Hypertension

ORIGINAL ARTICLE

Frailty Index Offers Greater Discrimination Than Age for Optimal Blood Pressure Targets: A Pooled Analysis of Two Randomized Trials

Yizhen Lyu*, Wenming Bian*, Yezhou Liu, Yetong Liu, Jiaheng Zhang, Zhaojie Song, Yamei Liu, Tao Chen, Chao Li

BACKGROUND: Contemporary hypertension guidelines emphasize individualized blood pressure (BP) management, often incorporating age; yet chronological age alone may be insufficient to guide optimal treatment. The frailty index offers a multidimensional measure of biological aging and may better guide BP management.

METHODS: We pooled participant-level data from SPRINT (Systolic Blood Pressure Intervention Trial) and ACCORD (Action to Control Cardiovascular Risk in Diabetes). The frailty index was calculated using a 31-item Rockwood cumulative-deficit model, with frailty defined as a frailty index >0.21. Participants were also categorized by age (<65 versus ≥65 years). Systolic BP (SBP) time in target range (TTR) was calculated using linear interpolation across 10 mm Hg intervals. Restricted cubic splines and stratified Cox models were used to assess the association between TTR within predefined SBP targets and major adverse cardiovascular events.

RESULTS: A total of 19 230 participants were included in the analysis (mean age, 65.2 years; 49.0% women; 68.2% classified as frail). Restricted cubic spline analyses showed a J-shaped relationship between average SBP and major adverse cardiovascular events, with clearer separation by frailty than by age. Among frail individuals, greater time spent within SBP intervals between 110 and 140 mm Hg was associated with lower major adverse cardiovascular event risk (hazard ratios per 10% increase in TTR, 0.92–0.94), whereas among nonfrail individuals, greater time spent below 130 mm Hg was associated with lower risk (hazard ratios per 10% increase in TTR, 0.89–0.98). Age demonstrated limited discrimination. Findings were consistent in separate analyses of SPRINT and ACCORD.

CONCLUSIONS: The frailty index, rather than chronological age, more accurately discriminates optimal SBP targets in hypertensive patients, whereas chronological age may remain a more practical tool in resource-limited settings. ***(Hypertension.* 2026;83:1556–1565. DOI: 10.1161/HYPERTENSIONAHA.125.26397.)** • **Supplement Material**.

Key Words: blood pressure ■ frailty ■ hypertension ■ risk assessment

See editorial by Cameron

Contemporary hypertension guidelines increasingly emphasize individualized blood pressure (BP) management,[1–4] with some providing age-related considerations when formulating systolic BP (SBP) targets.[1] The 2023 European Society of Hypertension (ESH) guideline recommends lower SBP targets for adults <65 years (<130 mm Hg) and more lenient targets for those aged 65 to 79 years (<140 mm Hg, with <130 mm Hg if tolerated).[1] However, individuals of the same chronological age can differ substantially in their underlying health status,[5] and emerging evidence suggests that chronological age alone may be insufficient to guide antihypertensive treatment decisions across heterogeneous populations.[6,7] As a result, continued reliance on chronological age may lead to undertreatment of some older adults—particularly those who are robust—while failing

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/HYPERTENSIONAHA.125.26397.

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Hypertension is available at www.ahajournals.org/journal/hyp

NOVELTY AND RELEVANCE

What Is New?

Frailty Index (FI), a multidimensional measure of accumulated health deficits, demonstrated greater discrimination of systolic blood pressure ranges associated with cardiovascular risk than chronological age in pooled analyses of SPRINT (Systolic Blood Pressure Intervention Trial) and ACCORD (Action to Control Cardiovascular Risk in Diabetes).

FI-defined grouping revealed distinct J-shaped associations systolic blood pressure and major adverse cardiovascular events among frail and nonfrail individuals, whereas similar patterns were less clearly distinguished when using chronological age alone.

What Is Relevant?

Chronological age, widely used in current hypertension guidelines, may not fully capture physiological heterogeneity among older adults.

FI reflects accumulated health deficits across multiple domains, which are closely associated with cardiovascular risk.

FI could serve as a practical and more precise tool for guiding individualized systolic blood pressure targets in clinical practice.

Clinical/Pathophysiological Implications?

Incorporating FI into hypertension management may reduce overtreatment in vulnerable patients and prevent undertreatment in robust older adults, supporting a shift from age-based to phenotype-based blood pressure targets.

Future trials should evaluate FI-guided treatment strategies prospectively and explore simplified FI tools for routine clinical use.

Nonstandard Abbreviations and Acronyms

ACCORD	Action to Control Cardiovascular Risk in Diabetes
BP	blood pressure
ESH	European Society of Hypertension
FI	frailty index
HR	hazard ratio
MACE	major adverse cardiovascular events
RCS	restricted cubic spline
SBP	systolic blood pressure
SPRINT	Systolic Blood Pressure Intervention Trial
TTR	time-in-target range

to identify more vulnerable patients whose frailty is not captured by age alone.

Frailty index (FI) is a measure of accumulated health deficits across multiple domains, reflecting global vulnerability associated with biological aging.[8–10] Recent studies examining the relationship between frailty and adverse health outcomes suggest that FI better reflects individual biological aging than chronological age, indicating its potential clinical utility, although definitive evidence remains limited.[11–13] Furthermore, several investigations have specifically examined the benefits in frail populations through analyses of existing trial data, aiming to clarify whether frail individuals derive similar advantages from treatment as their nonfrail counterparts.[14,15] However, it remains uncertain whether FI offers greater discrimination than chronological age in identifying optimal BP targets and whether these targets are consistent with current guideline recommendations.

Therefore, in this pooled analysis of 2 randomized clinical trials (SPRINT [Systolic Blood Pressure Intervention Trial] and ACCORD [Action to Control Cardiovascular Risk in Diabetes]), we classified participants by both FI and chronological age and applied the time in target range (TTR) approach to evaluate their associations with major adverse cardiovascular events (MACE) across different BP control targets, as well as to assess their alignment with current guideline-recommended targets, to determine whether FI offers greater clinical utility than chronological age. These findings may help inform more individualized, risk-based approaches to hypertension management.

METHODS

Data Availability

All data and materials have been made publicly available at the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center and can be accessed at http://biolincc.nhlbi.nih.gov/home/.

Data Sources and Study Population

This pooled analysis utilized participant-level data from 2 major randomized controlled trials: the SPRINT (n=9361) and the ACCORD (n=10 251).[16,17] The study designs and primary results of both trials have been previously published.[16,17] Participants were excluded if they had missing key covariate data or experienced the primary outcome before the first follow-up. Further details on the study population, inclusion and exclusion criteria, and data harmonization are provided in Figure 1 and the Supplementary Methods.

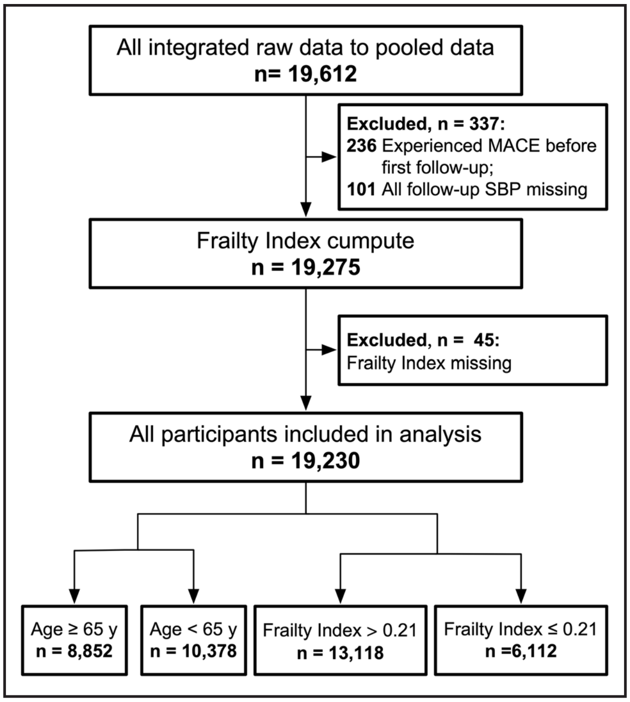

Figure 1. Research flowchart and the exclusion criteria.
A total of 19 612 individual-level records were included in the pooled data set. After applying exclusion criteria, 19 230 participants were categorized into 2 age groups: <65 years (n=10 378) and ≥65 years (n=8852). Frailty status was determined using a deficit-accumulation frailty index (FI), with FI >0.21 classified as frail (n=13 118) and FI ≤0.21 classified as nonfrail (n=6112). SBP indicates systolic blood pressure.

Both the SPRINT and ACCORD trials were approved by their respective institutional review boards. This study was granted a waiver of ethical approval by the ethical review board of the First Affiliated Hospital of Xi'an Jiaotong University (MC-KYLLSL-2023-005).

Ascertainment of Frailty

Frailty was assessed using the validated Rockwood cumulative-deficit approach,[18,19] following established methodological guidance from Searle et al[19] and prior FI applications in SPRINT,[14,20] ACCORD[15] and other large clinical trials.[11,21] A 31-item FI was constructed using variables available in both data sets.[14,15] Item selection adhered to the standard criteria for Rockwood-style FIs[19]: (1) each item reflects a health-related deficit; (2) the deficit increases in prevalence with age; (3) the deficit does not saturate prematurely; (4) the set of items collectively spans multiple physiological and functional systems; and (5) when used longitudinally, items remain consistent over time. Consistent with the methodological recommendations that typically include at least 30 to 40 deficits to ensure statistical stability and multisystem coverage,[19] our 31-item FI falls within the accepted range for a robust cumulative-deficit FI.

The items for FI calculation were derived from vital signs, comorbidities, laboratory data, and health-related quality-of-life measures (see Table S1 for the complete item list). Binary variables (eg, myocardial infarction) were scored as 0 or 1 (absent/present); ordinal variables (eg, self-reported functional limitations) were scored from 0 to 1 in 0.2 or 0.25 increments to reflect severity; and continuous variables were categorized as normal/abnormal (0/1).

For each participant, the FI was calculated as the proportion of accumulated deficits among nonmissing items. Participants with fewer than 15 available items were excluded. In line with widely used thresholds in prior SPRINT,[14,20] ACCORD,[15] and population-based FI studies,[11,21] frailty was defined as FI >0.21 and nonfrailty as FI ≤0.21.[22,23]

Study Outcomes

In the present study, the primary outcome was the incidence of the first MACE. MACE was defined as the composite occurrence of any of the following events: myocardial infarction, stroke, or cardiovascular mortality. Each outcome was identified and adjudicated according to the prespecified criteria and end point definitions used in the original SPRINT and ACCORD trials.[17,24] All events were centrally adjudicated and independently validated within the context of the parent studies to ensure consistency and comparability of outcome assessment.

TTR Calculation

TTR for SBP was defined as the percentage of follow-up time during which each participant's SBP remained within a specified target interval.[25] SBP TTR was estimated using linear interpolation between consecutive study visits, under the assumption that SBP changed linearly between measurements.[26] TTR was calculated for SBP intervals in 10 mm Hg increments across the full SBP range, with additional boundary categories for SBP <110 mm Hg and ≥150 mm Hg to capture extreme BP levels.

Statistical Analysis

Baseline characteristics were summarized as means with standard deviations for continuous variables, and as counts with percentages for categorical variables. Between-group comparisons were conducted using the Wilcoxon rank-sum test for continuous variables and the χ^2 test for categorical variables.

Restricted cubic spline (RCS) functions with 3 knots (10th, 50th, and 90th percentiles) were incorporated within Poisson regression models to examine potential nonlinear associations between average SBP and MACE incidence rates. RCS models were adjusted for age, sex, race, body mass index, baseline SBP, smoking status, and diabetes status.

Cox proportional hazards models were fitted to evaluate the association between SBP TTR and the risk of MACE. TTR for each predefined SBP interval was evaluated in separate Cox models, without specifying a single SBP interval as a fixed reference group. Models were adjusted for the same covariates as the RCS analyses, including age, sex, race, body mass index, baseline SBP, smoking status, and diabetes status, and were stratified by trial (SPRINT versus ACCORD). Hazard ratios (HRs) were estimated per 10% increase in TTR. Interaction terms for age and sex were included to assess potential effect modification. The proportional hazards assumption was assessed using Schoenfeld residuals. Sensitivity analyses were conducted by separate evaluation of each study. All statistical analyses were performed using R (version 4.4.2, R Foundation for Statistical Computing). Statistical significance was defined as a 2-sided $P<0.05$.

RESULTS

A total of 19 612 individual records were pooled for analysis. Of these, 337 participants were excluded because they experienced a primary MACE event before the first follow-up visit (n=236), which precluded calculation of SBP TTR, or because of the absence of any follow-up SBP data (n=101). FI was computed for the remaining 19 275 participants; a further 45 were excluded for having fewer than 15 nonmissing items required for FI computation, and thus were considered as having missing FI values. The final analytic cohort comprised 19 230 participants, who were subsequently categorized by age group (≥65 years: n=8852; <65 years: n=10 378) and frailty status (FI >0.21: n=13 118; FI ≤ 0.21: n=6112; Figure 1). The mean baseline age was 65.2±8.5 years, with 49.0% female and 63.8% White participants. The study involved an average of 17.7±7.7 SBP measurements per individual during the study period. Baseline characteristics by age and frailty strata are detailed in the Table, and the distribution of age and FI values is shown in Figures S1 and S2. The distribution of participants across these age and frailty subgroups, and the transitions between them, were visualized using a Sankey diagram (Figure 2), enabling a clear depiction of how individuals were allocated within and moved between categories.

RCS analyses demonstrated a J-shaped association between average visit SBP and the incidence rate of MACE in both age (Figure 3A) and frailty status (Figure 3B). When grouped by age (Figure 3A), the MACE incidence curves showed substantial overlap, with only modest differences observed between groups. Both younger and older participants demonstrated similar patterns—a J-shaped curve with the lowest MACE incidence around 120 to 130 mm Hg—indicating that age alone was less effective in differentiating cardiovascular risk or optimal SBP range compared with frailty status. However, the separation between frail and nonfrail groups was more pronounced (Figure 3B), and frail participants consistently exhibited higher MACE rates across the SBP spectrum. For frail individuals, the lowest incidence of MACE was observed when average SBP was maintained within a relatively narrow range of 120 to 130 mm Hg, with no evidence of additional benefit at lower SBP levels. In contrast, among nonfrail individuals, MACE risk continued to decrease with further SBP reduction below 130 mm Hg, without a clearly defined lower threshold.

A similar pattern was observed in the stratified Cox proportional hazards models assessing the association between SBP TTR and MACE risk, where TTR within each predefined SBP interval was modeled separately as a continuous exposure (per 10% increase in follow-up time spent within that interval) and grouped by age and frailty status (Figure 3C and 3D). Grouped by age demonstrated much less pronounced separation across SBP categories, with similar HRs observed for both age groups within each SBP range (Figure 3C). For example, among participants aged ≥65 years, the HRs for MACE were 0.92 (95% CI, 0.88–0.97), 0.93 (95% CI, 0.88–0.98), and 0.95 (95% CI, 0.91–0.99) for the 110 to 120, 120 to 130, and 130 to 140 mm Hg categories, respectively, with no appreciable differences from the younger group. However, among frail individuals (Figure 3D), each 10% increase in time spent within the 110 to 120 mm Hg SBP range was associated with a lower risk of MACE (HR, 0.93 [95% CI, 0.90–0.96]), while for 120 to 130 mm Hg and 130 to 140 mm Hg, the corresponding HRs were 0.92 (95% CI, 0.88–0.96) and 0.94 (95% CI, 0.91–0.97), respectively. In contrast, at SBP levels below 110 mm Hg and above 140 mm Hg, the risk of MACE

Table. Baseline Characteristics According to Age and Frailty Index

	Age, y		FI		
Characteristics	<65, n (%)=10 378 (54.0%)	≥65, n (%)=8852 (46.0%)	Nonfrail (FI ≤ 0.21), n (%)=6112 (31.8%)	Frail (FI >0.21), n (%)=13 118 (68.2%)	Overall, n=19 230
Patient age, mean (SD)	58.8 (3.9)	72.7 (5.8)	65.6 (8.5)	65.0 (8.5)	65.2 (8.5)
Female, n (%)	5195 (50.1)	4236 (47.9)	2547 (41.7)	6884 (52.5)	9431 (49.0)
White People, n (%)	5936 (57.2)	6326 (71.5)	3994 (65.3)	8268 (63.0)	12 262 (63.8)
Baseline SBP, mm Hg; mean (SD)	136.6 (16.5)	139.4 (16.3)	131.9 (13.9)	140.7 (16.8)	137.9 (16.4)
Baseline DBP, mm Hg; mean (SD)	79.2 (11.1)	73.2 (10.9)	75.8 (10.1)	76.7 (11.9)	76.4 (11.4)
BMI, kg/m^2; mean (SD)	32.2 (5.7)	30.5 (5.2)	29.9 (5.2)	32.3 (5.6)	31.6 (5.6)
CVD history, n (%)	2763 (26.6)	2582 (29.2)	612 (10.0)	4733 (36.1)	5345 (27.8)
Diabetes history, n (%)	6663 (64.2)	3508 (39.6)	2143 (35.1)	8028 (61.2)	10 171 (52.9)
MACE outcome, n (%)	656 (6.4)	826 (9.3)	276 (4.5)	1206 (9.2)	1482 (7.7)
SBP visit times per participant*, mean (SD)	17.5 (7.7)	18.0 (7.7)	18.2 (6.9)	17.5 (8.1)	17.7 (7.7)

BMI indicates body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; FI, Frailty index; MACE, major adverse cardiovascular events; and SBP, systolic blood pressure.

*SBP measurement times per individual=Total SBP measurement times/Number of participants.

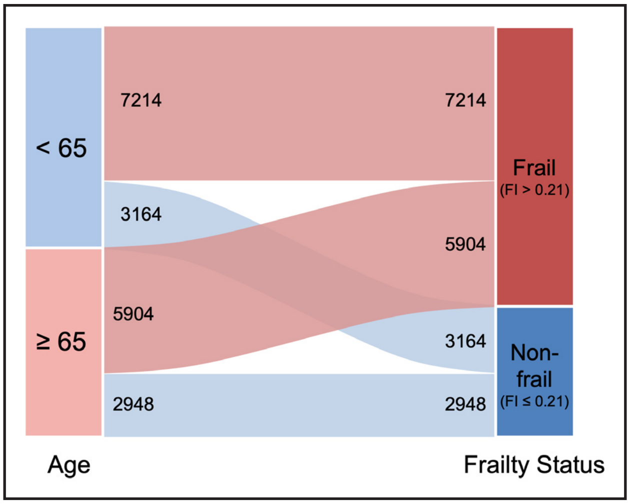

Figure 2. Distribution of frailty status across age groups. This alluvial diagram illustrates the flow of participants from 2 age categories (<65 years and ≥65 years) to frailty status (frail and nonfrail) as defined by the frailty index (FI). Frailty was classified using an FI threshold of 0.21, with FI >0.21 indicating frail status and FI ≤0.21 indicating nonfrail status. Among individuals aged <65 years, 7214 were frail and 3164 were nonfrail, whereas among those aged ≥65 years, 5904 were frail and 2948 were nonfrail. The width of each stream is proportional to the number of participants within each transition.

increased, with HRs of 1.01 (95% CI, 0.97–1.06) for <110 mm Hg, 1.11 (95% CI, 1.06–1.16) for 140–150 mm Hg, and 1.17 (95% CI, 1.14–1.21) for ≥150 mm Hg. For nonfrail individuals, a higher proportion of follow-up time spent within the 110 to 120 mm Hg and 120 to 130 mm Hg SBP ranges was associated with a lower risk of MACE, with HRs of 0.90 (95% CI, 0.84–0.96) and 0.98 (95% CI, 0.90–1.06), respectively. Notably, a higher proportion of follow-up time spent within SBP <110 mm Hg remained associated with a lower risk (HR, 0.89 [95% CI, 0.80–0.99]), whereas risk increased for higher SBP levels: 1.07 (95% CI, 1.01–1.14) for 130–140 mm Hg, 1.21 (95% CI, 1.10–1.33) for 140–150 mm Hg, and 1.18 (95% CI, 1.04–1.34) for ≥150 mm Hg. These associations between SBP categories, frailty status, and MACE risk were robust and remained evident in both the ACCORD and SPRINT trial populations (Table S2; Figure S3).

Further subgroup analyses by age and frailty (Figure 4; Table S3) showed that, in the RCS analyses (Figure 4A and 4B), the association between average visit SBP and MACE incidence exhibited a similar J-shaped pattern across age groups, while frail individuals consistently showed higher incidence rates than nonfrail individuals across the SBP spectrum. In the corresponding TTR-based Cox models (Figure 4C and 4D) among frail individuals, each 10% increase in TTR within the 130 to 140 mm Hg SBP range was associated with a lower risk of MACE, with HRs of 0.93 (95% CI, 0.89–0.98) for age <65 years and 0.94 (95% CI, 0.90–0.99) for age ≥65 years. In contrast, among nonfrail participants, this protective effect was absent and even reversed, with higher TTR at 130–140 mm Hg linked to increased risk (HR, 1.13 [95% CI, 1.04–1.23] for age <65 years; HR, 1.00 [95% CI, 0.90–1.10] for age ≥65 years). Notably, in frail individuals, higher TTR at SBP <110 mm Hg was associated with increased risk (age <65 years: HR, 0.99 [95% CI, 0.93–1.05]; age ≥65 years: HR, 1.03 [95% CI, 0.97–1.10]), while in nonfrail individuals, the association remained neutral or protective (HRs <1).

DISCUSSION

The findings of this pooled analysis of SPRINT and ACCORD revealed that patients with frailty had consistently higher risks of MACE across the SBP spectrum compared with nonfrail individuals. Among frail patients, a higher proportion of follow-up time spent within SBP intervals between 110 and 140 mm Hg (including 110–120, 120–130, and 130–140 mm Hg) was associated with lower MACE risk, closely aligning with guideline-recommended targets, whereas nonfrail patients benefited from stricter control, with optimal SBP below 130 mm Hg or potentially even lower. Although the protective association of higher TTR was attenuated at lower SBP levels in frail individuals, the overall pattern suggests that FI-based grouping may better discriminate optimal SBP ranges associated with lower risk than chronological age.

Our findings also highlight the need for cautious interpretation of the J-shaped curve at lower SBP levels, particularly among frail individuals. In this subgroup, the attenuation or reversal of benefit at SBP <110 mm Hg may partly reflect reverse causation, whereby low SBP serves as a marker of underlying illness, such as impaired cardiac output, cachexia, autonomic dysfunction, or advanced multimorbidity, rather than a harmful effect of BP lowering itself. Although our models adjusted for comorbidities, illness-related reductions in SBP cannot be fully excluded. By contrast, in nonfrail individuals, SBP <110 mm Hg remained associated with neutral or lower risk, suggesting that low SBP in robust patients may reflect effective risk-factor control rather than underlying morbidity.

Contemporary hypertension guidelines differ in how they incorporate age into treatment recommendations.[1–4] While the 2023 ESH guideline provides explicit age-grouped SBP targets—recommending an initial BP target of <130/80 mm Hg for adults under 65 years, <140/80 mm Hg for those aged 65 to 79 years (with <130/80 mm Hg as an optional goal if well tolerated), and 140 to 150 mm Hg for patients aged ≥80 years (with consideration of 130–139 mm Hg if well tolerated).[1] These age thresholds partly reflect physiological differences: in younger adults, elevated BP is usually driven by reversible hemodynamic and early vascular changes, allowing for safer intensive lowering; whereas

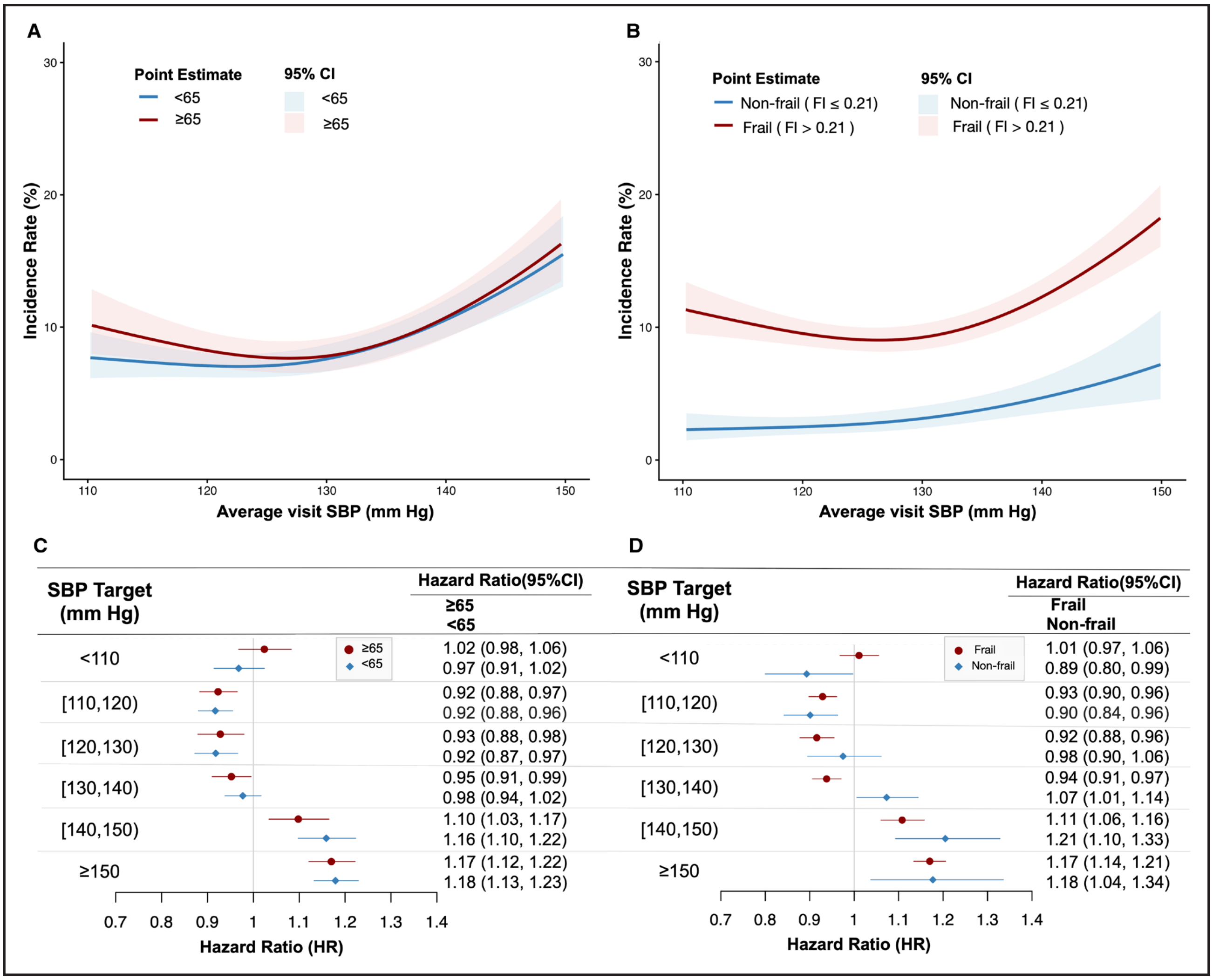

Figure 3. Associations of average systolic blood pressure (SBP) and time in target range with major adverse cardiovascular events (MACE) by age group and frailty status.

Restricted cubic spline (RCS) curves showing the association between average visit SBP and the incidence rate of MACE, grouped by chronological age (<65 vs ≥65 years; **A**) and frailty status (Frailty Index [FI] ≤0.21 vs FI >0.21; **B**). Shaded areas represent 95% CI. Stratified Cox proportional hazards models showing the association between SBP time in target range (TTR) and risk of MACE across SBP target intervals, grouped by age (**C**) and frailty status (**D**). Hazard ratio (HR) represents the change in MACE risk per 10% increase in TTR within each target interval.

in older adults, arterial stiffening, widened pulse pressure, and more comorbidities increase the risk of hypotension and related adverse events, leading to more conservative targets.[27] The 2024 ESH and 2024 European Society of Cardiology guidelines emphasize individualized treatment based on comorbidities, frailty, orthostatic symptoms, and treatment tolerance, and do not assign different SBP targets solely on the basis of chronological age. These differences reflect the increasing recognition that age alone does not fully capture physiological heterogeneity among older adults. However, our study, together with previous research,[6,28] demonstrates that age-based stratification alone does not sufficiently capture the heterogeneity in health status among patients. In our analyses, chronological age also showed a J-shaped pattern with MACE risk, but its discriminatory capacity was limited, with largely overlapping curves across age groups. Older and younger participants exhibited similar patterns in the association between TTR across different BP targets and MACE risk. This finding did not provide clear support for the age-specific BP targets recommended in the 2023 ESH guideline, suggesting that chronological age may have limited value in distinguishing optimal BP targets. By contrast, FI-based grouping provides a more nuanced and clinically relevant approach for identifying optimal BP targets across diverse patient populations.

FI is a quantitative measure of accumulated health deficits across multiple physiological domains, offering a multidimensional assessment of biological aging and vulnerability.[18,19] Unlike chronological age, which offers only a crude approximation of physiological decline, FI

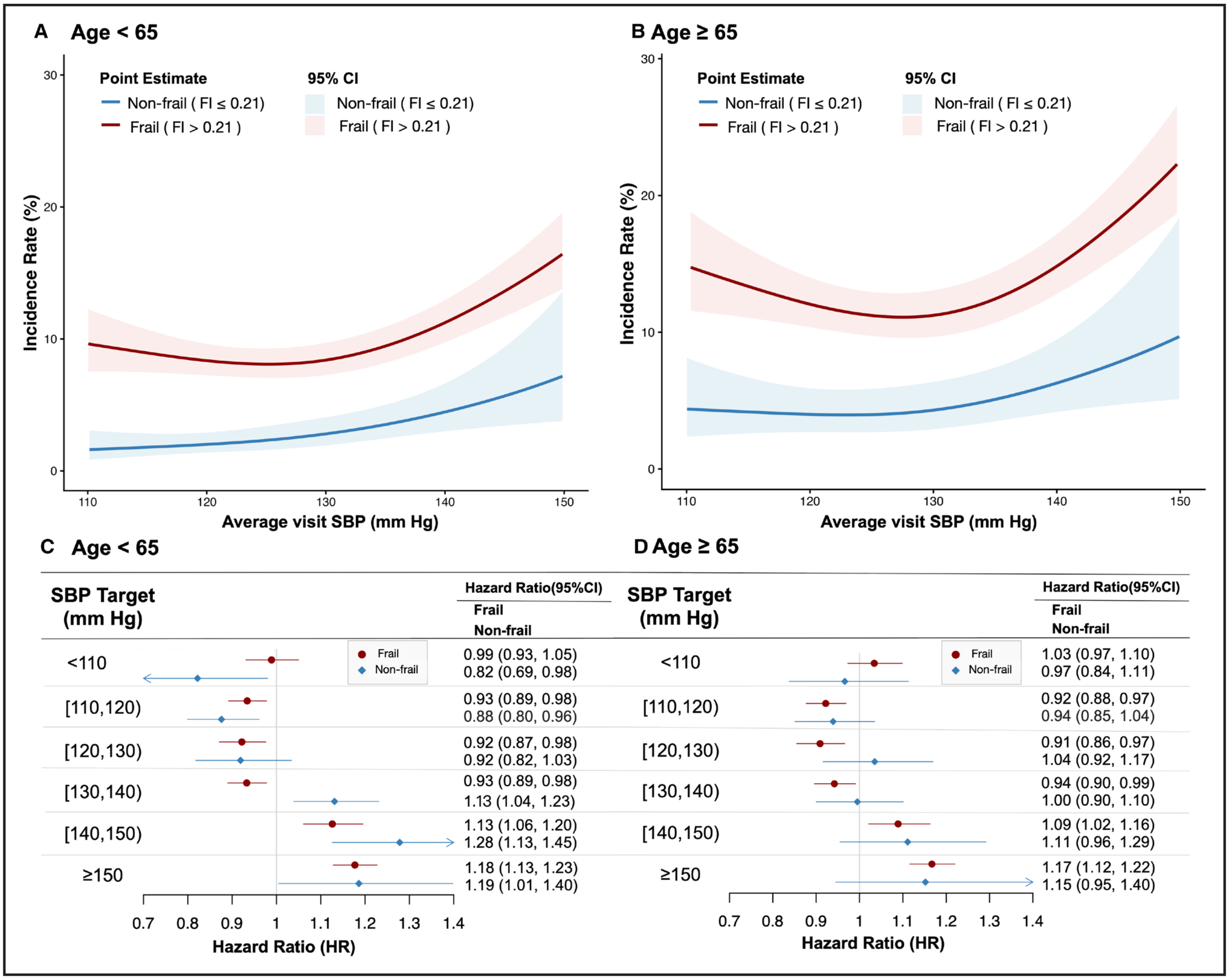

Figure 4. Associations of average systolic blood pressure (SBP) and time in target range with major adverse cardiovascular events (MACE) within age groups, by frailty status.

Restricted cubic spline (RCS) curves showing the association between average visit SBP and the incidence rate of MACE, first grouped by chronological age (<65 years in **A**; ≥65 years in **B**), and further grouped within each age group by frailty status (Frailty index [FI] ≤0.21 vs >0.21). Shaded areas represent 95% CI. Stratified Cox proportional hazards models showing the association between SBP time in target range (TTR) and the risk of MACE across predefined SBP target intervals in <65 years participants (**C**) and ≥65 years participants (**D**). Hazard ratios (HRs) represent the change in MACE risk per 10% increase in TTR within each SBP target interval, separately estimated for frail or nonfrail individuals.

systematically integrates comorbidities, functional status, labs, and symptoms to provide a comprehensive assessment of patient risk.[19,29] Previous research has consistently demonstrated that FI is associated with increased cardiovascular morbidity and mortality.[15,30–32] Similar to well-established risk factors such as diabetes[30] and cardiovascular disease history,[33] which show a J-shaped association with SBP in higher-risk populations, FI can identify individuals at elevated cardiovascular risk and exhibits a similar pattern. Collectively, these observations support the proposition that FI may offer superior discriminatory capacity over chronological age for identifying high-risk individuals. Building on these prior findings, our analysis applying FI to the entire study population, revealing distinct differences in optimal BP targets and MACE outcomes between frail and nonfrail groups, differences not observed when stratifying by age alone. In light of these advantages, our findings suggest that incorporating FI into routine risk stratification could facilitate more individualized BP management, optimizing cardiovascular outcomes while minimizing unnecessary treatment burden in robust patients and avoiding overtreatment in vulnerable populations. This supports a paradigm shift from age-centric to frailty-centric risk stratification in hypertension guidelines.

In addition to stratifying MACE risk by FI, this study used the TTR method to evaluate BP control. Unlike traditional approaches based on single-time-point or mean BP measurements, TTR summarizes repeated BP measurements over follow-up into a single proportion representing the amount of time spent within predefined SBP ranges, providing an integrated summary of BP control across follow-up.[25,34] This metric captures both the consistency and stability of BP management, factors closely linked to cardiovascular outcomes.[35] The use of TTR enables a more nuanced summary of BP exposure over follow-up, which may complement traditional single-time-point or mean BP metrics, particularly in heterogeneous populations, and is well-suited for use in large-scale clinical data sets and real-world practice, facilitating robust risk stratification and individualized management.[25,34,36–38] Our findings suggest that incorporating both FI and TTR into hypertension management may improve risk prediction and guide more personalized treatment decisions. Future work should focus on standardizing TTR metrics and integrating them into routine care pathways across diverse health care settings.

Our study has several limitations. First, the items used for FI calculation may vary across studies. Although we harmonized variables between the 2 trials as much as possible, the development of a standardized approach for FI construction would facilitate broader and more consistent application in future research and clinical practice. In addition, the FI derives its predictive ability from the multidomain accumulation of deficits rather than from any single component, and preliminary exploration of FI domains did not identify individual items with discriminatory capacity comparable to the full FI. This inherent characteristic of the cumulative-deficit model may limit the feasibility of simplifying FI for routine clinical use. Second, both trials excluded individuals with certain high-risk clinical conditions such as a history of stroke or advanced heart failure, which may limit the generalizability of our findings to some higher-risk patient populations. Third, our age-based analyses were constrained by the available sample distribution. We selected 65 years as the age threshold because the 2023 ESH guideline defines individuals aged ≥65 years as older persons for treatment stratification. However, the pooled data set contained relatively few adults aged ≥80 years, limiting our ability to evaluate guideline-defined distinctions between the 65–79 and ≥80 age categories. Thus, our results may not fully capture risk patterns at the oldest ages. Fourth, SPRINT and ACCORD primarily included participants from North American and European populations, which may limit the generalizability of our findings to other ethnicities and health care settings. Future studies should validate these results in more diverse populations, including Asian, African, and low-to-middle-income country cohorts, to assess potential differences in FI distribution, BP target effects, and cardiovascular risk profiles. These considerations also have implications for clinical implementation: in high- and middle-income countries, where older adults generally have better health status and access to comprehensive electronic medical records, frailty assessment may provide greater clinical value and enable more individualized BP management. By contrast, in low-income settings, maintaining age-based BP targets may remain a more feasible and practical approach, given limited resources and the lack of routinely available data necessary for FI calculation. In addition, TTR is calculated using BP measurements obtained over the entire follow-up period and therefore depends on survival and remaining event-free. As a result, TTR should be interpreted as a descriptive summary of BP control during follow-up rather than a causal or time-updated exposure, and its use may introduce bias related to differential follow-up duration.

In conclusion, our findings demonstrate that while both chronological age and frailty relate to SBP-associated MACE risk, the FI more accurately identifies optimal SBP targets among patients with hypertension. For frail individuals, greater time spent within specific SBP intervals between 110 and 140 mm Hg (including 110–120, 120–130, and 130–140 mm Hg) was associated with lower MACE risk, whereas among nonfrail individuals, lower risk was observed with greater time spent in SBP intervals below 130 mm Hg. The FI-based approach is particularly applicable in regions with higher health standards and robust electronic medical records, whereas age may remain a more practical criterion in resource-limited settings.

PERSPECTIVES

Our findings highlight the potential clinical value of incorporating frailty assessment into hypertension management, particularly in determining optimal SBP targets for populations with heterogeneous physiological reserve. Current guidelines increasingly emphasize individualized treatment strategies, yet practical tools that quantify biological vulnerability remain limited. The FI, as demonstrated in this pooled analysis of 2 major randomized trials, offers a multidimensional framework that more accurately captures risk heterogeneity than chronological age.

These results suggest that FI-based risk stratification may help refine BP treatment targets in clinical settings. Integration of FI into electronic health records and clinical decision-support systems may further enhance risk stratification and guide personalized SBP goals. Future research should explore simplified or automated FI-based tools for use in routine care, evaluate their performance in more diverse populations, and examine whether FI-guided BP management improves clinical outcomes in prospective studies. By shifting focus from age-centric thresholds to biologically informed measures of vulnerability, FI-based stratification may enable more precise, equitable, and patient-centered hypertension care.

ARTICLE INFORMATION

Received November 11, 2025; accepted February 12, 2026.

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Sources of Funding

This work was supported by the National Natural Science Foundation of China (No. 82322060).

Disclosures

None.

Supplemental Material

Supplemental Methods
Tables S1–S3
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References 1–3
STROBE Checklist

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