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ORIGINAL ARTICLE

Association between atrial fibrillation and systemic inflammation with muscle mass and strength trajectories in old age

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Abstract The long-term impact of atrial fibrillation (AF) and systemic inflammation on muscle health and, hence, functional decline remains unclear. This study investigates the link between AF and longitudinal trajectories of muscle mass and strength, considering the role played by systemic inflammation. Data were obtained from 2048 participants (≥60 years) in the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), followed for 12 years. Muscle mass and strength were assessed using calf circumference, handgrip strength, and chair stand test. Inflammatory marker interleukin-6 (IL-6) and the stress-response mediator growth differentiation factor-15 (GDF-15) were measured at baseline. Linear mixed models examined the longitudinal changes in muscle outcomes according to AF status and the combination of AF status with inflammatory markers. Participants with AF experienced a steeper increase in the duration of the chair stand test (β = 1.49; 95% CI: 0.82 to 2.16). High levels of GDF-15 amplified declines in muscle mass (β = −0.12; 95% CI: −0.20

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to − 0.05) and chair stand test performance (β = 2.48; 95% CI: 1.66 to 3.30) in individuals with AF. Participants with AF and high IL-6 levels also experienced an accelerated decline of calf circumference (β = − 0.12; 95% CI: − 0.19 to − 0.05) and chair stand test performance (β = 2.20; 95% CI: 1.39 to 3.01). AF is associated with a steeper decline in muscle mass and strength over time, exacerbated by elevated inflammatory biomarkers, underscoring the importance of systemic inflammation in AF-related functional decline.

Keywords Atrial fibrillation · Inflammation · GDF-15 · IL-6 · Muscle mass · Muscle strength

Introduction

Atrial fibrillation (AF), the most common arrhythmia, has increased by 30% over the past two decades due to improved diagnostics and population aging. Its prevalence increases sharply with age, from 6.4% at 65–69 years to 28.5% at ≥ 85 years [1, 2].

In older adults, AF may reflect a state of systemic biological vulnerability that accompanies the process of aging itself, while at the same time it may contribute to accelerate aging and increased risk of physical decline [3]. AF has been consistently associated with poorer physical performance, including reduced grip strength, decreased muscle mass, and slower walking speed [4–7]. It is frequently accompanied by a chronic pro-inflammatory state [8, 9], which may co-occur with the processes underlying sarcopenia and functional decline. In this context, biomarkers reflecting inflammatory and stress-response pathways are of particular interest for risk stratification and monitoring in older adults.

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An international expert consensus recognised interleukin-6 (IL-6), growth differentiation factor 15 (GDF-15), muscle mass, handgrip strength, and the chair stand test as validated biomarkers of age-related functional decline [10]. These biomarkers became increasingly relevant also in the context of AF [11], where age-related decline, cardiovascular risk factors, and other comorbidities frequently co-exist [12]. Increased levels of both IL-6 and GDF-15 have been shown to be associated with a higher risk of AF and AF-related adverse outcomes [13, 14]. Elevated IL-6 plays a role in the pathophysiology of AF, leading to its development, recurrence, and poor long-term health outcomes such as thrombosis and bleeding [13, 15]. Accordingly, GDF-15 has been identified as a predictor for AF-related adverse outcomes, including major bleeding [14]. In addition to their associations with cardiovascular health, increased levels of IL-6 and GDF-15 are consistently linked to reduced muscle strength, poor physical performance, and slower gait speed [14, 16–19]. Of note, GDF-15 levels are significantly higher in sedentary individuals compared to active individuals, independent of age, suggesting an association between GDF-15, reduced muscle performance and increased inflammation [20]. These findings highlight the potential of GDF-15 and IL-6 as biomarkers for identifying individuals with AF at a higher risk of functional decline and AF-related adverse outcomes, suggesting their possible role in the development of targeted preventive interventions.

This population-based study of people aged 60 years and older aimed to assess the interplay between AF and baseline inflammatory markers in relation to trajectories of muscle mass and strength over a 12-year follow-up.

Methods

Study population

We used data from the Swedish National study on Aging and Care in Kungsholmen (SNAC-K), an ongoing prospective study that includes adults aged 60 years and older, from central Stockholm, Sweden. The initial phase (2001–2004) of the study included individuals from 11 age cohorts (ages 60, 66, 72, 78, 81, 84, 87, 90, 93,

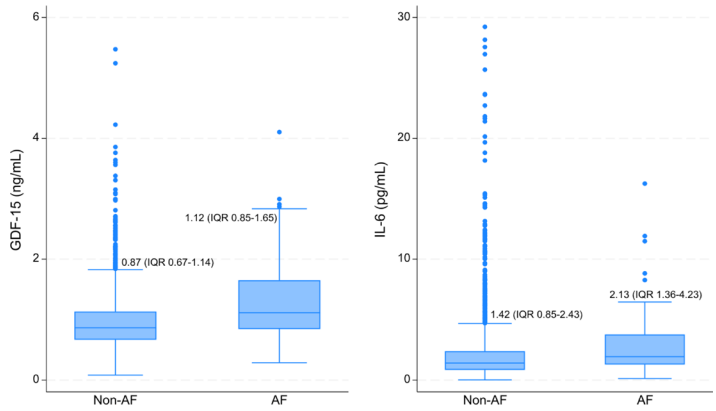


Fig. 1 Baseline inflammatory markers by AF status

Notes: The values higher than 30 pg/mL for IL-6 were excluded from the boxplot due to extreme outlier distribution (24 participants), which may affect the graphical interpretation. This threshold was applied just for visualization purposes; we kept all the data for statistical analysis.

96, and ≥ 99 years), who were followed up every 6 years (those aged < 78 years) or every 3 years (those aged ≥ 78 years). The baseline SNAC-K cohort included 3363 participants, of whom 1315 were excluded for the following reasons: 321 with dementia, 191 residing in institutions, 4 with multiple sclerosis, 40 with Parkinson's or Parkinsonism, 422 without baseline data for handgrip strength, 22 without baseline data for chair-stand tests, 22 without baseline data for calf circumference, and 1248 without baseline GDF-15 and IL-6 measurements (Fig. 1). After applying these criteria, 2048 participants remained in the study, including 1917 non-AF and 131 AF individuals. Data from baseline to the 12-year follow-up were considered.

The SNAC-K study complies with the principles of the Declaration of Helsinki and was approved by the Regional Ethical Review Board in Stockholm. Written informed consent to participate in the study was collected from all participants or the next of kin for those with cognitive impairment.

Study variables

Atrial fibrillation

The presence of AF at baseline was ascertained through the physician's interview, examination, and electrocardiogram (ECG), with undetectable discrete P waves and irregular ventricular rate on a 12-lead ECG [7]. In addition, data from health records in the Swedish National Patient Register comprising hospital and specialized outpatient care, were integrated to retrieve atrial fibrillation diagnoses in individuals with a recorded history.

Muscle mass

Muscle mass was assessed using calf circumference measurement, in line with the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) consensus [21]. Low muscle mass was defined as a calf circumference below the 20th sex-specific percentile of our sample, specifically, < 34 cm for men and < 32 cm for women. These thresholds are consistent with previously established cut-offs for moderately to severely reduced calf circumference [22, 23].

Muscle strength

The assessment of muscular strength involved handgrip strength for upper limb strength, and chair stand test for lower limb strength. While the handgrip strength test was performed seated with the arm at 90°, with higher scores indicating greater strength, the chair stand test measured the participant's ability to stand up five times as quickly as possible, with shorter time indicating greater lower limb strength [24]. Low muscle strength is indicated by handgrip strength of less than 27 kg for males and less than

16 kg for women, or by requiring more than 15 s to complete five rises from a chair [21]. Participants who were unable to perform the handgrip test were given a value of 0 kg. The highest reported value of 75 s was assigned to individuals who could not complete the chair stand test due to physical limitations.

Inflammatory biomarkers

Blood samples were collected at baseline without fasting. Serum samples were obtained post-centrifugation and stored at − 80 °C at the Karolinska Institutet BioBank. Baseline IL-6 was measured at Accelerator Laboratory Services, Quanterix Corp., in Billerica (MA, USA), using Simoa CorPlex Human Cytokine Panel 1 on the Quanterix® SP-XTM imaging and analysis platform. GDF-15 was quantified in serum samples using a custom designed Magnetic Luminex Assays—Human Premixed Multi-Analyte assay at the Affinity Proteomics-Stockholm Unit of the SciLifeLab (Solna, Sweden). The average intra- and inter-coefficient variations for replicated samples were 4.5% and 5.9%, respectively. Inflammatory biomarkers were converted into z-scores using the baseline mean and standard deviation of the total sample, facilitating the comparison of coefficients.

Covariates

This study included multiple covariates, including age, sex, educational attainment (primary or high school and above), civil status (partnered or unpartnered), alcohol intake (never, light to moderate, or heavy), and smoking (never, former, or current smoker). Physical activity scores were classified as (a) inadequate, ≤ 2 or 3 times per month of light and/or moderate/intense exercise; (b) health-enhancing, light exercise several times per week; and (c) fitness-enhancing, moderate/intense exercise several times per week [25]. Body mass index (BMI) was calculated as measured weight divided by measured height squared (kg/m^2). Chronic diseases were identified through clinical interviews, examinations, laboratory parameters, medication use, and the National Patient Register, and coded according to the International Classification of Diseases (ICD) 10th revision. For this study, we considered cerebrovascular disease, heart failure (HF), diabetes mellitus, chronic kidney disease (CKD), and chronic obstructive pulmonary disease (COPD).

Statistical analysis Baseline characteristics were reported using numbers and percentages and either mean and standard deviation (SD) or median and interquartile range [IQR]. The comparisons of characteristics between groups were performed using the χ^2 test for categorical variables and either Student's *t*-test or the Mann–Whitney *U* test for continuous variables, depending on data distribution. Linear mixed-effect models with random intercept and random slope were used to assess the association between AF, baseline inflammatory biomarkers, and changes in muscle mass and strength over 12 years of follow-up time. An interaction between each exposure and time in years was entered in the models, with the resulting β coefficients indicating the annual change in muscle mass and strength in relation to the exposure. Specifically, a model was first fitted to explore the change in muscle outcomes between individuals with and without AF over follow-up time (AF status × year). To further investigate the influence of baseline inflammation, a four-level categorical variable was constructed by combining AF status with biomarker levels (non-AF with low biomarker, non-AF with high biomarker, AF with low biomarker, and AF with high biomarker). This approach was applied separately for GDF-15 and IL-6, with biomarker levels classified as low when the baseline z-score was below the median and high when above. The 4-level variables represent baseline clinical profiles and were entered into the model as the exposure groups. Their interactions with time (profiles x year) were included to assess whether the annual rate of change in muscle mass and strength differed across profiles.

Accordingly, the β coefficients from these models indicate the estimated differences in annual change in muscle outcomes for each exposure group relative to the reference category (non-AF with low biomarker).

Adjustments included age, sex, education, diabetes mellitus, HF, CKD, COPD, smoking status, alcohol, BMI, and physical activity score.

In sensitivity analysis, to assess the robustness of the association between AF and muscular outcomes, we performed additional linear mixed models by adjusting for cerebrovascular disease. Cerebrovascular disease may confound or mediate the observed estimations due to their potential shared vascular or

inflammatory pathways with both AF and muscular impairment [26]. In additional analyses, we introduced AF x biomarker x time interaction terms, with biomarkers modelled categorically, to test whether AF status modifies the biomarker-time association. The three-way interaction beta coefficient represents the difference in the biomarker-related annual change in muscle outcomes between individuals with and without AF. In addition, to examine whether cognitive decline in individuals with AF might influence the loss of muscle mass and strength, we conducted a sensitivity analysis excluding incident dementia cases within the first 6 years of follow-up. Analyses were performed using STATA SE 19 (StataCorp, Texas, USA). A two-tailed p-value < 0.05 was considered statistically significant in all analyses.

Results

Baseline characteristics of participants with AF (6.4%) compared to those without AF are presented in Table 1. Participants with AF were older, less likely to be female, and had lower-level education, and a higher prevalence of CKD, HF, and cerebrovascular diseases. They also showed a longer duration of the chair stand test and lower handgrip strength. Figure 1 shows elevated baseline levels of both GDF-15 (1.12 ng/mL vs. 0.87 ng/mL, p-value < 0.001) and IL-6 (2.13 pg/mL vs 1.42 pg/mL, p-value < 0.001) in participants with AF.

Over the 12-year follow-up, participants with AF had a significant annual increase in chair stand test duration compared to those without AF (β per year 1.49 [95% CI 0.82 to 2.16]). Although handgrip strength and calf circumferences declined over time in both groups, these changes were not statistically significant (Table 2).

When AF status was combined with inflammatory markers, individuals without AF and high GDF-15 levels showed accelerated annual decline in calf circumference (β per year − 0.08 [95% CI − 0.10 to − 0.05]) and handgrip strength (β per year − 0.11 [95% CI − 0.17 to − 0.06]), as well as greater annual increase in chair stand test duration (β per year 1.22 [95% CI 0.95 to 1.49]) compared to those without AF and low GDF-15. Participants with AF and a low GDF-15 had increased duration of chair stand test compared with the reference group, while those with both AF and high GDF-15 experienced steeper declines in calf circumference, and chair stand test performance, but not in handgrip strength, relative to the reference group (Table 3).

High IL-6 levels, regardless of AF status, were associated with a greater annual increase in chair stand duration (non-AF: β per year 0.81 [95% CI 0.54 to 1.09]; AF: β per year 2.20 [95% CI 1.39 to 3.01]) and reduced calf circumference (non-AF: β per year − 0.02 [95% CI − 0.05 to − 0.001]; AF: β per year − 0.12 [95% CI − 0.19 to − 0.05]) compared to the reference group (non-AF, low IL-6) (Table 4). Participants with AF and high IL-6 levels experienced significantly greater annual decline in calf circumference (β per year − 0.12 [95% CI − 0.19 to − 0.05]) and annual increase in chair stand test duration (β per year 2.20 [95% CI 1.39 to 3.01]) compared to the reference group. Even though grip strength declined in all AF/IL-6 profiles, these changes were not statistically significant.

Participants with AF and high GDF-15 experienced the steeper decline in chair stand performance (from 18.5 to 58.1 s), and notable reductions in handgrip strength and calf circumference (Fig. 2). In addition, calf circumference significantly decreased in participants with high GDF-15, regardless of AF status. High IL-6 levels also correlated with reduced calf circumference and decline in both handgrip strength and chair stand performance. Particularly, individuals with AF and high IL-6 showed the greatest decline in chair stand performance (from 18.2 to 56.3 s) (Fig. 2). Supplementary Table 1 and 2 present the absolute predicted trajectories of muscle outcomes over 12 years for each AF/biomarker profile, derived from the adjusted mixed-effects models.

Sensitivity analyses showed that additional adjustment for cerebrovascular disease did not alter the significant increase in chair stand duration among AF participants and the combined impact of AF and elevated inflammatory markers in muscle decline over time (Supplementary Table 3).

Since participants with high inflammatory biomarker levels, both with and without AF, showed a steeper decline in muscle outcome, we conducted additional interaction analyses to evaluate whether AF status modified the association between those biomarkers and muscle decline. In these analyses, AF did not significantly modify the association between GDF-15 or IL-6 and longitudinal changes in muscle

Table 1 Baseline characteristics by AF status

Variables	Overall (N = 2048)	Non-AF (N = 1917; 93.6%)	AF (N = 131; 6.4%)	*p* value
Age (years)	66.6 [60.6, 78.2]	66.5 [60.6, 78.2]	78.2 [72.1, 81.8]	**< 0.001**
Sex (female)	1228 (60.0)	1164 (60.7)	64 (48.9)	**0.010**
Education level				**0.022**
Elementary	262 (12.8)	237 (12.4)	25 (19.1)	
High school or more	1786 (87.2)	1680 (87.6)	106 (80.9)	
Civil status				0.183
Partnered	1092 (53.3)	1030 (53.7)	62 (47.3)	
Unpartnered	956 (46.7)	887 (46.3)	69 (52.7)	
Smoking				0.664
Never	887 (43.3)	828 (43.2)	59 (45.0)	
Former or current	1151 (56.2)	1079 (56.3)	72 (55.0)	
Alcohol consumption				0.148
Never	544 (26.6)	504 (26.3)	40 (30.5)	
Light to moderate	1118 (54.6)	1047 (54.6)	71 (54.2)	
Heavy	379 (18.5)	363 (18.9)	16 (12.2)	
Physical activity				0.106
Inadequate	436 (21.3)	401 (20.9)	35 (26.7)	
Health enhancing	1082 (52.8)	1011 (52.7)	71 (54.2)	
Fitness enhancing	530 (25.9)	505 (26.3)	25 (19.1)	
BMI (kg/m^2)				0.434
< 18.5	22 (1.1)	22 (1.1)	0 (0.0)	
18.5–25	851 (41.6)	797 (41.6)	54 (41.2)	
25–30	883 (43.1)	820 (42.8)	63 (48.1)	
≥ 30	286 (14.0)	272 (14.2)	14 (10.7)	
MMSE	29.0 [29.0, 30.0]	29.0 [29.0, 30.0]	29.0 [28.0, 30.0]	0.140
Comorbidities				
Number of chronic diseases	3.4 (2.1)	3.3 (2.0)	5.5 (2.3)	**< 0.001**
Chronic kidney diseases	559 (27.3)	503 (26.2)	56 (42.8)	**< 0.001**
COPD	73 (3.6)	67 (3.5)	6 (4.6)	0.517
Diabetes	157 (7.7)	143 (7.5)	14 (10.7)	0.179
Heart failure	98 (4.8)	63 (3.3)	35 (26.7)	**< 0.001**
Cerebrovascular diseases	81 (4.0)	66 (3.4)	15 (11.5)	**< 0.001**
Number of drugs	3.0 [1.0, 5.0]	2.0 [1.0, 5.0]	5.0 [3.0, 8.0]	**< 0.001**
Muscle mass and performance				
Calf circumference (cm)	36.6 (3.3)	36.6 (3.3)	36.7 (3.3)	0.800
Low muscle mass*	164 (8.0)	155 (8.1)	9 (6.9)	0.620
Chair stand test (s)	13.0 [10.0, 17.0]	12.0 [10.0, 17.0]	15.0 [12.0, 24.5]	**< 0.001**
Low lower limb strength*	646 (31.5)	581 (30.3)	65 (49.6)	**< 0.001**
Handgrip strength (kg)	26.2 (11.4)	26.3 (11.4)	24.5 (11.4)	0.078
Low upper limb strength*	459 (22.4)	411 (21.4)	48 (36.6)	**< 0.001**

Numbers are expressed as mean (standard deviation), median [interquartile range] or number (percentage) as appropriate. *P* values refer to the comparison between individuals with and without AF, and significancy defined as $p < 0.05$. Abbreviations: *MMSE*, mini-mental state examination; *BMI*, body mass index; *COPD*, chronic obstructive pulmonary disease. *Low muscle mass was defined as a calf circumference below the 20th sex-specific percentile of our sample, specifically, < 34 cm for men and < 32 cm for women. * Low upper limb strength was defined as handgrip strength < 27 kg for males and < 16 kg for women, and low lower limb strength was defined as chair stand test duration > 15 s to complete five rises from a chair

Missing data: smoking ($n = 10$), alcohol consumption ($n = 7$), BMI ($n = 6$)

mass or strength, indicating that the biomarker-related declines were similar in individuals with and without AF (Supplementary Table 4).

To minimize the potential confounding effect of cognitive decline, we performed a sensitivity analysis excluding participants who developed dementia within the initial 6 years of follow-up. The

Table 2 Association between atrial fibrillation and annual change in muscle mass and strength

	Calf circumference change per year		Chair stand test change per year		Handgrip Strength change per year	
	β (95% CI)	*p*-value	β (95% CI)	*p*-value	β (95% CI)	*p*-value
AF	−0.05 (−0.11, 0.01)	0.088	**1.49 (0.82, 2.16)**	**< 0.001**	−0.13 (−0.28, 0.02)	0.078

The table presents the outcomes of linear mixed effect models. Adjustments involved age, sex, and education, diabetes, HF, CKD, COPD, smoking, alcohol, BMI, physical activity. Bold characters indicate statistically significant results, defined as $p < 0.05$

Table 3 Association between atrial fibrillation and annual change in muscle mass and strength by blood GDF-15 level

AF status and GDF-15 marker levels	Calf circumference change per year		Chair stand test change per year		Handgrip Strength change per year	
	β (95% CI)	*p* value	β (95% CI)	*p*-value	β (95% CI)	*p*-value
Non-AF, low GDF-15	ref	ref	ref	ref	ref	ref
Non-AF, high GDF-15	**−0.08 (−0.10, −0.05)**	**< 0.001**	**1.22 (0.95, 1.49)**	**< 0.001**	**−0.11 (−0.17, −0.06)**	**< 0.001**
AF, low GDF-15	−0.02 (−0.12, 0.09)	0.770	**1.12 (0.03, 2.20)**	**0.045**	−0.21 (−0.44, 0.01)	0.066
AF, high GDF-15	**−0.12 (−0.20, −0.05)**	**0.002**	**2.48 (1.66, 3.30)**	**< 0.001**	−0.15 (−0.34, 0.04)	0.115

The table presents the outcomes of linear mixed effect models analyzing longitudinal annual changes in muscle mass and strength in relation to the baseline clinical profiles defined by AF status and categorized GDF-15 levels. Adjustments involved age, sex, and education, diabetes, HF, CKD, COPD, smoking, alcohol, BMI, physical activity. Bold characters indicate statistically significant results, defined as $p < 0.05$

Table 4 The change in muscle mass and strength over follow-up time by combined baseline IL-6 marker level and AF status

AF status and IL-6 marker levels	Calf circumference change per year		Chair stand test change per year		Handgrip strength change per year	
	β (95% CI)	*p* value	β (95% CI)	*p*-value	β (95% CI)	*p*-value
Non-AF, low IL-6	ref	ref	ref	ref	ref	ref
Non-AF, high IL-6	**−0.02 (−0.05, −0.001)**	**0.042**	**0.81 (0.54, 1.09)**	**< 0.001**	−0.30 (−0.84, 0.25)	0.283
AF, low IL-6	0.05 (−0.05, 0.16)	0.320	1.10 (−0.07, 2.26)	0.065	−2.20 (−4.63, 0.24)	0.077
AF, high IL-6	**−0.12 (−0.19, −0.05)**	**0.002**	**2.20 (1.39, 3.01)**	**< 0.001**	−1.02 (−2.82, 0.78)	0.269

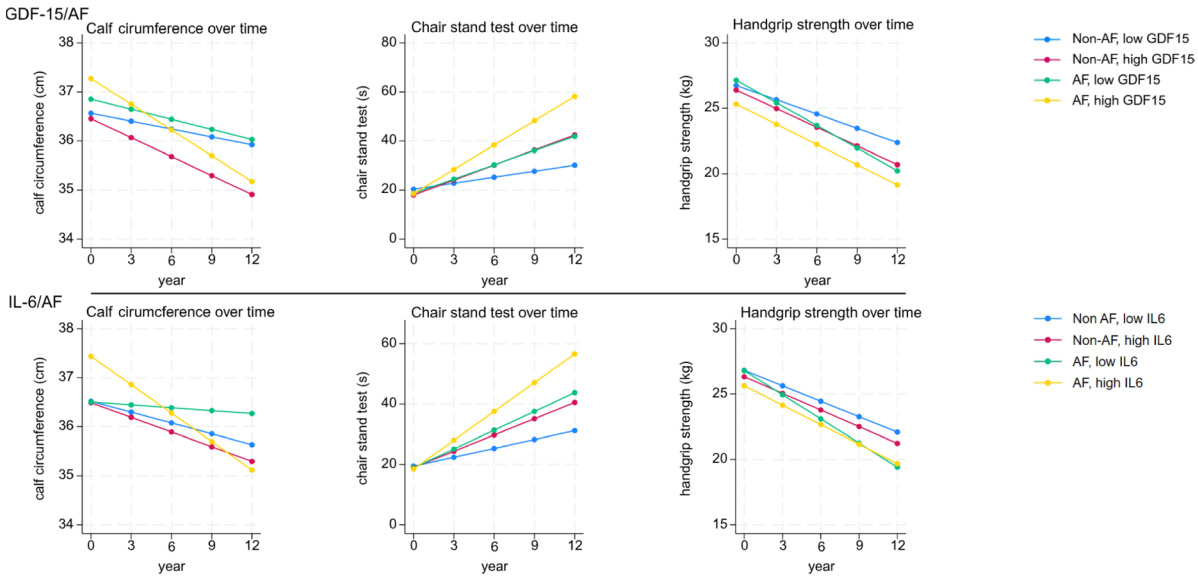
The table presents the outcomes of linear mixed effect models analyzing longitudinal annual changes in muscle mass and strength in relation to the baseline clinical profiles defined by AF status and categorized IL-6 levels. Adjustments involved age, sex, and education, Diabetes, HF, CKD, COPD, smoking, alcohol, BMI, physical activity. Bold characters indicate statistically significant results, defined as $p < 0.05$

associations between AF and muscle mass or strength decline, as well as those observed for the AF/biomarkers profiles, remained broadly consistent with the main analyses (Supplementary Table 5).

Compared with participants included in the analysis, those excluded due to missing data or exclusion criteria were older and had a higher burden of comorbidities ($p < 0.05$). This indicates that the analytical sample may represent a relatively healthier subset of the original cohort (Supplementary Table 6).

Discussion

In this longitudinal population-based study, we explored the 12-year trajectories of muscle mass and strength in older adults with and without AF, while considering the baseline levels of the inflammatory markers GDF-15 and IL-6. Our findings showed that AF was associated with a steeper decline in the chair stand test performance. Declines in muscle mass



Notes: Predicted muscle outcomes from linear mixed models adjusted for age, sex, education, diabetes, HF, CKD, COPD, smoking, alcohol, BMI, physical activity.

Fig. 2 Predicted longitudinal changes of muscle outcomes by AF and levels of inflammatory biomarkers

and lower-limb strength were also greater in the AF/high-biomarker profiles compared to the non-AF/low-biomarker profiles, suggesting that individuals with AF and elevated inflammatory markers exhibited the most pronounced deterioration over time.

Our study revealed that individuals with AF showed a significant increase in duration to complete the chair stand test over the 12-year follow-up period, even after adjusting for clinical and socio-demographic covariates. The chair stand test assesses lower limb functionality and neuromuscular coordination [24, 27], indicating a decline in functional capacity. This result aligns with previous studies indicating that AF is linked to impaired lower limb function and mobility limitations, including longer chair-stand test durations, after adjusting for comorbidities and demographic variables [4, 6, 28]. AF may impair functional mobility through multiple pathways, including reduced cardiac output and cerebral blood flow, and an increased risk of stroke, that can contribute to cognitive and motor deficits. Its association with frailty may further increases the energy cost of walking, while polypharmacy and low physical activity, both common in AF, can also negatively affect mobility [4, 6]. Although no consensus exists on a cut-off defining clinically meaningful deterioration in chair-stand performance, previous population-based work [29] suggests that a decline of approximately one second per year is associated with increased disability risk. Thus, the average annual change observed in individuals with AF in our study falls within a range considered clinically relevant in older adults.

Although previous studies found a significant decline in handgrip strength among patients with AF [4, 28], our overall findings did not show statistically significant reductions in handgrip strength or calf circumference. This may suggest that the association between AF and muscle decline was not uniform across all participants, but rather more evident in specific subgroups of AF combined with higher inflammatory levels. Consistent with this interpretation, we observed that individuals with elevated circulating levels of GDF-15 and IL-6, particularly those with AF, experienced more substantial losses in muscle mass and both upper and lower limb strength over time. These findings suggest a possible concurrent effect of systemic inflammation and mitochondrial stress on musculoskeletal deterioration in the context of AF, a condition already characterized by altered hemodynamics and cellular stress. Notably, GDF-15,

a cytokine induced by cellular stress, has emerged as a sensitive biomarker of mitochondrial dysfunction to the point of being classified as mitokine [30–32]. This latter is upregulated in response to mitochondrial damage, oxidative stress, and impaired mitochondrial protein synthesis, all of which are commonly observed in aging and chronic disease states, including AF [30, 33]. Elevated GDF-15 has been linked to impaired physical function, frailty and sarcopenia [18, 19, 32], and evidence from the Atherosclerosis Risk in Communities Study (ARIC) indicates that high GDF-15 levels also predict the long-term risk of incident AF [34], underscoring its position at the intersection of cardiovascular and functional decline. In our cohort, individuals with higher baseline GDF-15 levels, regardless of AF status, had significant declines in both muscle mass and lower limb strength, suggesting that GDF-15 may contribute to, rather than merely reflect, impaired muscle performance. Similarly, IL-6, a pleiotropic cytokine involved in immune regulation, has been associated to mitochondrial stress and fragmentation, reduced oxidative phosphorylation, and increased reactive oxygen species in skeletal muscle [18], all of which contributes to muscle wasting. Elevated IL-6 contributes to oxidative stress in skeletal muscle by impairing the nuclear factor erythroid 2-related factor 2 antioxidant response (Nrf2), thereby promoting muscle degradation and functional decline [35]. In our study, higher IL-6 levels were associated with were associated with poorer chair stand performance and reduced muscle mass regardless of AF. These findings corroborate prior studies showing that IL-6 is a pro-inflammatory cytokine linked to muscular decline and impaired physical performance, including poor performance at the chair stand test, and increased cardiovascular risk [17, 36]

Taken together, these findings emphasize the relevance of assessing inflammatory and mitochondrial stress markers such as GDF-15 and IL-6 when evaluating muscle health in older adults with AF. These biomarkers may provide insight into the underlying cellular dysfunction that possibly leads to progressive muscle impairment and may represent interconnected manifestation of underlying aging processes. The convergence of systemic inflammation and AF-related physiological stressors, including endothelial dysfunction, heightened oxidative stress, reduced nitric oxide bioavailability, mitochondrial energy deficits, and compromised skeletal muscle perfusion, provides a possible framework for understanding why AF often co-occur with accelerated functional decline [6]. Rather than implying a causal pathway, these patterns may reflect a shared vulnerability state in which AF, chronic systemic inflammation, and declining muscle function emerge as interconnected features of biological aging. Nevertheless, it should be noted that, although aging is frequently accompanied by low-grade inflammation [37], circulating inflammatory marker levels are dynamic and may fluctuate in response to transient stressors, acute illnesses, or short-term physiological changes. As a result, a single time-point biomarker measurement may be subject to regression dilution bias [38], potentially attenuating the underlying association between inflammation, AF and longitudinal muscle decline. Additionally, AF status was only assessed at baseline, which prevents us from determining how AF and systemic inflammation relate both at the onset and over time. Future studies incorporating repeated assessments of inflammatory markers and AF status will be essential to clarify the temporal dynamics and to better understand the underlying pathophysiological mechanisms.

Clinical implications

Results from our investigation underscore the importance of incorporating functional and muscular assessments in longitudinal studies of AF-related aging populations. The observed decline in chair stand performance among individuals with AF may reflect progressive impairments in the interplay between the musculoskeletal and cardiovascular systems. Regular evaluations of lower limb function may therefore be a practical and cost-effective approach for monitoring functional decline in clinical settings. Although inflammatory biomarkers were measured only at baseline, their associations with long-term muscle trajectories support their role in risk stratification for older adults with AF. Circulating GDF-15 and IL-6, rather than serving solely as diagnostic markers, could be integrated into a multidimensional geriatric assessment to complement clinical and functional evaluation with information on systemic inflammation and mitochondrial stress. Such combined assessment could help identify older individuals with AF who are at heightened risk of accelerated functional decline and who may benefit from timely preventive

strategies. The interplay between systemic inflammation and AF-related muscle deterioration highlights the potential benefits of inflammation-targeted interventions to preserve physical function. In individuals with AF and elevated inflammatory markers, integrated management approaches, including targeted physical training (e.g., lower limb strengthening and endurance training), nutritional interventions and lifestyle modifications may help mitigate future physical decline. Early interventions may reduce the risk associated with AF, including falls, cognitive impairment, bleeding, and other cardiovascular complications [6]. Future longitudinal and interventional studies are needed to evaluate concurrent changes in inflammatory biomarkers and muscle performance, and to determine whether biomarker-guided preventive strategies can attenuate muscle decline and improve long-term functional outcomes in older adults with AF.

Strengths and limitations

Key strengths of this study include the longitudinal population-based design, the application of two different muscle strength measurements, and the repeated assessments over 12 years within the SNAC-K cohort. In addition, results were adjusted for several confounders, and the robustness of the findings was confirmed with sensitivity analysis. However, several limitations warrant discussion. First, SNAC-K participants are healthier and of higher socioeconomic status compared with the general Swedish population, potentially affecting the generalizability of our results. In addition, 39% of the original cohort was excluded due to missing data on key variables and exclusion criteria. Comparison of included and excluded participants showed that excluded participants were older and had higher burden of comorbidities. Therefore, the association between AF, inflammation, and muscle decline may be underestimated or potentially distorted due to healthy participant bias. Calf circumference was used as a proxy for muscle mass, in line with the EWGSOP2 recommendations [21] indicating that it may be used when more precise methods (e.g., bioelectrical impedance analysis) are unavailable. However, it is an indirect measure and may be influenced by adiposity or peripheral edema, particularly relevant in AF, where fluid retention is common. However, edema would be expected to inflate calf circumference and thereby bias results toward underestimating true muscle loss. The fact that the association persisted despite this potential attenuation suggests that the underlying relationship between inflammation, AF, and muscle mass decline is unlikely to be explained by measurement limitations alone.

Moreover, biomarker assessments were restricted to baseline values, without the possibility of evaluating changes over time in inflammatory levels. AF status was defined at baseline, and we did not model incident AF during follow-up. Consequently, some participants classified as non-AF at baseline may have developed AF later, and we cannot fully disentangle whether muscle decline preceded or followed AF onset in these individuals. This temporal ambiguity raises the possibility of reverse causation or shared underlying pathology rather than a strictly causal effect of AF on muscle decline. Accordingly, our findings should be interpreted as reflecting long-term associations and differential trajectories rather than definitive causal relationships. Finally, although we accounted for several key confounders, residual confounding from unmeasured factors such as subclinical cardiac conditions, or nutritional status and protein intake, may still be present.

Conclusion

Our study indicates that community-dwelling older adults with AF experience a significant progressive decline in lower limb function, as assessed by the chair stand test. Moreover, elevated baseline levels of GDF-15 and IL-6, both separately and together with AF, were associated with a substantial reduction in muscle mass and strength over time. These findings underline the role of AF in age-related muscle degeneration and suggest that systemic inflammation may exacerbate this process, accelerating functional decline. In clinical practice, GDF-15 and IL-6 could be incorporated into routine AF follow-up, helping identify individuals who may benefit from more intensive monitoring and tailored interventions to mitigate musculoskeletal deterioration and prevent AF-related adverse outcomes.

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Author contribution The study concept was designed by DLV, and DC; AMO and FT contributed to the data preparation and analysis concept. Data analysis and the first draft of the manuscript were performed by DC; all authors commented and improved on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability SNAC-K data are available upon request made digitally through https://www.snac-k.se/ conditional to approval from the study steering group.

Declarations

Ethics approval and consent to participate The Swedish National study on Aging and Care (SNAC-K) study complies with the principles of the Declaration of Helsinki and was approved by the Regional Ethical Review Board in Stockholm. Written informed consent to participate in the study was collected from all participants or the next of kin for those with cognitive impairment.

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Conflict of interest None.

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