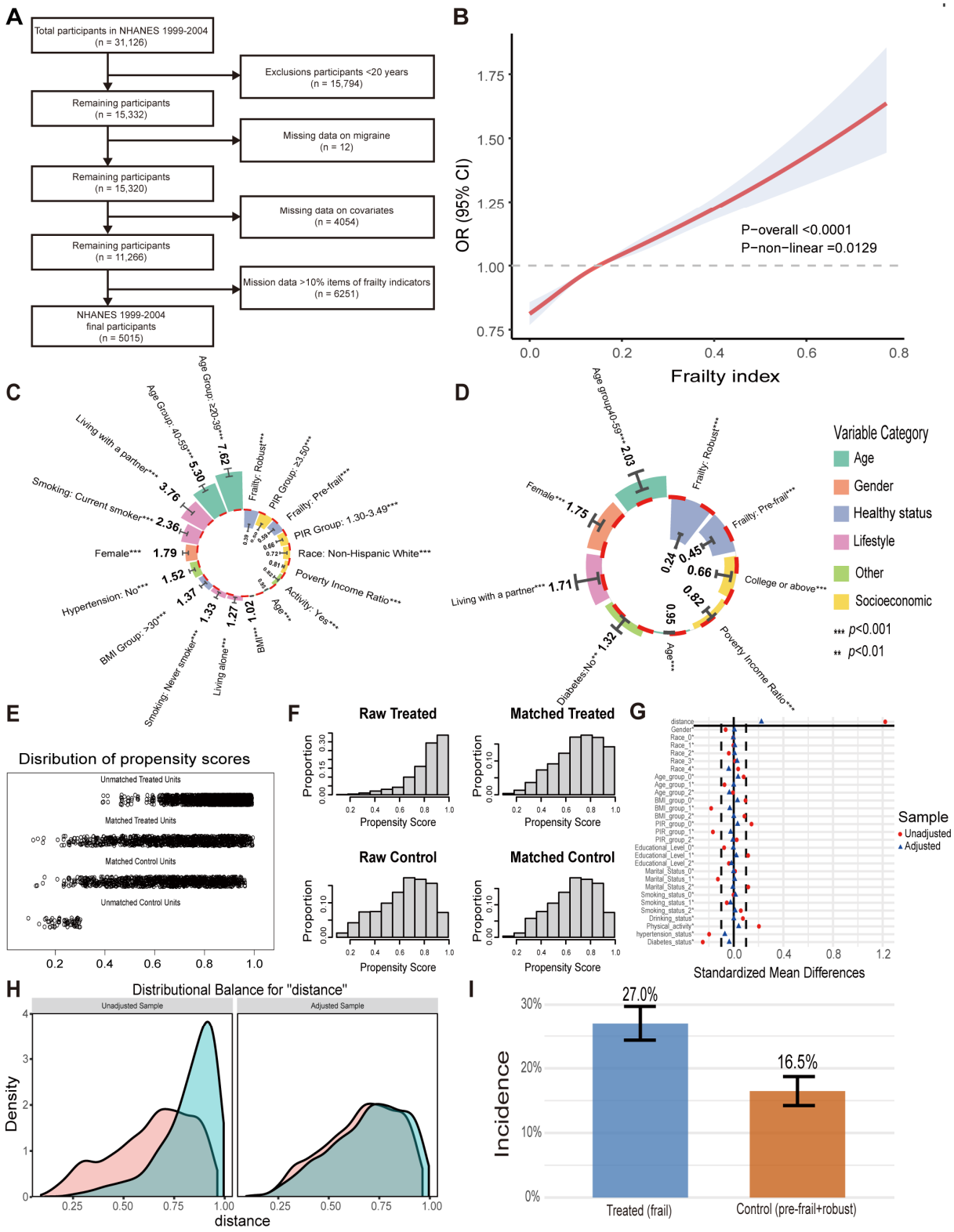

Figure 3. Epidemiological analysis based on NHANES. (**A**) Flowchart of participant selection in NHANES. (**B**) Dose-response association of FI with migraine prevalence. The solid red line represents the odds ratio (OR), and the shaded area represents the 95% confidence interval (CI). The model was adjusted for age, gender, race, BMI, poverty income ratio (PIR), educational level, marital status, smoking and drinking behaviors, physical activity, hypertension and diabetes. The dotted horizontal grey line represents the reference (OR = 1). (**C**,**D**) Statistical significance in univariate and multivariate logistic regression models displayed as donut chart. Variables with OR < 1, along with their estimates and CIs, are shown inside the ring, whereas those with OR > 1 are placed outside. Variables are categorized and color-coded: cyan, age; slate blue, health status; orange, gender; pink, lifestyle factors; yellow, socioeconomic factors; green, other. Significance levels are indicated as *** $p < 0.001$ and ** $p < 0.01$. The treated group represents frail individuals; the control group represents pre-frailty and robust individuals. (**E**) Density distribution of treated (frail) and control

(pre-frailty and robust) units before and after propensity score matching. (**F**) Sample sizes and proportions in treated and control groups before and after matching. (**G**) Standardized mean differences of covariates before and after matching (Red, unadjusted; Blue, adjusted). (**H**) Distributional balance of distance measures for treated and control units before and after matching. (**I**) Comparison of migraine prevalence between matched treated and control groups. The *p*-value was calculated using a conditional logistic regression model, with a matching ID incorporated as a stratification variable to properly account for the dependent nature of the matched pairs.

3.3. Risk Prediction Model for Migraine Based on the Interaction of FI and Age

In adults aged over 20, migraine probability peaked between ages 20–40 and decreased significantly, reaching a lower plateau around age 61. Three-dimensional interaction plots indicated an approximately positive linear relationship between FI and migraine probability in both the overall population aged 20–85 years (Figure 4A(c))

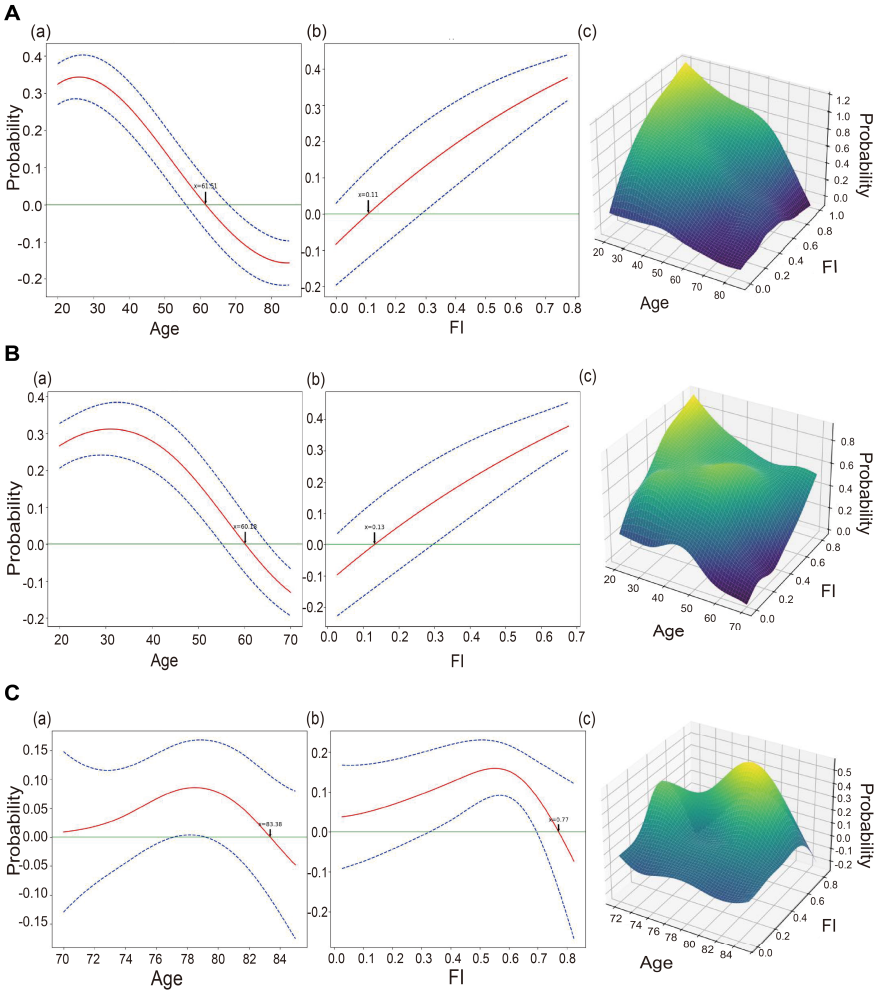

Figure 4. Interactive effects of FI and age on the probability of migraine. Curves show smoothed fits of age-probability or FI-probability relationships across age groups. (**A**) Smoothed effects for ages 20–85 years. (**B**) Smoothed effects for ages 20–70 years. (**C**) Smoothed effects for ages 70–85 years. Left panels (**a**) display the smoothed effect of age on migraine probability (x-axis: age; y-axis: migraine probability). Middle panels (**b**) display the interactive smoothed effect of FI on migraine probability (x-axis: FI; y-axis: migraine probability). The surface height in the right panels (**c**) shows the three-dimensional distribution of migraine probability under the combined effects of age and FI across the specified age groups. The red solid line represents a smooth curve formed by the observed values, and the two dotted lines indicate the upper and lower bounds of the fitted confidence interval.

A prominent interaction between FI and age was observed in the under-70 population (Figure 4B(c)). While the age effect was consistent with the overall trend (Figure 4B(a)), migraine probability increased markedly at an estimated FI threshold of 0.13 (Figure 4B(b)).

However, in adults over 70, migraine probability exhibited a distinct inverse U-shaped relationship with both age and FI, peaking at approximately 83 years and an FI of 0.77 before declining (Figure 4C(a)). This nonlinear association (Figure 4C(b)) appeared as a clear concave surface in the three-dimensional visualization (Figure 4C(c)).

3.4. Longitudinal Cohort Profiling and Predictive Effect Modeling in the Adults aged ≥ 45 years

Following the participant selection process (Figure 5A), 3852 individuals were included in the four-wave longitudinal cohort. In the four-wave longitudinal cohort, FI accumulated over time across all three groups (Robust, Pre-frail, and Frail), with the Frail group showing the highest accumulation and the Robust group the lowest. Survival curves differed significantly among groups (Log-rank $p < 0.0001$), indicating substantial disparities in migraine risk across frailty states (Figure 5B).

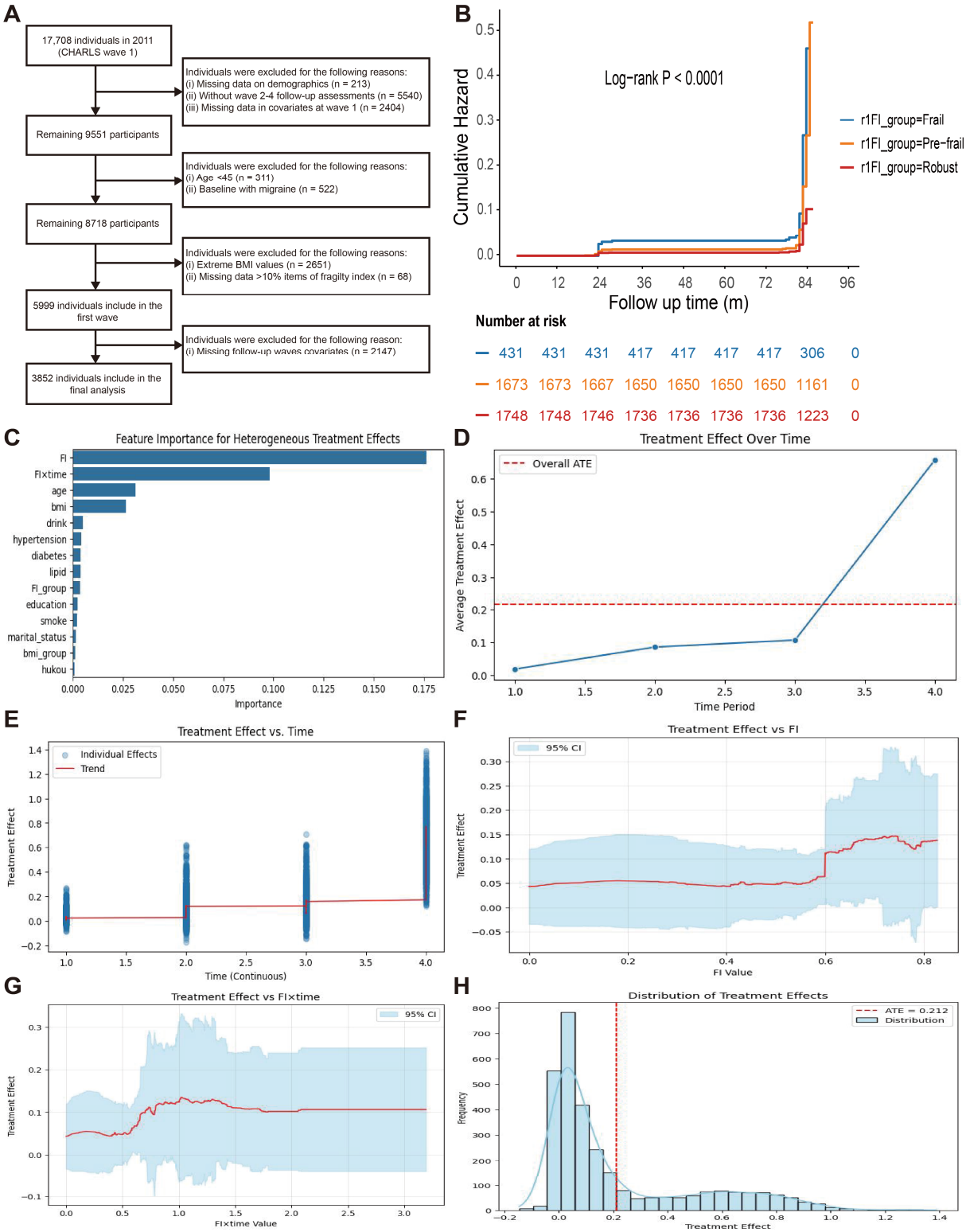

Figure 5. Framework for longitudinal analysis and machine learning-based predictive models. (**A**) Flowchart for participant selection in CHARLS. (**B**) Cumulative incidence curves for migraine by frailty status (Frail, Pre-frail, and Robust); group differences were compared using the log-rank test. (**C**) Feature importance for heterogeneous

treatment effects (x-axis: relative importance; y-axis: features). (**D**) Average treatment effect (ATE) of FI over time (x-axis: time period; y-axis: ATE). (**E**) Time-varying treatment effect of FI (x-axis: time period; y-axis: treatment effect). (**F**) Treatment effect across FI values (x-axis: FI; y-axis: treatment effect; light blue shading indicates the 95% CI). (**G**) Treatment effect across FI × time values (x-axis: FI × time; y-axis: treatment effect; light blue shading indicates the 95% CI). (**H**) The frequency distribution of the treatment effect of FI (x-axis: treatment effect; y-axis: frequency; red line: mean ATE)

Variable importance from the causal forest model indicated that FI, the FI × time interaction, and age were the top contributors to heterogeneous treatment effects (Figure 5C). The estimated predictive effect of FI on migraine remained relatively stable throughout the follow-up, supporting a sustained positive longitudinal association of FI on migraine incidence (Figure 5D). Clinical factors, like BMI, drinking, and hypertension showed moderate importance for personalized strategies, while socioeconomic factors had lesser influence.

Individualized treatment effect trajectories clustered around the overall trend, indicating population-level consistency (Figure 5E). Furthermore, the line chart (Figure 5F) revealed a substantial change in the treatment effect of FI on migraine at a specific FI value, reinforcing FI's potential predictive role. A sudden change in the treatment effect is observed when FI reached 0.6 (Figure 5F), suggesting that values above this threshold may correspond to shifts in biochemical mechanisms or indicators related to migraine onset. In other words, the machine learning analysis illustrates how current FI influences the probability of developing migraine.

The estimated effect was strongest at lower FI × time values and declined slightly, though remained positive, with increasing FI × time, while wider confidence intervals at higher levels indicated greater uncertainty (Figure 5G), suggesting the effect is most pronounced early but remains relevant over time. The distribution of individual estimated predictive effects was right-skewed (ATE = 0.212 ± 0.279), with most values between −0.2 and 0.2 and a minority of extremes (Figure 5H), highlighting substantial interindividual heterogeneity in susceptibility to FI-related migraine.

4. Discussion

This multi-level investigation suggests that the FI is a robust predictor of migraine risk across the adult lifespan, with age acting as a critical effect modifier rather than a simple confounder. Across multiple data sources, we consistently observed a positive association between FI and migraine risk that persisted after comprehensive covariate adjustment and propensity-score matching. The identification of a nonlinear dose-response relationship, with a marked inflection near an FI of 0.6, informs clinical risk stratification. The age-dependent heterogeneity in the FI-migraine association manifesting as a positive linear relationship in individuals younger than 70 years but an inverted U-shaped or negative correlation in older adults, highlights the complexity of systemic vulnerability across the life course. By establishing FI as a quantifiable dimension of biological age that predicts migraine susceptibility, this work bridges the conceptual gap between systemic frailty and neurological vulnerability, offering a scalable framework for risk assessment that could refine prevention strategies amid rising migraine incidence.

The biological plausibility of the frailty-migraine association rests on convergent pathophysiological mechanisms, particularly chronic inflammation and neuroinflammatory processes. Inflammaging, characterized by persistent low-grade inflammation with elevated inflammatory markers, is a fundamental feature of frailty that drives multi-organ vulnerability [38,39]. In migraine pathophysiology, trigeminal-vascular sensitization and neuroinflammatory processes, including CGRP and microglial pathway activation, are established mechanisms of pain sensitization [40–42]. The threshold effects observed in our study, risk elevation beginning at an FI of 0.11–0.13 and a nonlinear risk transition at an FI of 0.6, align with a biological model in which accumulated inflammatory burden progressively lowers the threshold for cortical spreading depression and trigeminal activation. The consistent longitudinal predictive signal and nonlinear threshold characteristics provide indirect support for these mechanistic pathways, suggesting that therapeutic interventions targeting systemic inflammation might offer dual benefits for both frailty and migraine prevention.

The negative FI-migraine correlation in elderly populations likely reflects survivor bias, diagnostic challenges, and age-related neurophysiological changes rather than a true reversal of the biological relationship. Selective survival of healthier individuals may exclude those with both conditions [43,44]. This inverse association should, therefore, be interpreted with extreme caution and should not be taken to imply that frailty protects against migraine in advanced age. Additionally, migraine presentation in older adults frequently deviates from classic patterns, manifesting as painless aura, tension-type overlap, or medication-overuse headache, leading to systematic underdiagnosis [45]. The age-related decline in cortical excitability, altered CGRP responsiveness, and desensitization of pain-modulation pathways may fundamentally alter migraine phenotype, potentially shifting toward other chronic pain syndromes [40–42]. Three-dimensional visualization demonstrated that age modifies

the shape of the FI-migraine relationship rather than merely shifting its magnitude, supporting age as an effect modifier. This distinction has important implications for clinical application, indicating that FI interpretation must be age-contextualized. Future studies with competing-risk analysis could clarify the extent of "silent migraine" in elderly populations and refine risk-prediction models across the age spectrum.

The identification of an FI of 0.6 as an exploratory threshold for migraine risk transition carries potential clinical implications for risk stratification and intervention timing, approximating the frailty threshold identified across multiple cohorts, beyond which mortality and disability risks escalate dramatically [46–47]. The convergence of our migraine-specific threshold with this established systemic vulnerability boundary suggests that migraine risk may undergo mechanistic transformation as individuals approach functional collapse. The dual-threshold model emerging from our analysis with early risk elevation at an FI of 0.13 and a dramatic transition at an FI of 0.6 provides a framework for staged intervention strategies. These thresholds suggest early prevention at an FI of 0.13 and intensive management beyond an FI of 0.6, addressing both migraine triggers and systemic vulnerability. The threshold concept also suggests potential biomarker candidates for mechanistic studies, as the transition point at an FI of 0.6 may correspond to critical changes in inflammatory mediators, autonomic function, or metabolic markers that could be targeted therapeutically. Clinical implementation could involve embedding simplified FI assessment within headache clinics or primary care settings, generating individualized risk profiles that integrate age and sex to guide resource allocation.

Despite providing novel insights, this study has several limitations. Reliance on large existing databases not specifically designed to study the frailty-migraine association introduces constraints. Definitions of migraine differed across cohorts. GBD used model-based epidemiological estimates while NHANES and CHARLS used self-reported diagnoses with potential recall bias. In particular, NHANES defined migraine as a severe headache or migraine during the past 3 months, while CHARLS defined it as concurrent headache and stomach pain [16,22]. Moreover, the variables and number of items used for FI construction were different between databases (36 indicators in GBD, 39 in NHANES, and 32 in CHARLS), which may affect the comparability across studies [13].

Although we employed advanced predictive effects models to estimate causal effects, the observational design precludes complete elimination of unmeasured confounding, such as genetic predisposition or early-life stress. Moreover, the FI thresholds of 0.13 and 0.6 should be considered as exploratory cut-offs and not validated clinical thresholds as they are not yet externally validated. Future research should address these limitations through several approaches. Prospective cohort studies should measure FI regularly from a young age while employing the IHS gold-standard migraine diagnosis. Integration of multi-omics and biomarker measurements, including inflammatory markers and CGRP levels, would help test the proposed inflammaging-neuroinflammation hypothesis. Randomized controlled trials evaluating whether multidimensional interventions targeting frailty can reduce migraine incidence would provide the highest level of evidence. Development of multidimensional risk-prediction models incorporating FI, genetic risk scores, and biomarker profiles would facilitate personalized prevention strategies.

5. Conclusions

This multi-level investigation highlights the FI as a potential, scalable predictor of migraine risk that operates through age-dependent mechanisms. The identification of critical thresholds and the characterization of age as an effect modifier provide a framework for precision prevention strategies tailored to biological rather than chronological age. Integration of frailty assessment into migraine risk evaluation could enhance clinical decision-making, particularly in younger populations, where rising incidence demands innovative approaches to risk stratification and early intervention.

Supplementary Materials

The additional data and information can be downloaded at: https://media.sciltp.com/articles/others/2609160952135970/TI-26050065-SI.pdf.

Author Contributions

H.Z. conceived and designed the study. H.Z. and S.J. conducted the formal analysis. H.Z. and S.J. specified methodology. H.Z. and S.J. conducted the visualization. H.Z. and S.J. wrote the manuscript. H.Z. provided project administration, supervision, and validation and revised the manuscript. H.Z. and H.L. reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The NCHS institutional Ethics Review Board approved the study design of NHANES (Protocol #98-12). Ethical approval for all the CHARLS waves was granted from the Institutional Review Board at Peking University. The IRB approval number for the main household survey, including anthropometrics, is IRB00001052-11015. As this study exclusively utilized publicly available, anonymized secondary data, no additional ethics approval was required. This complies with national and international guidelines on the use of de-identified data for research purposes (e.g., the Declaration of Helsinki).

Informed Consent Statement

Not applicable.

Data Availability Statement

The GBD data used in this study is publicly available at http://ghdx.healthdata.org/, accessed on 15 July 2025. The NHANES data used in this study is publicly available at https://wwwn.cdc.gov/nchs/nhanes/ accessed on 15 July 2025. The CHARLS data used in this study is publicly available at https://charls.pku.edu.cn/ accessed on 15 July 2025.

Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

Abbreviations

FI = frailty index, OR = odds ratio, 95% CI = 95% confidence interval, GBD = Global Burden of Disease, NHANES = National Health and Nutrition Examination Survey, CHARLS = China Health and Retirement Longitudinal Study, GBD-FI = Global Burden of Disease frailty index, BMI = body mass index, PIR = poverty income ratio, PSM = propensity score matching, LinearGAM = Linear Generalized Additive Model, EAPC = estimated annual percentage change, RCS = restricted cubic spline, ATE = average treatment effect, CATE = conditional average treatment effect.

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