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The association between frailty and incident cardiovascular disease events in community-dwelling healthy older adults

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Declaration of competing interest

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CRediT authorship contribution statement

We certify that all authors contributed significantly to this publication. A.R.M. Saifuddin Ekram conceptualized and designed the study, searched the literature, analyzed data, interpreted results and drafted the manuscript. John J. McNeil, Robyn L. Woods, Andrew M. Tonkin, Lawrence Beilin, Sara E. Espinoza, Christopher M. Reid, Mark R. Nelson, Anne B. Newman, and Michael E. Ernst conducted the ASPREE clinical trial. Andrew M. Tonkin, Lawrence Beilin, Joanne Ryan, Sara E. Espinoza, Christopher M. Reid, Mark R. Nelson, Anne B. Newman, John J. McNeil, Michael E. Ernst and Robyn L. Woods reviewed, edited and contributed to the writing. All authors read and approved the final manuscript.

Statement of ethics

The ASPREE clinical trial is registered with the International Standard Randomized Controlled Trial Number Register (ISRCTN83772183) and clinicaltrials.gov (NCT01038583). ASPREE was conducted according to the Declaration of Helsinki 1964 as revised in 2008, the National Health and Medical Research Council (NHMRC) guidelines on human experimentation, the Federal Patient Privacy Law, Health Insurance Portability and Accountability Act (HIPAA), and the International Conference of Harmonization Guidelines for Good Clinical Practice (ICH-GCP). The ASPREE trial also followed the Code of Federal Regulations related to clinical research areas. It was approved by the Monash University Human Research Ethics Committee (MUHREC) (IRB00002519; ethics #2006/745MC) and other allied institution ethics committees. The Intellectual Property and Ethics Committee has approved this current project of Monash University (Reference no. V6VVQTXZ; 29 November 2019) as well as MUHREC (ethics #2021/30049). The ASPREE Steering Committee was responsible for the trial's overall management and conduct.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2023.100289.

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Abstract

Study objective: This study examined the association between frailty and incident cardiovascular disease (CVD) events, major adverse cardiovascular events (MACE), and CVD-related mortality.

Design: Longitudinal cohort study.

Setting: The ASPirin in Reducing Events in the Elderly (ASPREE) clinical trial in Australia and the United States.

Participants: 19,114 community-dwelling older adults (median age 74.0 years; 56.4 % females).

Interventions: Pre-frailty and frailty were assessed using a modified Fried phenotype and a deficit accumulation Frailty Index (FI) at baseline.

Main outcome measures: CVD was defined as a composite of CVD death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for heart failure; MACE included all except heart failure. Cox proportional hazards regression was used to analyze the association between frailty and CVD outcomes over a median follow-up of 4.7 years.

Results: Baseline pre-frail and frail groups had a higher risk of incident CVD events (Hazard Ratio (HR): 1.31; 95 % Confidence Interval (CI): 1.14–1.50 for pre-frail and HR: 1.63; 95 % CI: 1.15–2.32 for frail) and MACE (pre-frail HR: 1.26; 95 % CI: 1.08–1.47 and frail HR: 1.51; 95 % CI: 1.00–2.29) than non-frail participants according to Fried phenotype after adjusting for traditional CVD risk factors. Effect sizes were similar or larger when frailty was assessed with FI; similar results for men and women.

Conclusion: Frailty increases the likelihood of developing CVD, including MACE, in community-dwelling older men and women without prior CVD events. Screening for frailty using Fried or FI method could help identify community-dwelling older adults without prior CVD events who are more likely to develop CVD, including MACE, and may facilitate targeted preventive measures to reduce their risk.

Keywords

Cardiovascular disease; Frailty; Heart failure; Mortality; Myocardial infarction; Stroke

1. Introduction

Frailty is an important geriatric condition conceptualized as an increased vulnerability to stressors because of the significant depletion of physiological reserves [1,2]. It is gaining importance as a predictor of increased morbidity and mortality as older adults age [3]. This is particularly relevant for cardiovascular disease (CVD), as the prevalence and incidence of CVD also markedly increase with age [4]. Previous research on the relationship between frailty and CVD outcomes in community-dwelling older adults produced mixed results,

with some studies finding a link between frailty and CVD [5-8]. In contrast, some studies found no association [9,10] (Table S1). There are several underlying reasons for these mixed outcomes. For example, the tools used to assess frailty varied between studies and were assessed in study populations with specific pre-existing cardiovascular diseases, e.g., acute coronary syndrome [8] or heart failure [11]. In addition, some of the studies were conducted among relatively younger participants with specific high cardiovascular risks, e.g., diabetes mellitus [12,13], peripheral arterial disease [14], or participants who had specific chronic conditions, e.g., knee osteoarthritis [15], and some recruited participants from acute hospital settings [6]. Moreover, in some studies, CVD outcomes were self-reported by participants, where the accuracy of diagnosis may be called into question [9,10,16,17]. Accordingly, less is known about the effect of frailty on incident CVD outcomes in community-dwelling older persons who do not have symptomatic CVD or other major geriatric illnesses such as dementia or persistent physical disability.

The present study, therefore, aimed to examine the association of frailty, measured by a modified Fried phenotype and a deficit accumulation Frailty Index (FI), with incident CVD events and their sub-types, i. e., myocardial infarction (MI), hospitalization for heart failure (HHF), stroke, and CVD-related mortality, and the composite of major adverse cardiovascular events (MACE) among community-dwelling older adults without previous CVD, cognitive impairment or physical disability at baseline, in participants from the ASPREE (ASPirin in Reducing Events in the Elderly), a primary prevention trial of low-dose aspirin [18].

2. Methods

2.1. Participants

All 19,114 participants from the ASPREE trial were included in this post hoc analysis. The ASPREE trial was conducted between 2010 and 2017 in Australia and the United States (US). Community-dwelling men and women in Australia and the US who were 70 years of age or older (or ≥65 years of age among African-Americans and Hispanics in the US) (median age 74.0 years, interquartile range or IQR: 6.1 years) and who did not have overt CVD, cognitive impairment, persistent physical disability, or a known life-limiting illness were enrolled. Full details regarding the sampling procedure and study design of the ASPREE clinical trial have been published previously [19].

2.2. Assessment of frailty

Two methods, which have some overlap but many differences, were used for assessing frailty and pre-frailty at study enrolment. Fried phenotype assesses physical frailty (physical phenotype), whereas the deficit accumulation FI assesses frailty by including deficits across multiple health-related domains.

2.2.1. Modified Fried frailty phenotype—A modified version of Fried phenotype [1,20] included a low body mass index (BMI) of <20 kg/m^2 substituting for unintentional weight loss, slowest 20 % in gait speed adjusted for height and gender, and lowest 20 % in grip strength adjusted for BMI and gender [21]. At baseline, participants were classified

as frail if they met at least three of the following five criteria and pre-frail if they met one or two of the criteria: (1) BMI < 20 kg/m^2, ("Shrinking"); (2) ranking in the lowest 20 % of grip strength ("Weakness"); (3) the participant endorsed "I felt that everything I did was an effort" and/or "I could not get going" for three or more days during the last week, according to the Center for Epidemiological Studies-Depression 10 (CES-D10) scale [22] ("Exhaustion"); (4) time to walk 3 m (10 ft) was in the lowest 20 % taking into account gender and height ("Slowness"); and (5) no walking outside home in last two weeks, or the longest amount of time walking outside without sitting down to rest was <10 min ("Low activity") according to LIFE disability questionnaire responses [23-25].

2.2.2. Deficit accumulation frailty index (FI)—A deficit accumulation FI of 66 items was constructed using data collected at baseline across multiple domains, including sociodemographic factors, lifestyle factors, chronic medical conditions, morbidities, physical activity, functional engagement, mental health, cognition, laboratory/pathology values and self-rated health status. This construct was based on methods described by Searle et al. [26] and from the Systolic Blood Pressure Intervention Trial (SPRINT) [27]. Each item was categorized on a scale from zero to 1.0, with zero being no deficit and 1.0 being a total deficit. Details of the items and the scales used are published elsewhere [28]. The FI was calculated as the average number of deficits across all items. Participants were classified as non-frail (≤0.10), pre-frail (>0.10 and ≤0.21) or frail (>0.21), consistent with cut-offs used previously [27].

2.2.3. Cardiovascular disease (CVD) events—The primary endpoint of the ASPREE trial was a composite of death, dementia, or persistent physical disability [18]. CVD was one of the secondary endpoints. In the current study, we used CVD events as primary outcomes. In addition, sub-group analyses were conducted for MACE, fatal coronary heart disease, non-fatal myocardial infarction (MI), fatal or non-fatal stroke, and hospitalization for heart failure (HHF). CVD was defined as a composite of fatal coronary heart disease, non-fatal myocardial infarction, fatal or non-fatal stroke, or hospitalization for heart failure (Table S2). The individual components of the CVD composite were not prespecified as separate endpoints but were evaluated in a post hoc analysis to assist in interpreting the composite endpoint. In both Australia and the US, source documentation, including clinical notes, hospitalization records, and imaging studies (computed tomographic scans, magnetic resonance images and echocardiography), was requested for clinical events that were thought to be potential endpoint events. The non-prespecified endpoint of MACE was a composite of fatal coronary heart disease (excluding death from heart failure), non-fatal myocardial infarction, or fatal or non-fatal ischaemic stroke [18]. A participant contributed only the first event for a composite endpoint (CVD or MACE). For CVD sub-types, if a participant had more than one event, then that participant contributed an event to each CVD sub-type.

2.2.4. Covariates—Covariates included traditional non-modifiable and modifiable CVD risk factors, i.e., age, gender, ethno-racial origin, smoking, hypertension, diabetes mellitus and dyslipidemia [29,30].

2.2.5. Ethics and governance—All participants provided written informed consent. The ASPREE trial was conducted following the principles of the Declaration of Helsinki and approved by local institutional review boards at each site. The trial was registered with ClinicalTrials.gov (NCT01038583) and International Standard Randomized Controlled Trial Number Registry (ISRCTN 83772183).

2.2.6. Statistical analysis—The frequency of non-frailty, pre-frailty and frailty was determined at baseline. Incident CVD events and their sub-types were determined longitudinally over a median follow-up of 4.7 years (IQR: 3.6 to 5.7 years). Demographic data were described using means and standard deviations or percentages where appropriate and analyzed using analysis of variance (ANOVA) and chi-square, respectively. Collinearity between variables was assessed by running the variance inflation factor (VIF) analysis and examining the correlation matrix. There was no significant collinearity between variables. The associations between frailty categories at baseline and incident CVD events (along with sub-types), MACE and CVD-related mortality over the follow-up period were examined by Cox proportional-hazards regression model and reported as the hazard ratios (HRs) with 95 % confidence intervals (CIs). Proportional hazard assumptions were checked using Schoenfeld residuals. Progressive adjustments were made using traditional CVD risk factors as covariates. The final model was adjusted for non-modifiable and modifiable CVD risk factors (covariates described above) for the associations between frailty and incident CVD events. A Fine-Gray competing-risks regression analysis of the adjusted model was used to examine the significance of the relationships between frailty and CVD outcomes. Supplemental analyses were performed for CVD sub-types (non-fatal myocardial infarction, HHF and non-fatal stroke), where mortality was treated as a competing risk for individual first events, and Fine-Gray competing risks regression analyses for sub-distribution hazard ratio (SHR) and 95 % CIs were performed. Cumulative incidences were used to show event risks based on regression models. Interaction terms in Cox proportional hazards models were used to test for heterogeneity of effect between subgroups. Subgroups of potential relevance to the risk of CVD included sex, smoking, hypertension, diabetes, dyslipidemia, education and low-dose aspirin vs. placebo, using both frailty scales. In addition, landmark survival analysis (sensitivity analysis) was conducted by designating the first and second annual visits after enrolment as the landmark time and analyzing only those subjects who survived until the landmark time. Statistical analysis was performed using STATA, version 17 [31].

3. Results

Of the 19,114 participants enrolled, just over half were female (56.4 %), their median age was 74.0 years (IQR: 6.1 years), 37.8 % of the study population was ≥75 years, and the majority of the enrolled participants were non-Hispanic Whites [32]. Of this cohort of older persons, 55.3 % never smoked, and only 3.9 % were current smokers (Table 1). Pre-frail and frail participants were older and more likely to be women than non-frail participants. Older pre-frail and frail participants had more CVD events. The study population's most prevalent modifiable traditional CVD risk factor was hypertension (74.3 %); 65.2 % had dyslipidemia, while 10.7 % had diabetes mellitus at baseline (Table 1). Over the median 4.7-years (IQR:

3.6 to 5.7 years) follow-up period, out of 922 incident CVD events, 450 (48.8 %) and 36 (3.9 %) occurred among Fried pre-frail and frail groups, respectively; and 459 (49.8 %) and 128 (13.9 %) occurred among FI-defined pre-frail and frail participants, respectively. Pre-frail and frail participants developed more MACE, CVD-related deaths and all CVD sub-types, i.e., MI, HHF and stroke, according to both frailty scales (Table 1).

Both Fried phenotype and FI-defined pre-frailty and frailty had significant associations with incident CVD events and CVD sub-types during follow-up, shown in Table 2. In a Cox proportional hazards model adjusted for CVD risk factors, pre-frail and frail participants were more likely to develop incident CVD events (HR: 1.31; 95 % CI: 1.14, 1.50 for pre-frail and HR: 1.63; 95 % CI: 1.15, 2.32 for frail participants, respectively) according to Fried phenotype (Table 2, Model 2). Participants who were pre-frail or frail as determined by Fried phenotype had a similarly elevated risk of developing sub-types of CVD (apart from a fatal and non-fatal stroke); and they had a higher risk of CVD-related mortality, which is characterized as any death from stroke (including hemorrhagic stroke) or coronary heart disease (HR: 1.83; 95 % CI: 1.34, 2.50 for Fried pre-frail and HR: 2.73; 95 % CI: 1.50, 4.97 for Fried frail). Likewise, Fried pre-frail and frail participants were at increased risk of developing MACE (HR: 1.26; 95 % CI: 1.08, 1.47 for pre-frail and HR: 1.51; 95 % CI: 1.00, 2.29 for frail).

The effect sizes for incident CVD events, sub-types including stroke, MACE and fatal CVD were similar or larger when frailty was assessed using the FI than with the Fried phenotype (Table 2, Model 2). The cumulative incidences of CVD events, MACE, and HHF according to Fried phenotype defined frailty (Fig. 1A, C and E) and FI-defined frailty (Fig. 1B, D and F) at baseline are shown in the main Fig. 1. Supplementary Figs. S1A-F show the cumulative incidences of fatal CVD events, MI, and stroke according to Fried phenotype defined frailty (Fig. S1A, C and E) and FI-defined frailty (Fig. S1B, D and F) categories at baseline, respectively.

The significance of the associations between frailty and CVD outcomes persisted even after Fine-Gray competing-risks regression analysis in the adjusted model (Table S3, Model 2). In addition, landmark survival analysis for Fried phenotype and FI-based frailty categories and incident CVD events demonstrates that effect sizes remained significant when accounting for early incidences after standard CVD risk variables were adjusted (Table S4, Model 2).

For sub-group analysis, stratified Cox proportional hazards of incident CVD events according to sex, education, low-dose aspirin vs. placebo, smoking status, hypertension, diabetes mellitus and dyslipidemia using both frailty scales are shown in Table 3. There was no significant interaction between Fried phenotype defined or FI-defined pre-frailty and frailty with CVD risk factors like age, sex, smoking status, ethno-racial origin, hypertension, dyslipidemia and diabetes mellitus with respect to incident CVD events (all p values >0.1) except FI-defined frailty with age (p-value 0.04).

Among the components of Fried phenotype, slowness or gait speed demonstrated significant association with incident CVD events, MACE, and other sub-types of CVD events. In contrast, other Fried components showed variable relationships (Table S5). Frailty categories

and methods of assessing frailty did not show significant differences in CVD-related or non-CVD-related mortality (Table S6).

4. Discussion

The current study examined the association of Fried phenotype and deficit accumulation FI-defined pre-frailty and frailty with incident CVD events, MACE, CVD-related mortality and sub-types of CVD (MI, HHF and stroke) among community-dwelling older adults without previous CVD events, cognitive impairment or physical disability during a median 4.7-year follow-up. The major findings of this study are: (1) participants at baseline who exhibited pre-frailty or frailty, as measured by the Fried frailty phenotype and deficit accumulation FI, were older, more often women, African-American or Hispanic/Latino in origin, and had a high prevalence of current smoking, hypertension, diabetes mellitus and dyslipidemia compared with non-frail participants; and (2) compared with non-frail participants, pre-frail and frail older participants had a higher risk of developing incident CVD, MACE, including CVD-related mortality and CVD sub-types (particularly myocardial infarction and HHF), even after adjusting for traditional non-modifiable and modifiable CVD risk factors. These findings indicate that older adults with pre-existing pre-frailty or frailty may be at greater risk for increased CVD events in the presence or absence of traditional CVD risk factors.

4.1. Frailly and incident CVD events and their sub-types

Previous systematic reviews and meta-analyses reported that frailty was associated with an increased risk of CVD compared to robust or non-frail patients [12,16]; however, the cohort studies included in those meta-analyses had limitations. For example, they used self-reported CVD events, including angina pectoris and transient ischaemic attack, hospitalized participants with specific conditions at baseline, such as acute coronary syndrome, or registry data to identify outcome events. Registry data may have limitations due to how it was collected, which may not be systematic across the population. Another meta-analysis [12] included eight studies (n = 565,039; all diabetic participants), but only one study examined CVD outcomes [13]. Furthermore, that single study [13] included relatively young participants (mean age 56.4 ±13.8 years) and used the FRAIL scale for assessing frailty. Other longitudinal studies have also yielded mixed associations between frailty and CVD events [10]. For example, some extensive cohort studies of older community-dwelling individuals reported no significant associations between Fried phenotype-defined or FI-defined frailty and CVD events [9,10] while other studies have demonstrated a significant relationship between frailty and CVD events [5-8,15]. In contrast, our community-dwelling, relatively healthy study participants with no overt CVD at the outset demonstrate robust evidence that pre-frailty and frailty as assessed, either by Fried phenotype or deficit accumulation FI, significantly might increase the risk of incident CVD events and sub-types, particularly MI and HHF.

4.2. Frailty and MACE

Earlier studies have shown associations between frailty and MACE. Though the definition of MACE varied, the duration of all studies was short, and some studies focused on one among a variety of CVD events, including those related to peripheral arterial diseases, such

as stable claudication or aortic aneurysm repair [33,34]. However, in the National Health and Aging Trends Study [5], frail patients developed more CVD outcomes than did the pre-frail and non-frail groups over the 6-year follow-up, including MACE, where MACE was defined as death from any cause, acute MI, any subsequent CHD, stroke, or peripheral vascular disease, whichever came first. In our study, MACE was a composite of fatal coronary heart disease (excluding death from heart failure), non-fatal MI, or fatal or non-fatal ischaemic stroke, whichever came first. Even with the difference in definition, our findings align with previous findings that frail older adults are at greater risk of MACE. Additionally, our findings indicate that pre-frail individuals are also at risk of getting MACE than non-frail older adults [5].

4.3. Frailty and CVD mortality

Previous studies indicated that frailty measured by different scales is associated with increased mortality risk [35]. From other studies, it was unclear whether frailty predisposes to CVD-related death or whether the cause of death in frail individuals with CVD is predominantly noncardiovascular [7]. This is relevant because if frail individuals die predominantly from non-CVD causes, they are unlikely to benefit much from CVD risk prevention or treatments [6]. Our findings indicate that the risk of non-CVD-related death was similar to the risk of CVD-related death among pre-frail and frail persons compared with non-frail persons in the ASPREE cohort (Table S6). Moreover, a previous study demonstrated that in those with no history of CVD events, frailty was related to the extent of underlying subclinical CVD, measured by carotid ultrasound and ankle-arm index, left ventricular hypertrophy by electrocardiogram or echocardiography, and infarct-like lesions in the brain on magnetic resonance imaging [36]. Therefore, we performed sensitivity analyses to remove the possibility of a reverse causal relationship by excluding CVD events recorded during the first two years of the follow-up period. The risk of incident CVD events, MACE, fatal CVD and MI, remained significant (except for fatal CVD among FI-defined pre-frail groups) (Table S4). However, the effect sizes for HHF after annual visit 2, stroke and fatal CVD among FI-defined pre-frail groups probably lost significance because of underpowering. The progression of these subclinical atherosclerotic CVD events to overt clinical events among pre-frail and frail participants merits further exploration.

4.4. Strengths and limitations

The strengths of our study stem from the inclusion of a large cohort of physically and cognitively well-functioning community-dwelling older men and women free of prior overt CVD; the systematic assessment of frailty using two standard scales in the same cohort where one is a well-accepted physical frailty phenotype [1] and the other a more broad-ranging method of frailty assessment using accumulated deficits covering multiple domains [37]; and the formal adjudication of all CVD endpoints by clinical experts, masked to randomization. In terms of limitations, we used modified criteria for Fried phenotype definition, as we have previously published [21], which included a low BMI of <20 kg/m^2 substituting for unintentional weight loss, slowest 20 % in gait speed adjusted for height and gender and lowest 20 % in grip strength adjusted for BMI and gender. Previously other studies also used modified criteria depending on the availability of data [38]. Though the ASPREE trial had potential limitations in statistical power to examine some of the specific

CVD events, the sample size was sufficient to produce a good estimation of the impact of pre-frailty on CVD outcomes. In addition, the majority of participants in the study were White Australians, with minority racial and ethnic groups being underrepresented. Thereby, any inferences drawn from the findings about non-White ethnic groups should be cautiously interpreted. Moreover, we could not exclude subclinical CVD among our participants in the current analysis. Our initially healthy trial participants were selected by strict inclusion and exclusion criteria, and they had a lower prevalence of pre-frailty and frailty, which might underestimate the strength of the relationship with CVD endpoints across the general population of the same age. Nevertheless, pre-frail and frail ASPREE participants had higher levels of current smoking, hypertension, dyslipidemia and diabetes mellitus than their non-frail counterparts, contributing to their increased risk of CVD events. Results of these post hoc analyses should not be considered conclusive or causal, but rather exploratory and subject to further investigation. Furthermore, the original study's sample size and limited CVD outcomes, the likelihood of type I and type II errors, and residual confounding (e.g., related to socioeconomic factors) that cannot be excluded, mean the results should be interpreted cautiously.

5. Conclusion

Those with pre-frailty or frailty, as measured by Fried frailty phenotype and deficit accumulation FI at baseline, were more likely to be older, women, African-American or Hispanic/Latino in origin, and had a high prevalence of current smoking, hypertension, diabetes mellitus and dyslipidemia as compared to non-frail participants. Pre-frail and frail older participants had a higher risk of incident CVD, MACE, and CVD sub-types (especially MI and HHF) over a median 4.7-year follow-up compared to non-frail individuals. This risk persisted even after accounting for traditional non-modifiable and modifiable CVD risk factors. In addition, pre-frail and frail older adults were at higher risk of fatal CVD, i.e., death from stroke or coronary heart disease. Frailty assessment with the FI appeared to provide a more robust relationship with CVD risk across sub-groups, including women. In a world where a healthy life expectancy is evolving into a standard summary measure of population health [39], addressing frailty status in community-dwelling older adults [40], particularly those with pre-frailty where earlier intervention may reap even greater benefits, along with the assessment of CVD risk factors, could contribute to improved CVD prevention strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations:

ASPREE	ASPirin in Reducing Events in the Elderly
CI	confidence interval
CVD	cardiovascular disease
FI	frailty index
HR	hazard ratio
MACE	major adverse cardiovascular events

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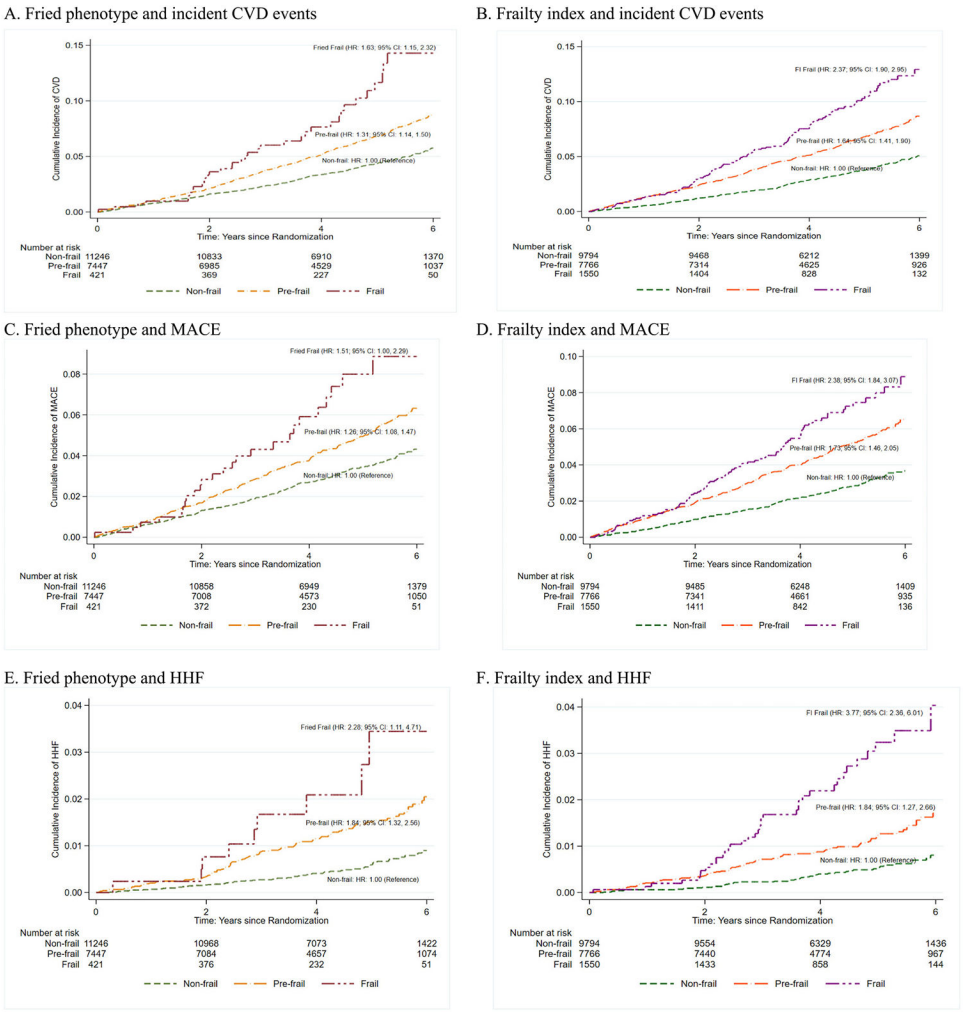

Fig. 1.

Cumulative incidence graphs of incident CVD events (A & B), MACE (C & D), and HHF (E & F) according to Fried phenotype defined frailty (A, C & E) or FI-defined frailty (B, D & F) categories at baseline. For definitions of CVD, MACE and HHF, please refer to Supplementary Table 2. The hazard ratios (HR) and 95 % confidence intervals (CI) are adjusted for age, sex, ethno-racial origin, smoking history, hypertension, diabetes mellitus and dyslipidemia; the line representing unadjusted analyses results and adjusted results are given in the parentheses (Table 2 for full details). Dashed lines (green) represent non-frail, dash-dot lines (orange) represent pre-frail and dash-dot-dot lines (maroon) represent frail groups. CVD, cardiovascular disease; MACE, major adverse cardiovascular events; HHF, hospitalization for heart failure.

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Table 1

Cardiovascular disease (CVD) risk factors and incident CVD events, according to frailty categories.

Characteristics, n (%)	Fried phenotype (n = 19,114)					Frailty index (n = 19,110)[a]				
	Total (N = 19,114)	Non-frail (n = 11,246)	Pre-frail (n = 7447)	Frail (n = 421)	p-Value	Total (N = 19,110)	Non-frail (n = 9794)	Pre-frail (n = 7766)	Frail (n = 1550)	p-Value
CVD risk factors at baseline										
Age, y (median, IQR)	74.0 (6.1)	73.4 (5.0)	75.0 (7.2)	77.9 (9.0)		74.0 (6.1)	73.3 (5.1)	74.6 (6.7)	76.0 (8.0)	
Age group (n, %)					<0.001					<0.001
65–74 y	11,164 (58.4)	7307 (65.0)	3718 (49.9)	139 (33.0)		11,161 (58.4)	6374 (65.1)	4123 (53.1)	664 (42.8)	
75–84 y	7218 (37.8)	3764 (33.4)	3232 (43.4)	222 (52.7)		7217 (37.8)	3242 (33.1)	3232 (41.6)	743 (47.9)	
>85 y	732 (3.8)	175 (1.6)	497 (6.7)	60 (14.3)		178 (1.8)	178 (1.8)	411 (5.3)	143 (9.2)	
Sex (n, %)					<0.001					<0.001
Male	8332 (43.6)	5059 (45.0)	3126 (42.0)	147 (34.9)		8331 (43.6)	4973 (50.8)	2969 (38.2)	389 (25.1)	
Female	10,782 (56.4)	6187 (55.0)	4321 (58.0)	274 (65.1)		10,779 (56.4)	4821 (49.2)	4797 (61.8)	1161 (74.9)	
Ethno-racial, n (%)					<0.001					<0.001
Australian white	16,361 (85.6)	10,090 (89.7)	5968 (80.2)	303 (72.0)		16,359 (85.6)	8420 (86.0)	6661 (85.8)	1278 (82.5)	
US white	1088 (5.7)	513 (4.6)	533 (7.2)	42 (10.0)		1088 (5.7)	649 (6.6)	364 (4.7)	75 (4.8)	
African-American	901 (4.7)	279 (2.5)	574 (7.7)	48 (11.4)		899 (4.7)	338 (3.5)	430 (5.5)	131 (8.5)	
Hispanic/Latino	488 (2.6)	218 (1.9)	248 (3.3)	22 (5.2)		488 (2.6)	234 (2.4)	207 (2.7)	47 (3.0)	
Other	275 (1.4)	146 (1.3)	123 (1.6)	6 (1.4)		275 (1.4)	152 (1.5)	104 (1.3)	19 (1.2)	
Smoking history (n, %)					<0.001					<0.001
Current	735 (3.9)	358 (3.2)	346 (4.7)	31 (7.4)		734 (3.8)	275 (2.8)	367 (4.7)	92 (5.9)	
Former	7799 (40.8)	4579 (40.7)	3054 (41.0)	166 (39.4)		7799 (40.8)	3704 (37.8)	3404 (43.8)	691 (44.6)	
Never	10,580 (55.3)	6309 (56.1)	4047 (54.3)	224 (53.2)		10,577 (55.4)	5815 (59.4)	3995 (51.5)	767 (49.5)	
Hypertension[b] (n, %)	14,195 (74.3)	8210 (73.0)	5630 (75.6)	355 (84.3)	<0.001	14,193 (74.3)	6593 (67.3)	6259 (80.6)	1341 (86.5)	<0.001
Diabetes[c] (n, %)	2045 (10.7)	1004 (8.9)	964 (12.9)	77 (18.3)	<0.001	2044 (10.7)	520 (5.3)	1144 (14.7)	380 (24.5)	<0.001
Dyslipidaemia[d] (n, %)	12,467 (65.2)	7492 (66.6)	4735 (63.6)	240 (57.0)	<0.001	12,464 (65.2)	5643 (57.6)	5670 (73.0)	1151 (74.3)	<0.001
Incident CVD[e]	922 (4.8)	436 (3.9)	450 (6.0)	36 (8.6)	<0.001	922 (4.8)	335 (3.4)	459 (5.9)	128 (8.3)	<0.001
Fatal CVD[f]	203 (1.1)	67 (0.6)	122 (1.6)	14 (3.3)	<0.001	203 (1.1)	66 (0.7)	95 (1.2)	42 (2.7)	<0.001
MACE[g]	701 (3.7)	343 (3.1)	333 (4.5)	25 (5.9)	<0.001	701 (3.7)	254 (2.6)	356 (4.6)	91 (5.9)	<0.001

Characteristics, n (%)	Fried phenotype (n = 19,114)					Frailty index (n = 19,110)[a]				
	Total (N = 19,114)	Non-frail (n = 11,246)	Pre-frail (n = 7447)	Frail (n = 421)	p-Value	Total (N = 19,110)	Non-frail (n = 9794)	Pre-frail (n = 7766)	Frail (n = 1550)	p-Value
MI[h]	355 (1.9)	180 (1.6)	161 (2.2)	14 (3.3)	<0.001	355 (1.3)	127 (1.3)	186 (2.4)	42 (2.7)	<0.001
HHF[i]	171 (0.9)	61 (0.5)	101 (1.4)	9(2.1)	<0.001	171 (0.9)	49 (0.5)	85 (1.1)	37 (2.4)	<0.001
Stroke[j]	403 (2.1)	199 (1.8)	192 (2.6)	12 (2.9)	<0.001	403 (2.1)	154 (1.6)	198 (2.6)	51 (3.3)	<0.001

Abbreviations: CVD: Cardiovascular disease; DM: Diabetes mellitus; HHF: Hospitalization for heart failure; HTN: Hypertension; IQR: Interquartile range; MACE: Major adverse cardiovascular events; MI: Myocardial infarction; SD: Standard deviation

[a]Four participants were excluded because they had recorded a response to less than the minimum of 50 items for deficit accumulation FI.

[b]Hypertension was defined as treatment for high blood pressure or blood pressure of >140/90 mmHg at the ASPREE trial entry.

[c]DM was defined based on participants' reports of diabetes mellitus or a fasting glucose level of at least 126 mg per deciliter (≥7 mmol per liter) or receipt of treatment for diabetes.

[d]Dyslipidaemia was defined as the receipt of cholesterol-lowering medication or as a serum cholesterol level of at least 212 mg per deciliter (≥5.5 mmol per liter) in Australia and at least 240 mg per deciliter (≥6.2 mmol per liter) in the United States or as a low-density lipoprotein level of >160 mg per deciliter (>4.1 mmol per liter).

[e]CVD was a prespecified secondary endpoint of the ASPREE clinical trial. It was defined as a composite of fatal coronary heart disease (death from myocardial infarction, sudden cardiac death, or any other death in which the underlying cause was considered to be coronary heart disease), non-fatal myocardial infarction, fatal or non-fatal stroke (including hemorrhagic stroke), or hospitalization for heart failure.

[f]Fatal CVD was defined as any death from stroke (including hemorrhagic stroke) or coronary heart disease.

[g]MACE was a composite of fatal coronary heart disease (excluding death from heart failure), non-fatal MI, or fatal or non-fatal ischemic stroke.

[h]Fatal or non-fatal MI: Fatal coronary heart disease was defined as death from MI, sudden cardiac death, or any other death in which the underlying cause was coronary heart disease. Non-fatal MI was based on joint guidelines of the European Society of Cardiology and the American College of Cardiology.

[i]HHF was defined as any unplanned overnight or longer stay in a hospital environment (emergency department, observation unit, or in-patient care unit) or a similar facility for which the principal reason for admission was heart failure.

[j]Stroke was defined according to the World Health Organisation (WHO) definition as rapidly developing clinical signs of focal (or global) disturbance of cerebral function lasting >24 h (unless interrupted by surgery or death) with no apparent cause other than of vascular origin. This definition excludes cases of primary cerebral tumor, cerebral metastasis, subdural hematoma, post-seizure palsy, brain trauma, and transient ischemic attack. A fatal stroke was defined as any death whose underlying cause was an obstruction or rupture in the intracranial or extracranial cerebral arterial system.

Table 2

The association between frailty and incident CVD events (and CVD sub-types).

Fried phenotype		**Model 1: Unadjusted[a]**		**Model 2: Adjusted[b]**	
	Non-frail	**HR (95 % CI)**		**HR (95 % CI)**	
		Pre-frail	**Frail**	**Pre-frail**	**Frail**
Incident CVD[c]	Reference	1.57 (1.37, 1.79)	2.47 (1.76, 3.47)	1.31 (1.14, 1.50)	1.63 (1.15, 2.32)
Fatal CVD[d]	Reference	2.66 (1.97, 3.58)	5.74 (3.23, 10.21)	1.83 (1.34, 2.50)	2.73 (1.50, 4.97)
MACE[e]	Reference	1.47 (1.27, 1.71)	2.16 (1.44, 3.24)	1.26 (1.08, 1.47)	1.51 (1.00, 2.29)
CVD sub-types					
MI[f]	Reference	1.36 (1.10, 1.68)	2.29 (1.33, 3.95)	1.25 (1.01, 1.56)	1.92 (1.10, 3.36)
HHF[g]	Reference	2.51 (1.82, 3.44)	4.44 (2.21, 8.94)	1.84 (1.32, 2.56)	2.28 (1.11, 4.71)
Stroke[h]	Reference	1.46 (1.20, 1.78)	1.79 (1.00, 3.20)	1.19 (0.97, 1.46)	1.10 (0.61, 2.00)
Frailty index		**Model 1: Unadjusted[a]**		**Model 2: Adjusted[b]**	
	Non-frail	**HR (95 % CI)**		**HR (95 % CI)**	
		Pre-frail	**Frail**	**Pre-frail**	**Frail**
Incident CVD[c]	Reference	1.81 (1.57, 2.08)	2.72 (2.22, 3.33)	1.64 (1.41, 1.90)	2.37 (1.90, 2.95)
Fatal CVD[d]	Reference	1.86 (1.36, 2.54)	4.31 (2.93, 6.35)	1.49 (1.07, 2.08)	3.14 (2.05, 4.81)
MACE[e]	Reference	1.84 (1.57, 2.16)	2.52 (1.98, 3.20)	1.73 (1.46, 2.05)	2.38 (1.84, 3.07)
CVD sub-types					
MI[f]	Reference	1.92 (1.53, 2.40)	2.30 (1.62, 3.26)	1.91 (1.51, 2.42)	2.52 (1.74, 3.65)
HHF[g]	Reference	2.27 (1.60, 3.23)	5.36 (3.49, 8.21)	1.84 (1.27, 2.66)	3.77 (2.36, 6.01)
Stroke[h]	Reference	1.68 (1.36, 2.07)	2.33 (1.70, 3.20)	1.47 (1.18, 1.84)	1.84 (1.31, 2.58)

Abbreviations: CI: Confidence intervals; CVD: Cardiovascular disease; HHF: Hospitalization for heart failure; HR: Hazard ratio; MACE: Major adverse cardiovascular events; MI: Myocardial infarction

[a]Model 1: Unadjusted analysis results

[b]Model 2: Adjusted for non-modifiable (age, gender and ethno-racial origin) and modifiable CVD risk factors (smoking history, hypertension, diabetes mellitus and dyslipidemia)

[c]CVD: Fried phenotype: Model 1: *n* = 19,114; CVD = 922; Model 2: *n* = 19,113; CVD = 922; Model 3: *n* = 19,113; CVD = 922; Frailty index: Model 1: *n* = 19,110; CVD = 922; Model 2: n = 19,109; CVD = 922; Model 3: *n* = 19,109; CVD = 922.

[d]Fatal CVD (CVD-related mortality): Fried phenotype: Model 1: *n* = 19,114; Fatal CVD = 203; Model 2: *n* = 19,113; Fatal CVD = 203; Model 3: *n* = 19,113; Fatal CVD = 203; Frailty index: Model 1: *n* = 19,110; Fatal CVD = 203; Model 2: *n* = 19,109; Fatal CVD = 203; Model 3: *n* = 19,109; Fatal CVD = 203.

[e]MACE: Fried phenotype: Model 1: *n* = 19,114; MACE = 701; Model 2: *n* = 19,113; MACE = 701; Model 3: *n* = 19,113; MACE = 701; Frailty index: Model 1: *n* = 19,110; MACE = 701; Model 2: *n* = 19,109; MACE = 701; Model 3: *n* = 19,109; MACE = 701.

[f]Fatal or nonfatal MI: Fried phenotype: Model 1: *n* = 19,114; MI = 355; Model 2: *n* = 19,113; MI = 355; Model 3: *n* = 19,113; MI = 355; Frailty index: Model 1: *n* = 19,110; MI = 355; Model 2: n = 19,109; MI = 355; Model 3: n = 19,109; MI = 355.

[g] HHF: Fried phenotype: Model 1: n = 19,114; HHF = 171; Model 2: Model 1: n = 19,113; HHF = 171; Model 3: Model 1: n = 19,113; HHF = 171; Frailty index: Model 1: n = 19,110; HHF = 171; Model 2: Model 1: n = 19,109; HHF = 171; Model 3: Model 1: n = 19,109; HHF = 171.

[h] Fatal or nonfatal stroke: Fried phenotype: Model 1: n = 19,114; Stroke = 403; Model 2: n = 19,113; Stroke = 403; Model 3: n = 19,113; Stroke = 403; Frailty index: Model 1: n = 19,110; Stroke = 403; Model 2: n = 19,109; Stroke = 403; Model 3: n = 19,109; Stroke = 403.

Table 3

Stratified analysis of incident CVD events by frailty categories according to traditional CVD risk factors, education, and low-dose aspirin vs. placebo.

	n (f)	Non-frail	Model 1: Unadjusted[a]		Model 2: Adjusted[b]	
			Pre-frail	Frail	Pre-frail	Frail
			HR (95 % CI)		Adjusted HR (95 % CI)	
Fried phenotype						
Sex						
Male	8332 (508)	Reference	1.56 (1.30, 1.86)	2.68 (1.66, 4.33)	1.29 (1.07, 1.55)	1.80 (1.10, 2.94)
Female	10,782 (414)	Reference	1.65 (1.35, 2.01)	2.52 (1.55, 4.09)	1.33 (1.09, 1.64)	1.55 (0.94, 2.55)
Smoking						
Current	735 (50)	Reference	1.69 (0.93, 3.08)	3.64 (1.35, 9.82)	1.68 (0.90, 3.13)	3.23 (1.16, 9.03)
Former	7799 (438)	Reference	1.62 (1.33, 1.96)	2.50 (1.52, 4.10)	1.37 (1.13, 1.67)	1.88 (1.14, 3.13)
Never	10,580 (434)	Reference	1.49 (1.23, 1.80)	2.09 (1.22, 3.60)	1.22 (1.00, 1.49)	1.24 (0.71, 2.16)
Hypertension						
No	4919 (169)	Reference	1.39 (1.02, 1.88)	2.81 (1.14, 6.91)	1.08 (0.79, 1.50)	1.57 (0.62, 3.96)
Yes	14,195 (753)	Reference	1.60 (1.38, 1.85)	2.33 (1.61, 3.36)	1.34 (1.15, 1.56)	1.57 (1.08, 2.29)
Diabetes mellitus						
No	17,069 (813)	Reference	1.58 (1.38, 1.82)	2.24 (1.51, 3.30)	1.32 (1.14, 1.52)	1.51 (1.01, 2.25)
Yes	2045 (109)	Reference	1.37 (0.92, 2.04)	3.24 (1.58, 6.65)	1.23 (0.82, 1.85)	2.25 (1.06, 4.75)
Dyslipidemia						
No	6647 (334)	Reference	1.47 (1.18, 1.83)	2.69 (1.65, 4.38)	1.25 (1.00, 1.57)	1.76 (1.06, 1.57)
Yes	12,467 (588)	Reference	1.62 (1.37, 1.91)	2.24 (1.39, 3.61)	1.35 (1.14, 1.60)	1.58 (0.97, 2.56)
Education						
≤12y	10,955 (550)	Reference	1.62 (1.36, 1.92)	2.52 (1.64, 3.86)	1.36 (1.13, 1.62)	1.80 (1.16, 2.79)
>12y	8159 (372)	Reference	1.49 (1.21, 1.83)	2.35 (1.34, 4.13)	1.23 (0.99, 1.53)	1.34 (0.75, 2.39)
Treatment[c]						
No	9525 (448)	Reference	1.56 (1.29, 1.89)	2.59 (1.62, 4.15)	1.25 (1.03, 1.52)	1.50 (0.92, 2.43)
Yes	9589 (474)	Reference	1.57 (1.31, 1.89)	2.35 (1.43, 3.84)	1.36 (1.13, 1.65)	1.75 (1.06, 2.89)
Frailty index						
Sex						
Male	8331 (508)	Reference	2.15 (1.79, 2.58)	2.88 (2.07, 4.01)	1.85 (1.52, 2.24)	2.28 (1.61, 3.22)
FeMale	10,779 (414)	Reference	1.73 (1.38, 2.16)	3.27 (2.49, 4.31)	1.40 (1.11, 1.77)	2.24 (1.67, 3.00)
Smoking						
Current	734 (50)	Reference	1.18 (0.60, 2.31)	4.23 (2.03, 8.80)	1.02 (0.51, 2.05)	3.58 (1.61, 7.97)
Former	7799 (438)	Reference	1.74 (1.41, 2.14)	2.63 (1.97, 3.53)	1.68 (1.35, 2.09)	2.53 (1.85, 3.47)
Never	10,577 (434)	Reference	1.86 (1.52, 2.27)	2.32 (1.68, 3.19)	1.22 (1.00, 1.49)	1.24 (0.71, 2.16)
Hypertension						
No	4917 (169)	Reference	2.28 (1.67, 3.13)	3.09 (1.75, 5.47)	1.93 (1.38, 2.69)	2.71 (1.49, 4.93)
Yes	14,193 (753)	Reference	1.62 (1.38, 1.89)	2.45 (1.96, 3.05)	1.56 (1.33, 1.84)	2.30 (1.82, 2.92)

	n (f)	Non-frail	Model 1: Unadjusted[a]		Model 2: Adjusted[b]	
			Pre-frail	Frail	Pre-frail	Frail
			HR (95 % CI)		Adjusted HR (95 % CI)	
Diabetes mellitus						
No	17,066 (813)	Reference	1.84 (1.59, 2.14)	2.57 (2.04, 3.24)	1.63 (1.40, 1.90)	2.15 (1.69, 2.75)
Yes	2044 (109)	Reference	1.56 (0.91, 2.69)	3.15 (1.76, 5.62)	1.78 (1.02, 3.11)	3.61 (1.96, 6.66)
Dyslipidaemia						
No	6646 (334)	Reference	2.13 (1.70, 2.68)	3.04 (2.13, 4.35)	1.80 (1.42, 2.28)	2.51 (1.72, 3.67)
Yes	12,464 (588)	Reference	1.71 (1.43, 2.05)	2.65 (2.06, 3.41)	1.55 (1.28, 1.87)	2.28 (1.74, 2.99)
Education						
≤12y	10,951 (550)	Reference	1.77 (1.47, 2.13)	2.70 (2.08, 3.49)	1.62 (1.33, 1.97)	2.35 (1.78, 3.10)
>12y	8159 (372)	Reference	1.83 (1.48, 2.28)	2.67 (1.90, 3.74)	1.67 (1.33, 2.11)	2.30 (1.60, 3.32)
Treatment[c]						
No	9524 (448)	Reference	1.78 (1.45, 2.18)	3.37 (2.56, 4.44)	1.56 (1.26, 1.94)	2.83 (2.10, 3.82)
Yes	9586 (474)	Reference	1.83 (1.51, 2.22)	2.13 (1.57, 2.90)	1.70 (1.39, 2.09)	1.92 (1.39, 2.67)

Abbreviations: CI: Confidence interval; f: Number of failures (incident events); HR: Hazard ratio; n = number of participants.

[a]Model 1: Unadjusted analysis.

[b]Model 2: Adjusted for non-modifiable and modifiable CVD risk factors (age, sex and ethno-racial origin, smoking history, hypertension, diabetes mellitus and dyslipidemia).

[c]Treatment: placebo vs. low-dose aspirin.