Atrial fibrillation accelerates functional decline in older adults: a 15-year follow-up population-based study.

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Background

Atrial fibrillation (AF) is the most common arrhythmia worldwide, and its prevalence increases progressively with age(1). Due to the extended human longevity, it has been estimated that one out of three persons of European ancestry at index age of 55 years would develop AF(2). Individuals with AF often display characteristics of frailty, carry a higher burden of comorbidity, and exhibit a greater susceptibility to poor health outcomes when compared to those without AF(1–4). While extensive research has been conducted concerning the impact of AF on cardiovascular events, emerging interest lies in understanding its potential associations with non-cardiovascular outcomes, such as functional mobility(5). Functional mobility is the physiological ability of people to move independently and safely in a variety of environments to accomplish functional activities or tasks and to participate in activities of daily living (ADL), at home, work and in the community(6). The possible relationship between AF and functional mobility involves numerous interconnected pathways(7). Specifically, AF has been associated with reduced cerebral blood flow, increased stroke risk and a higher burden of comorbidities, potentially resulting in cognitive impairment and deficits in motor control(7–9). Additionally, AF is linked with frailty and the decreased physiological reserve of this condition may increase the energy cost while walking, further reducing functional mobility(8). Finally, individuals with AF are more often on polypharmacotherapy and present with low levels of physical activity, all factors that can negatively influence functional mobility(10,11). Understanding the associations between those factors and physical performance in older adults with AF can contribute to early detection,

prevention, and tailored interventions aimed at minimizing physical function decline in older adults with AF.

The walking speed (WS) test has been widely recognized as a good surrogate of physical function(12). It combines complex mechanisms of balance and energy, demanding the correct functioning of multiple organs and the musculoskeletal system(7,9). Deficits in walking speed are associated with adverse outcomes, such as hospitalizations, increased risk of falls, cognitive decline, and death(7,9,10,12,13). To date, however, few investigations have characterized WS trajectories associated with AF in older individuals (8,14); none has sought to determine the effect of AF-related incident events on WS decline over time.

In this study, we sought to evaluate the association of AF with physical function decline using data from a longitudinal study of community-dwelling older adults who have been followed for 15 years[15]. Our specific objectives were 1) to evaluate the association of prevalent AF with the motor function decline over 15 years, 2) to determine the interaction between AF-related incident events, including heart failure, stroke, and dementia, and WS decline over time in older individuals with AF, and 3) to determine the possible effect of oral anticoagulant therapy (OAC) on the WS decline among participants with AF.

Methods

Study Population

Data were collected from the Swedish National Study of Aging and Care in Kungsholmen (SNAC-K), which is an ongoing population-based study of community-dwelling and institutionalized older adults ≥60 years. The SNAC-K study involved 11 age cohorts at baseline, and they were assigned

to younger old groups (60, 66, and 72 years), and older old groups (78, 81, 84, 87, 90, 93, 96, and ≥99 years) living in the Kungsholmen district (Stockholm, Sweden). Those who accepted the invitation were evaluated for the first time between 2001 and 2004 and then followed up every 6 years for those aged <78 years or every 3 years for those aged ≥78 years. At each study wave, SNAC-K participants undergo an approximately five-hour comprehensive clinical and functional assessment carried out by trained physicians, nurses, and neuropsychologists. Physicians collect information on diagnoses of disorders or health conditions via physical examinations, medical history, examination of medical charts, self-reported information, and/or proxy interviews.

For the current study, we utilized 15-year follow-up data from 2001–2004 (Wave 1) to 2016-2019 (Wave 6). At baseline, 3363 people were examined (participation rate, 73%). Of these, we excluded individuals institutionalized at baseline (n=191) and participants with no follow-up WS measurement (n=31), leaving 3141 participants for the current analysis. Supplemental Figure 1 shows the flowchart of the study participants.

All parts of the SNAC-K study (including linkage with the Patient and Death Registers) were approved by the regional ethical review board in Stockholm. Written informed consent was obtained from all participants or, in case of persons with cognitive impairment, from proxies (next of kin or guardians).

Ascertainment of AF

AF was diagnosed at baseline through a physician's examination and electrocardiogram (ECG), where discrete P waves were undetectable and irregular ventricular rate was observed on a 12-lead-electrocardiogram(15). In addition, the Swedish National Patient Register, which includes

comprehensive records from hospital and specialist outpatient care, was reviewed to identify the presence and onset date of AF in patients with a known history of the condition.

Walking speed assessment

To assess WS, participants were asked to walk 6 meters at their usual speed at each study visit, or alternatively, 2.4 meters when participants reported that they walked slowly or when the assessment was carried out in restricted spaces. Walking speed was reported in meters/second (m/s).

Assessment of covariates

Educational attainment was ascertained by nurses through interviews and categorized as elementary, high school, and university or higher. Body mass index (BMI) was obtained by dividing the participants' weight in kilograms by their squared height in meters (kg/m^2). Physical activity was divided into inadequate (light exercise ≤2–3 times per month), health enhancing (moderate exercise ≤2–3 times per month), and fitness enhancing (intensive exercise several times per week). Smoking habits was obtained by nurse interview and categorized as current/former smoker or never smoked. Alcohol consumption was categorised as no/occasional, light-to-moderate (1–14 drinks per week for men or 1–7 drinks per week for women) or heavy (>14 drinks per week for men or >7 drinks per week for women) drinking. The assessment of basic activities of daily living (B-ADL)(16) was conducted through nurse interviews, evaluating impairment across six domains: bathing, dressing, toileting, continence, transferring from bed, and eating. Impairment levels were graded on a scale from 0 (indicating independence in all ADLs) to 6 (indicating the need for support in all six ADL domains). Similarly, instrumental activities of daily

living (I-ADL)(17)were assessed on a scale ranging from 0 (reflecting independence in all IADL) to 8 (indicating the need for support in all eight IADL domains). These encompass a person's capability in food preparation, medication management, shopping, communication, financial management, housekeeping, transportation, and laundry. Global cognitive function was measured with the Mini-Mental State Examination (MMSE) (18).

The clinical ascertainment and operationalization of chronic diseases in SNAC-K is reported elsewhere(19). The chronic use of OAC was assessed selecting patients who were receiving warfarin (ATC code BA01AA03) as home-therapy for AF. Incident stroke was defined as first-ever stroke occurring over the follow-up period among the stroke-free participants at baseline. The occurrence of stroke was ascertained through linkage to the Swedish National Patient Register(19). Dementia was diagnosed at each wave according to the Diagnostic and Statistical Manual of Mental Disorders (4th edition) criteria, using a validated three-step procedure(20). Incident heart failure was assessed at each wave by the SNAC-K physician based on clinical interviews and review of data from the Swedish National Patient Register(19).

Statistical analysis

The characteristics of the study population were summarized and reported as means and standard deviations (SD), or medians and interquartile ranges (IQR) for non-normally distributed continuous variables, and as frequencies and percentages for categorical variables.

To evaluate the effect of AF on WS decline across the 15-year follow-up period, we ran multivariable joint models accounting for non-random attrition due to death(21). Such joint models consist of two sub-models which were fitted simultaneously: a linear mixed-effects model with walking speed as the outcome and a Cox proportional-hazard model with death as the outcome of

interest. In addition, through the calculation of the association parameter α, joint modelling enables the estimation of the effect of the predictor (WS) on the hazard of mortality. In the linear mixed-effects sub-model, fixed effects included AF status, time, and the interaction between the two (AF × time). Random effects included a random intercept to allow for individual differences at baseline.

The linear mixed-effects models were first adjusted for sex, age, and education (Model 1), and then further for hypertension, stroke, heart failure (HF), COPD (Chronic Obstructive Pulmonary Disease), dementia, diabetes, physical activity, alcohol consumption, and BMI (Model 2). We also performed three-level interaction analyses and stratified analyses by demographic factors (sex, age), lifestyle factors (physical activity levels), and comorbidities (HF, history of stroke, COPD, diabetes, hypertension) to evaluate whether the effects of AF on WS decline could be modified by these factors or health conditions.

To assess the robustness of the associations between AF and WS decline, we conducted two sensitivity analyses. Firstly, to examine participants without significant frailty or impaired functional status at baseline, we performed three-level interaction analyses on a subset of individuals with a baseline WS greater than 0.5 m/s. Secondly, to mitigate potential confounding in AF participants, propensity scores were computed for each participant and incorporated into the joint model. These propensity scores included age, sex, education attainment, I-ADL, levels of physical activity, history of HF, type 2 diabetes mellitus, ischemic heart disease, alcohol consumption, baseline WS, COPD, BMI, chronic kidney disease (CKD), diagnosis of dementia at baseline, and history of stroke. The variables were selected upon clinical relevance and statistical significance in Table 1.

Additionally, in a subsample of individuals with AF free from dementia, history of stroke and HF, we ran a univariable and multivariable logistic regression (using age, sex, education, HF, COPD,

diabetes, hypertension, physical activity levels as covariates) to examine the association between AF (exposure) and AF-related incidents event (i.e., incident HF, incident stroke, incident dementia). Secondly, to estimate the effect of those AF-related incident events on WS decline, we further performed three joint models using incident HF and incident stroke (calculated as time-varying variables) and their interaction with time as fixed effects, based on the same adjustment strategy as indicated for Model 1 and 2.

To evaluate the effect of OAC on WS decline, we performed one last joint model with OAC, time and their interaction as fixed effects, and the intercept as random effects using the aforementioned Models 1 and 2 for the multivariable adjustment. OAC use was categorized into three subgroups: OAC users, non-OAC users, and non-AF participants as controls.

Finally, an alluvial plot was constructed to visually depict transitions over the 15-year follow-up period among participants with AF and those without AF. This plot illustrates changes in states based on normal walking speed (≥0.8 m/s) and slow walking speed (<0.8 m/s), along with occurrences of death and dropouts at each follow-up.

The level of significance was defined as two-tailed p value < 0.05. All analyses were performed using R software, Version 4.1.0, packages: tidyr, mgcv, lme4, JM, survival, ggplot, ggalluvial, car. (RStudio, Inc., Boston, MA, USA).

Results

Baseline characteristics of the study population are shown in Table 1. Of the 3141 participants, 285 (9.1%) had a diagnosis of AF at baseline. Compared to non-AF participants, those with AF were older, with levels of education, and a higher burden of comorbidities. Moreover, older adults

with AF were more likely to have a history of stroke, diabetes, HF and dementia at baseline. As depicted in Figure 1, participants with AF exhibited a propensity towards slower baseline walking speeds compared to those without AF.

Participants with AF had a faster WS decline than non-AF peers (β coefficient per year = −0.011, 95% confidence interval [CI]: −0.016 to −0.005) (Table 2), a trend consistent with the results obtained in the propensity score - adjusted joint model (Supplemental Table 1). Furthermore, by joint modelling, we confirmed that a decrease of WS over time, was significantly associated with an increased mortality risk, irrespective of the AF status (Supplemental Table 2).

The three-level interaction analyses showed that, the impact of AF on WS decline was more pronounced in persons without a history of stroke ($p_{interaction} = 0.019$), and in those with a higher baseline reported physical activity ($p_{interaction} = 0.014$) (Figure 2). In a subsample of participants with WS faster than 0.5 m/s, those conditions were not confirmed as significantly associated with a higher WS decline (p per interaction >0.05) (Supplemental Tables 1 and 2).

During the 15-year follow-up, older adults with AF had a higher incidence of stroke (17.6% vs 9.4%) and HF (25% vs 11.5%), compared to their peers. In multivariate logistic analysis, AF was associated with increased odds of incident HF and incident stroke; on the contrary, the relationship between AF and incident dementia was not confirmed after adjustment (Supplementary Table 5). As shown in Table 3, in the 132-HF-free and stroke-free participants with AF, incident HF and incident stroke were associated with a faster WS decline, as compared with participants never experiencing such conditions.

In terms of anticoagulation treatment, both OAC users and non-OAC users had a steeper decline in WS than participants without AF (Table 4). Baseline characteristics of OAC and non-OAC users are shown in Supplemental Table 6.

Discussion

Our long-term population-based cohort study showed that AF constitutes an independent risk factor for functional mobility decline over a 15-year follow-up, regardless of age, sex, education, lifestyle factors, BMI and relevant comorbidities. The detrimental effect of AF on WS decline over time persisted in all the clinical and demographical pre-specified subgroups; nonetheless, it was stronger in participants without a history of stroke at baseline, and in people with a higher baseline reported physical activity. Additionally, over the 15-year follow-up period, among AF participants who were free from HF, dementia, and stroke at baseline, the occurrence of incident stroke, and incident HF during the follow-up period was associated with a more rapid decline in motor function. Finally, we observed that the sustained decline in physical function among individuals with AF was not influenced by the use of anticoagulation therapy. These findings underscore the importance of recognizing AF as a significant contributor to the long-term deterioration of physical function, suggesting that interventions targeting AF management and its associated risk factors could potentially mitigate this decline. Our results align with the few previous studies showing a link between AF and motor impairment(8,14). However, the extended follow-up period, the utilization of joint models accounting for the competing risk of death, and the focus on incident events, provides a more comprehensive perspective on the temporal evolution of this relationship.

AF and physical frailty intersect through shared pathways, mutually influencing each other. Frailty appears to significantly impact the management and trajectory of AF, while AF may serve as an indicator of frailty. ((4,22–24). Frailty is a syndrome characterized by high biological vulnerability, decreased physiologic reserve, and reduced capacity to resist stressors, due to multiple impairments in inter-related systems, leading to reduced homeostatic reserve. Despite the pressing need for evidence to inform on functional trajectories and prognosis of individuals with

AF, tools for a better definition of the pre-frail state and its evaluation are lacking(17). Recent investigations have highlighted a growing use of frailty instruments, showing moderate to good inter-rater reliability(25,26), but a consensus on widespread implementation is lacking. The concept of frailty holds significant clinical implications. As demonstrated in the study by Diemberger et al(27), physicians' perceptions of frailty in AF patients vary, primarily influenced by age, sex, and weight, and notably differ from the results of objective frailty assessments. In this context, walking speed (WS) is widely recognized as a reliable proxy for physical frailty. Intriguingly, individuals with AF initially exhibiting a WS greater than 0.8 m/s were more prone to decelerate their pace into the lowest group compared to their non-AF counterparts. Furthermore, once participants transitioned to WS levels below 0.8 m/s, their susceptibility to mortality increased (Figure 1). This finding was further elucidated through joint modelling, reaffirming the robust association between WS and mortality over time, in line with prior research(28), underscoring a diminished risk of death in AF patients with higher walking distance and pace. In our study, individuals without stroke at baseline, and showing higher physical activity were less affected by AF in terms of WS decline. This observation could be attributed to the well-established adverse effects of stroke on physical functionality(29,30). On the other hand, a sensitivity analysis carried out in individuals with a WS faster than 0.5 m/s, did not confirm the significant effect-modifying role of history of stroke and physical activity on WS, suggesting the crucial impact of baseline functional status on physical mobility decline.

Hence, for patients with AF, regular and comprehensive assessment of cognitive abilities is advisable to prevent functional decline and deterioration in motor performance. Apart from stroke prevention and rhythm management, additional multidisciplinary preventive strategies, such as lifestyle modifications and early detection of these conditions, might alleviate the burden of motor

function decline among aging populations with AF. This is aligned with recommendations in current guidelines, for a holistic or integrated care approach to AF management(31) where adherence to the Atrial fibrillation Better Care (ABC) pathway is associated with improved clinical outcomes(32). Ongoing studies, such as the AFFIRMO(33) and the EHRA-PATH (34), which concentrate on outcomes among multimorbid patients receiving polypharmacotherapy, have the potential to offer a thorough assessment for people with AF. Specifically, they can address functional domains and establish a common interdisciplinary approach, fostering collaboration among geriatricians, cardiologists, rehabilitation specialists (e.g. physiotherapists) and primary care physicians to enhance the quality of life for this unique patient population.

In our sample, AF was significantly associated with incident stroke and incident HF; moreover, individuals developing those two conditions demonstrated a more pronounced WS decline compared to the control group, particularly those with stroke, underscoring the potential impact of cerebral disease on physical function.

In light of these results, early identification of high-risk stroke patients, is pivotal in promptly initiating motor support activities and more importantly, to assess the correct assumption of OAC (35). Indeed, one of the primary hypotheses regarding the physical impairment caused by AF posits that it results from either overt or silent ischemic strokes, which can damage the cortical and subcortical regions responsible for motor control(7–9). Consequently, the utilization of OAC could theoretically reduce the incidence of stroke and thereby decrease the occurrence of declining functional mobility. In the present study, despite of the expected benefit on stroke, functional capacity, cognitive impairment, and dementia(15,24,28,36) , the use of OAC did not significantly influence the WS decline over time.

This conflicting result can be attributed to several reasons. Firstly, the study population had low rates of baseline anticoagulant prescription (25%), consistent with previous findings from the Danish National Hospital registry(37) demonstrating that the proportion of older AF patients prescribed vitamin K antagonists ranged from 13% to 23% between 1995 and 2002. Additionally, the low prescription rate seems to reflect the well-established, common undertreatment with OAC in older individuals with AF(38). Furthermore, in older individuals with AF receiving OAC in the early 2000s, treatment quality was frequently suboptimal. This was highlighted in (39)a study by McCormick et al(39), which found that only one-fifth of patients achieved a time in therapeutic range ≥65%, with less than half maintaining an international normalized ratio within the therapeutic range of 2.0 to 3.0. Notably, non-anticoagulated individuals were older with a higher comorbidity burden and had substantially slower WS at baseline relative to anticoagulated counterparts, thereby potentially circumscribing their capacity for further physical performance gains. These results align with a previous study(23) reporting the negative association between OAC and frailty.

Moreover, these results are impacted by a small sample size, and thus evaluating the effect of OAC on motor function in larger cohorts or randomized clinical trials would be warranted. Notwithstanding, there are still conflicting data on the effect of OAC in older persons on reducing AF-related incident white matter lesions(40), which have been proven to be related to physical function(41). Taken together, these findings suggest that while OAC usage is relevant, baseline health status significantly influences walking speed decline, emphasizing the multifaceted nature of the relationship between AF and physical function.

Strengths and limitations

To our knowledge, this represents the first cohort study attempting to evaluate the effect of AF on the physical decline throughout a 15-year follow-up period, accounting for the impact of incident diseases and OAC usage in a population-based cohort. This research extends our knowledge of the independent effect of AF on WS decline in older, community-dwelling individuals.

The study has some limitations. First, concerning AF assessment, we could not differentiate between paroxysmal and permanent AF; however, the risk associated with poor outcomes seems to present across various clinical presentations of the arrhythmia. In this regard, data from an observational study by Boriani(42) and colleagues reported a higher mortality risk in asymptomatic versus symptomatic patients in terms of risk of stroke-, cardiovascular- and all-cause mortality [25]. Yet, we might not have captured patients with asymptomatic, paroxysmal AF during the follow-up. Furthermore, our study encountered limitations regarding the uncertainty duration of AF, and we recognize that our study may focus on comparing mobility decline between patients with known AF and those without AF. This aspect bears significant importance as the burden of AF has been correlated with diminished quality of life(43), heightened risks of cardiovascular hospitalization, ischemic stroke, and mortality (30). However, by evaluating prevalent AF cases, we may have overlooked the emergence of new AF cases, leading to a potential misclassification of incident AF as non-AF. Consequently, this could have diluted the strength of association between the presence of AF and walking speed. Additionally, the study population from central Stockholm consisted of individuals with a higher socioeconomic status than average Sweden, which may not be representative of all older adults. This may limit the generalizability of the findings to the broader population of older adults. Moreover, the study spanned a 15-year period, during which there may have been changes in the management of AF and its associated

comorbidities. Specifically, the OAC prescription standards might have been changed during follow-up, also due to the introduction of the Direct Oral Anticoagulants (DOACs). Similarly, we did not have an adherence measure of the treatment; indeed, more information on OAC use would help us to establish a greater degree of accuracy on the relationship between anticoagulant use and physical performance decline. Additionally, despite extensive adjustments and sensitivity analyses that statistically equalized the two groups, residual confounding may still exist, particularly considering the baseline population differences. For example, we did not include obstructive sleep apnea, which is associated with both AF and physical function decline, as a covariate in our analysis. Therefore, larger multicentre cohorts of patients with diagnosis of new AF compared to stably confirmed non-AF individuals are needed to confirm our findings. Finally, the study's observational nature limits its ability to establish causality. While associations between AF and WS decline, stroke, HF, dementia, and mortality were previously identified, it should be interpreted cautiously as causation cannot be definitively proven.

Conclusion

AF is associated with a substantial decline in physical function over time in older adults living in the community. The development of HF and ischemic events significantly contribute to greater motor function decline in patients with AF, while the use of anticoagulant therapy does not appear to be crucial in preventing this decline in physical performance.

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Disclosures

None.

Data Availability Statement

Data are available upon reasonable request. Data are from the SNAC-K Project, a population-based study on ageing and dementia (http://www.snac-k.se/). Access to these original data is available to the research community upon approval by the SNAC-K data management and maintenance committee. Applications for accessing these data can be submitted to Maria Wahlberg (Maria.Wahlberg@ki.se) at the Aging Research Center, Karolinska Institutet.

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Tables:

Table 1. Characteristics of the study population.

Table 2. Association between atrial fibrillation (AF) and walking speed accounting for the competing risk of death (joint models).

Table 3. Association between incident heart failure (HF) and incident stroke (as time varying variables) and walking speed in AF participants without baseline HF, stroke and dementia, accounting for the competing risk of death (joint models).

Table 4. Association between use of Oral Anticoagulants (OAC) and walking speed decline accounting for the competing risk of death (joint models).

Figure Legends

Figure 1. Transitions of walking speed measurements over 15 years of follow-up among individuals without AF (panel a), and with AF (panel b).

Figure 2. Association between AF and walking speed accounting for the competing risk of death (Model 2, joint models), stratified by sex, age, heart failure, stroke, chronic obstructive pulmonary disease, diabetes, levels of physical activity and hypertension.

Table 1. Characteristics of the study population.

Characteristics	All participants (n=3141)	Non-AF (n=2856)	AF (n=285)	p-value
Age, mean (SD)	73.7 (10.7)	73.0 (10.5)	81.2 (9.5)	0.015
Female sex, n (%)	2000 (63.6)	1837 (64.3)	163 (57.2)	<0.001
Education, n (%)				<0.001
Elementary	518 (16.4)	457 (16.0)	61 (21.4)	
High school	1551 (49.4)	1397 (48.9)	154 (54.0)	
University	1060 (33.7)	995 (34.8)	65 (22.8)	
Smoking habits, n (%)				0.129
Never	1454 (46.3)	1321 (46.2)	133 (46.6)	
Former/current	1655 (52.7)	1509 (52.8)	146 (51.2)	
Alcohol consumption, n (%)				0.005
Never/Occasionally	1096 (35.2)	974 (34.4)	122 (44.3)	
Light/Moderate	1507 (48.5)	1381 (48.7)	126 (45.8)	
Heavy	503(16.2)	476 (16.8)	27(9.8)	
Physical activity, n (%)				<0.001
Inadequate	963 (30.6)	835 (29.2)	128 (44.9)	
Health enhancing	1517 (48.2)	1395 (48.8)	122 (42.8)	
Fitness enhancing	661 (21.0)	626 (21.9)	35 (12.3)	
Body Mass Index (BMI), n (%)				0.001
BMI 18.5 – 25	1311 (41.7)	1198 (41.9)	113 (39.6)	
BMI > 25	1569 (49.9)	1440 (50.4)	129 (45.2)	
BMI < 18.5	80 (2.5)	64 (2.2)	16 (5.6)	
MMSE score, median (IQR)	29(2)	29(2)	28(3)	<0.001
1 + impaired B-ADL (%)	39 (1.2)	32(1.1)	7 (2.5)	0.09
1 + impaired I-ADL (%)	270 (8.5)	217 (8.3)	53 (19.3)	<0.001
# comorbidities, median (IQR)	4 (3)	3 (3)	5 (3)	<0.001
Hypertension, n (%)	2192 (69.8)	1992 (69.7)	200 (70.2)	0.778
COPD, n (%)	151 (4.8)	127 (4.4)	24 (8.4)	0.003
Stroke, n (%)	214 (6.8)	158 (5.5)	56(19.6)	<0.001
Diabetes mellitus, n (%)	278 (8.8)	240 (8.4)	38 (13.3)	<0.001
HF, n (%)	297 (9.4)	177 (6.2)	120 (42.0)	<0.001
Ischemic heart disease, n (%)	460 (14.6)	376 (13.1)	84 (29.5)	<0.001
CKD, n (%)	1059 (33.7)	905 (31.6)	154 (54.0)	<0.001
Dementia, n (%)	157 (4.9)	127 (4.4)	30 (10.5)	<0.001
Walking speed, mean (SD)	0.98 (0.45)	1.02(0.44)	0.71(0.43)	<0.001
Walking speed < 0.8 ms/s, n (%)	850(27.3)	703(24.8)	147(51.9)	<0.001
Death, n (%)	1752 (55.7)	1497 (47.6)	255 (89.5)	<0.001

Abbreviations: SD: standard deviation, IQR: interquartile range, B-ADL: basic activities of daily living, I-ADL: instrumental activities of daily living, COPD: Chronic Obstructive Pulmonary Disease, CKD: chronic kidney disease, MMSE: Mini Mental State Examination, HF: Heart Failure.

Table 2. Association between AF and walking speed accounting for the competing risk of death (joint models).

	Intercept β (95%CI)	Annual Change in WS β (95%CI)
Crude	-0.32 (-0.27; -0.22)	-0.010 (-0.015, -0.004)
Model 1	-0.11 (-0.16; -0.04)	-0.010 (-0.015, -0.004)
Model 2	-0.02 (-0.06; 0.02)	-0.011 (-0.016, -0.005)

Model 1: age + education + sex

Model 2: age + education + sex + hypertension + COPD + HF + stroke + dementia + BMI + diabetes + physical activity + alcohol consumption

Abbreviations: BMI: body mass index, COPD: Chronic Obstructive Pulmonary Disease, CKD: Chronic Kidney Disease, HF: Heart Failure, WS: Walking Speed

Table 3. Association between incident HF and incident stroke (as time varying variables) and walking speed in AF participants without baseline HF, stroke and dementia, accounting for the competing risk of death (joint models).

	Incident HF Change/year β (95%CI)	Incident Stroke Change/year β (95%CI)
Crude	-0.029 (-0.043; -0.015)	-0.031 (-0.046, -0.015)
Model 1	-0.027 (-0.041; -0.014)	-0.030 (-0.045, -0.015)
Model 2	-0.026 (-0.040; -0.013)	-0.030 (-0.047; -0.016)

Model 1: age + education + sex

Model 2: age + education + sex + hypertension + COPD + incident HF + incident stroke + BMI + T2DM + physical activity + alcohol consumption

Abbreviations: AF: atrial fibrillation, BMI: body mass index, COPD: Chronic Obstructive Pulmonary Disease, HF: heart failure, T2DM: type 2 diabetes.

Table 4. Association between use of OAT and walking speed decline accounting for the competing risk of death (joint models).

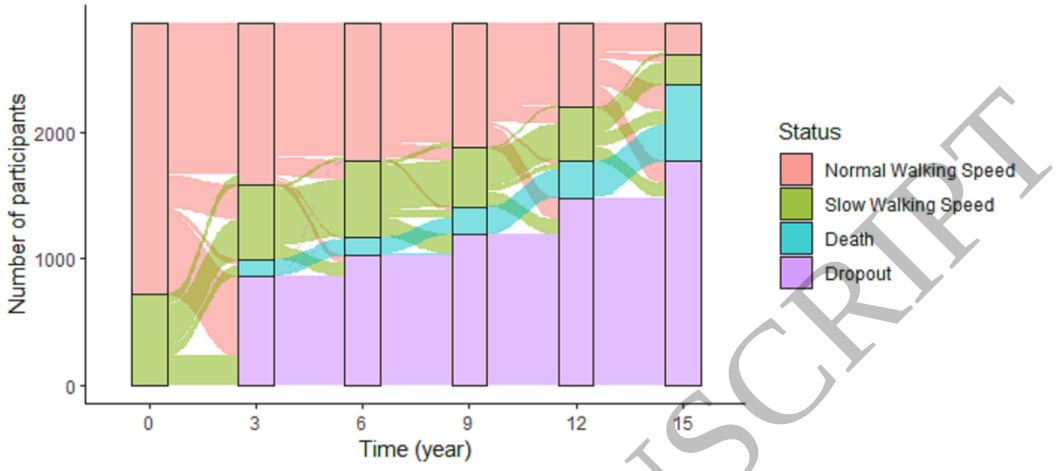
	Intercept β (95%CI)	Annual WS Change (95%CI)
Crude model		
No AF (ref.)	-	-
AF no OAT	-0.310 (-0.366; -0.255)	-0.008 (-0.015, -0.002)
AF with OAT	-0.186 (-0.262; -0.110)	-0.014 (-0.023, -0.005)
Model 1		
No AF (ref.)	-	-
AF no OAT	-0.143 (-0.195, -0.091)	-0.008 (-0.015; -0.002)
AF with OAT	-0.030 (-0.110; 0.049)	-0.015 (-0.024, 0.006)
Model 2		
No AF (ref.)	-	-
AF no OAT	-0.040 (-0.090; 0.008)	-0.010 (-0.016; -0.004)
AF with OAT	0.015 (-0.063, 0.094)	-0.014 (-0.022; -0.004)

Model 1: age + education + sex

Model 2: age + education + sex + hypertension + COPD + HF + stroke + dementia + BMI + diabetes + physical activity + alcohol consumption

Abbreviations: AF: atrial fibrillation, BMI: body mass index, COPD: Chronic Obstructive Pulmonary Disease, CKD: Chronic Kidney Disease, HF: heart failure, OAT: oral anticoagulant therapy, WS: Walking Speed.

a)



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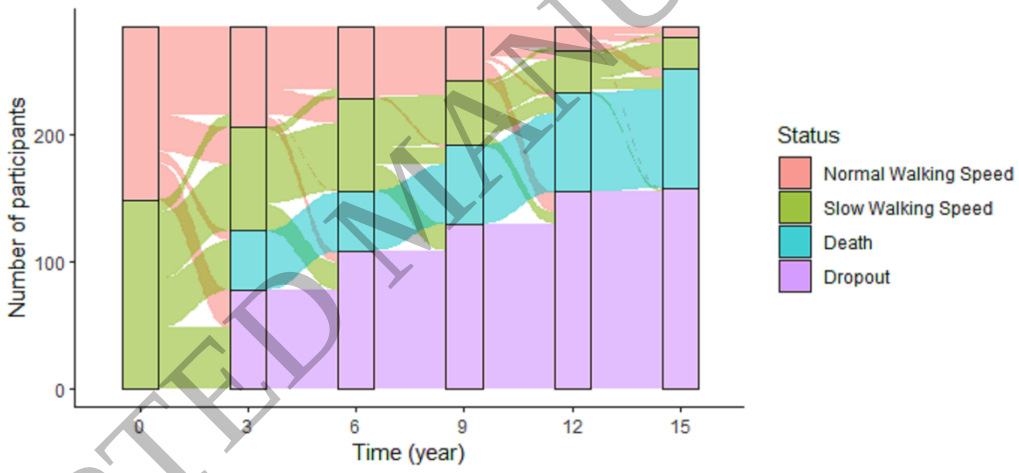

Figure 1
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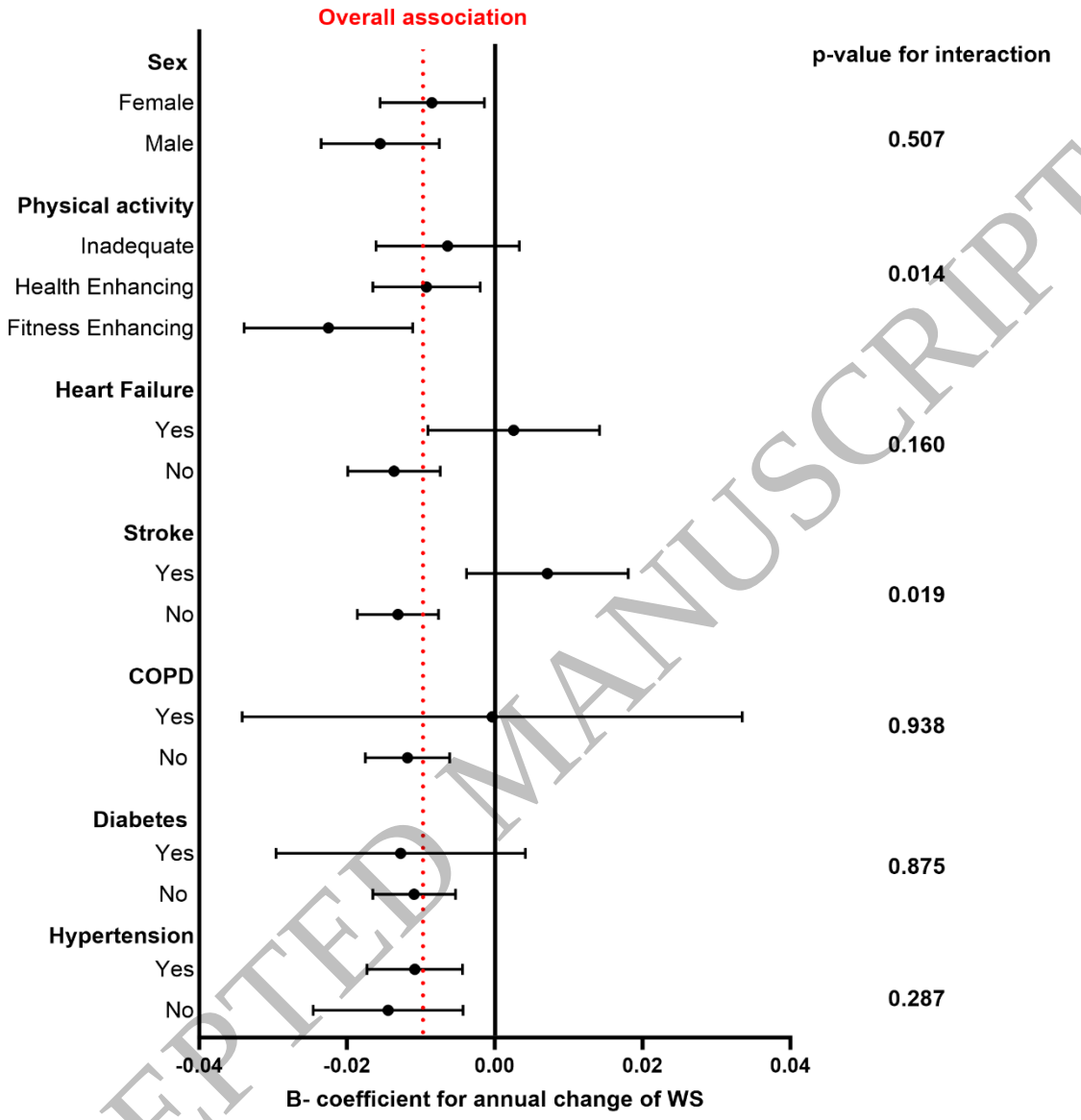

Figure 2
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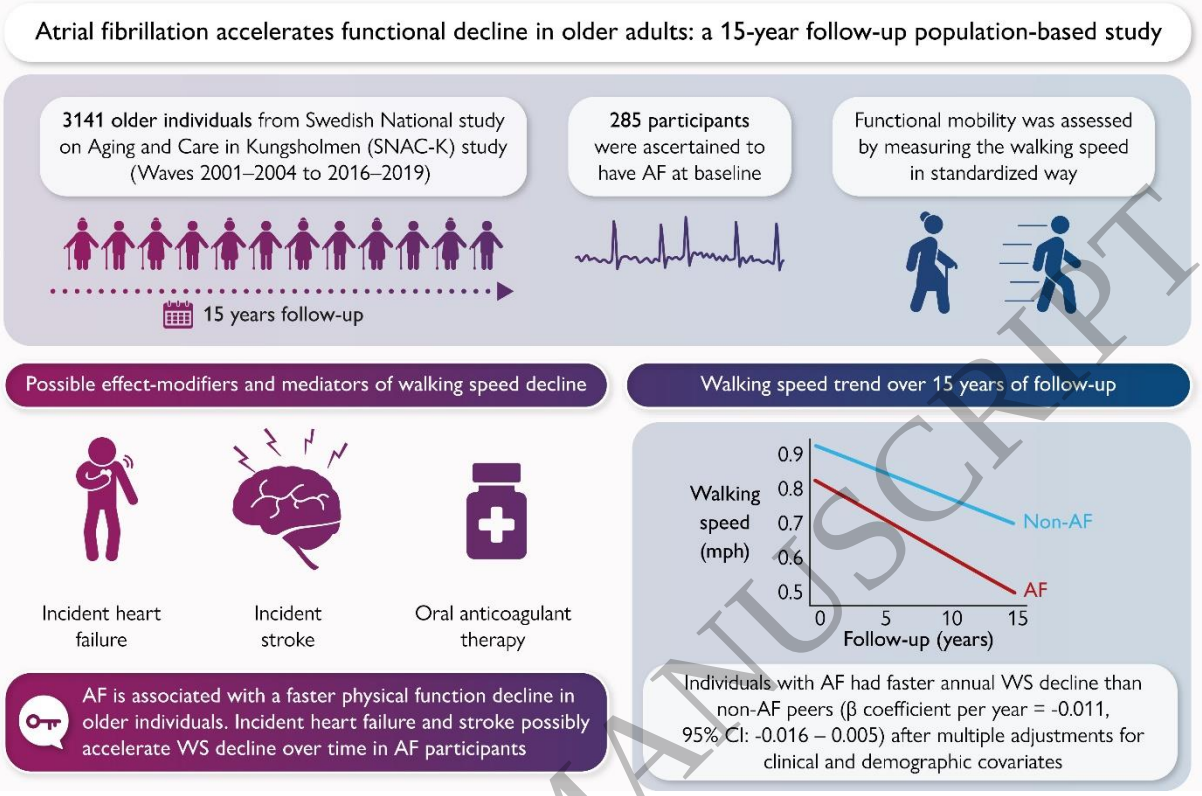

Graphical Abstract
159x105 mm (DPI)