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Original Research

Midlife physical activity trajectories are associated with reduced physical pre-frailty/frailty in older age: insights from the prospective ATTICA sub-study 2002-2024

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ABSTRACT

Background: Although physical activity in older adults has been associated with lower risk of frailty, it is unclear if midlife physical activity patterns are associated with pre-frailty/frailty status in older age.
Objectives: To investigate whether longitudinal midlife physical activity trajectories are associated with physical pre-frailty/frailty development in older age, independent of cardiometabolic risk and other lifestyle factors.
Design: Population-based prospective cohort study.
Settings: In-person assessments and telephone interviews of persons living in urban communities in Attica, Greece.
Participants: Surviving participants of the ATTICA cohort study (2002-2024) who were older than 33 years at baseline.
Measurements: Demographic, anthropometric, clinical, and lifestyle parameters were recorded at baseline and throughout the study. According to binary self-reported physical activity levels (<600 vs ≥600 metabolic equivalent minutes per week) at baseline, 5-year and 10-year follow-up, 4 ordered trajectories of physical activity were defined: persistently inactive, declining activity, inclining activity, and persistently active, and their association with the odds of pre-frailty/frailty development according to the phenotypic (FRAIL scale) model were investigated by applying multivariable logistic regression models.
Results: Relative to persistent inactivity, persistently active and inclining physical activity lifestyles were associated with 80% and 79% decreased odds of pre-frailty/frailty at 22-year follow-up, respectively, after adjusting for age, sex, years of education, baseline body mass index, hypertension, diabetes, and hypercholesterolemia. The population fraction of pre-frailtand frailty that could be attributed to unhealthy physical activity trajectories throughout midlife is 49.5% (95% confidence interval, 36.3 to 59.9), rising to 64.8% (95% confidence interval, 49.6 to 75.4) when also considering hypertension, diabetes mellitus, hypercholesterolemia, and obesity.
Conclusion: Steadily high or rising physical activity trajectories during midlife were associated with lower odds of physical pre-frailty/frailty in older age, independently of cardiometabolic risk factors. These findings support that achieving and maintaining higher physical activity levels across midlife may be one of the keys to healthy aging.

1. Introduction

Frailty is a complex syndrome of increased vulnerability to minor stressors, usually presenting in later life [1]. It is characterized by a progressive decline of multiple physiological systems which cannot be attributed solely to the effects of organ-specific diseases, and it can be

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conceptualized either as a phenotype of low physical function and multimorbidity [2,3], or as an accumulation of age-related deficits [4]; both approaches classify individuals as robust, pre-frail, or frail, based on validated cut-offs. The prevalence of pre-frailty and frailty in the community varies by age group, assessment instrument, and setting, ranging 3-15% for frail and 30-68% for prefrail persons among middle-aged adults (40-65 years) vs 4-30% for frail and 30-56% for prefrail persons among older adults (65+years) [5–8]. Depending on each person's individual traits and exposures, frailty may affect any or all three main aspects of health (physical, social and psychological), leading to disability, institutionalization, and mortality, and ultimately representing the opposite of healthy aging [9].

Frailty poses a significant challenge to healthcare and social support systems in aging societies, and there is a pressing need to implement effective preventive strategies on a population level [10]. The 2020 World Health Organization (WHO) plan of action for healthy aging stresses the need for policies to identify and reverse or delay the progression of frailty in older people [11]. Research consistently highlights that physical activity, particularly multicomponent programs incorporating resistance, aerobic, balance and flexibility training or mixed interventions, improves physical function and cognitive performance in frail and pre-frail individuals [12–14]. Furthermore, a breadth of high-quality evidence documents that physical activity programs for adults older than 65 years can prevent a multitude of age-related health problems, including falls, depression, sarcopenia, and cardiovascular diseases [15–18]. Recent longitudinal evidence has extended the investigation of physical activity across the adult life course to other geriatric syndromes, showing that higher levels of physical activity in midlife and later life are associated with a reduced risk of all-cause and Alzheimer's disease dementia [19]. However, evidence on the long-term association between physical activity at earlier ages and frailty in later life is insufficient, despite the fact that phenotypical manifestations of frailty in older age are likely preceded by a long period of biological damage accumulation throughout life [20]. Therefore, maintaining adequate physical activity from midlife may be particularly relevant for preserving physiological reserve before age-related deficits accumulate and frailty becomes clinically apparent, potentially by attenuating biological processes involved in frailty development [21].

A recent systematic review of interventions targeting pre-frailty and frailty in middle-aged adults (40–65 years) found that multicomponent exercise and resistance training showed promising effects in preventing or reversing pre-frailty and frailty, although the certainty of the evidence was limited [22]. Another meta-analysis of 10 cohort studies found evidence that high levels of physical activity as recommended by the WHO [23] were associated with a lower incidence of frailty [24]. However, in 8 of these studies, physical activity was only assessed at baseline [25–32]; of the other two that assessed it longitudinally [33, 34], only one included participants younger than 50 years, and all were Caucasian men of high socio-economic status [33]. Limited evidence on the association between long-term physical activity trajectories and frailty risk from population-based longitudinal cohorts is only now beginning to accumulate, usually involving follow-up periods shorter than 10 years [34–36] and cohorts older than 50 years at baseline [34–39].

The objective of this study was to investigate the relationship between physical activity trajectories of middle-aged adults and pre-frailty/frailty at the 22-year follow-up, while adjusting for potential confounders. We hypothesized that different longitudinal physical activity trajectories during midlife would be associated with different odds of pre-frailty/frailty in older age.

2. Methods

2.1. Study sample

This study was performed on a subset of the ATTICA cohort, a prospective population-based cohort study on a representative sample of the general population residing in the province of Attica, the greater area of Athens, Greece. Participants were recruited through a stratified random sampling procedure designed to represent the adult population of the region with respect to the age-gender-area distribution provided by the National Statistical Service according to the 2001 Census, and the mean participant age at enrollment was 45 years. The study's conceptual focus was to examine the role of sociodemographic, psychological, lifestyle, clinical, and biological factors in the development of cardiometabolic diseases. At enrolment, individuals with cardiovascular diseases (excluding essential hypertension), cancer, chronic inflammatory diseases, and any disorder precluding regular physical activity and function, as established in the initial medical visit in 2001-2002 (wave 1), were not eligible. Additional information regarding the cohort design and recruitment procedures has been reported previously [18,40]. Participants have been re-assessed at the 5-year (wave 2), 10-year (wave 3) and 20-year (wave 4), allowing longitudinal assessment of lifestyle behaviors, clinical characteristics, and cardiometabolic health using standardized protocols.

To assess pre-frailty and frailty, we invited the subset of participants that were older than 55 years in 2024 to an additional medical interview by a geriatrician and a physiotherapist specializing in frailty assessment. The flow of participants throughout the ATTICA waves to this subcohort has been described in detail in previous publications [41]. Briefly, among 2444 eligible participants ≥33 years old at baseline, we reached out to 1416 persons with complete data at the 20-year follow-up (2022). Of those, 24 had died between 2022 and 2024, and 818 were unreachable or withdrew consent, resulting in 574 persons (48±8 years at baseline; 50% male) with complete physical activity data from baseline (wave 1), 5-year (wave 2) and 10-year (wave 3) follow up assessments, and frailty assessment at 22-year follow-up. Baseline characteristics of participants included in the analysis were compared with those of the remainder of the baseline cohort (non-participants) to assess potential differences between groups.

2.2. Bioethics

The ATTICA study adheres to the ethical standards of the Declaration of Helsinki and has received approval from the Ethics Committee of the First Cardiology Department of the National and Kapodistrian University of Athens (#017/01.05.2001) and the Ethics Committee of the Harokopio University (#38/29.03.2022). Additional approval was obtained for the 2024 follow-up from the Ethics Committee of Laikon University Hospital (#182/02.09.2024). All participants were informed about the study's goals and procedures, and they gave their written consent to participate.

2.3. Measurements

Participant characteristics were assessed using a standardized protocol that combined interviewer-administered questionnaires, clinical examinations, anthropometric assessments, and laboratory analyses. Information was collected on sociodemographic characteristics, lifestyle behaviours, dietary habits, cardiometabolic health, biochemical markers, and psychological status. The measurements relevant to the objectives of the present study are described below:

2.3.1. Sociodemographic characteristics

We recorded age in years, biological sex as a binary variable, family status as a 4-level categorical variable (single, married, divorced, widowed), and time attending formal education in years.

2.3.2. Anthropometric and clinical measurements

We recorded longitudinal measurements of participants' body mass index (BMI), calculated as weight/height^2. Participants were classified as obese when BMI ≥30 kg/m^2, and as overweight when 25 kg/m^2 ≤

BMI <30 kg/m^2. Hypertension was defined as systolic/diastolic blood pressure (SBP) ≥140/90 mmHg or use of antihypertensive medication; hypercholesterolemia was defined as total cholesterol ≥200 mg/dL or use of lipid-lowering medication;and type 2 diabetes was defined as fasting blood glucose ≥126 mg/dL or use of antidiabetic agents. Detailed information about the anthropometric and clinical measurements in the ATTICA cohort are available elsewhere [40].

2.3.3. Dietary and smoking patterns

We used the MedDietScore questionnaire (range 0-55 points) to quantify participants' levels of adherence to the Mediterranean-style eating pattern at each follow-up interval, thus defining two groups: the low adherence group (i.e., MeDietScore ≤27) and the medium/high adherence (i.e., MedDiet-Score >27) [42]. This categorization was specifically applied to enable the construction of longitudinal adherence trajectories across repeated assessments of modifiable metabolic risk factors. Smoking was entered as a 3-level categorical variable: current smokers (≥1 cigarette/day, including those who had quit smoking <1 year before the assessment), former smokers (quit smoking ≥1 year) and never smokers.

2.3.4. Physical activity status evaluation

To capture physical activity levels at each follow-up interval, we used the Greek adaptation of the International Physical Activity Questionnaire- Short Form (IPAQ-SF; see Additional File 1) [43], which has been specifically designed as a tool for cross-national assessment of physical activity in adults and has demonstrated good reliability and acceptable validity properties both in developed and in developing countries [44]. The IPAQ-SF captures the self-reported frequency and duration of walking and of moderate- and vigorous- intensity physical activities performed during the previous 7 days. Physical activity intensity was characterized as light (e.g., slow walking, stationary cycling, or light stretching), moderate (e.g., brisk walking, outdoor cycling, or swimming at moderate effort), or vigorous (e.g., brisk uphill walking, long-distance running, fast or racing cycling, or fast swimming) All participants were additionally asked about the average daily number of stairs climbed and the number of city blocks walked during the week. According to the standardized IPAQ scoring protocol, responses were converted into weekly energy expenditure (MET-min/week) by multiplying the duration and frequency of walking, moderate-, and vigorous-intensity activities by 3.3, 4.0, and 8.0 METs, respectively, and summing these values to obtain the total MET-min/week score. Participants were subsequently classified into low, moderate, and high physical activity profiles according to the IPAQ scoring criteria. For the purposes of the present longitudinal trajectory analyses, participants were further dichotomized as physically inactive (<600 MET-min/week), corresponding to the low physical activity profile or physically active (≥600 MET-min/week), encompassing the moderate and high physical activity profiles, as an attempt to translate multiple measurements of a 4-level exposure into trajectories would result in an overwhelmingly complex analysis. The 600 MET-min/week threshold was selected as the minimum recommended level of physical activity, allowing us to examine longitudinal adherence to a clinically and public-health relevant activity target, in accordance with the IPAQ scoring protocol and the 600 MET-min/week WHO physical activity recommendations. [23,45].

2.3.5. Trajectories of lifestyle parameters

To examine longitudinal lifestyle trajectories through midlife, rather than snapshot baseline patterns, we created a 4-level categorical trajectory variable for each of the lifestyle parameters (physical activity, adherence to the Mediterranean diet, and cigarette smoking), according to whether lifestyle choices were healthy or unhealthy at each of the 3 follow-up intervals between 2002 and 2012 (wave 1 to wave 3): (i) healthy pattern at all follow-up intervals, (ii) unhealthy pattern in wave 1 progressing to a healthy pattern in waves 2 and/or 3, (iii) healthy pattern in waves 1 or 2 declining to an unhealthy pattern in wave 3, and (iv) unhealthy pattern at all waves, as summarized in *Table 2*. Specifically, physical activity trajectories were classified into four predefined categories that emerged from the collected longitudinal data and were used in the analysis: persistently inactive, declining PA (from active to inactive), inclining PA (from inactive to active), and persistently active. Because only nine of participants exhibited fluctuating patterns (active–inactive–active or inactive–active–inactive), these individuals were classified according to their predominant long-term activity pattern (persistently active or persistently inactive), reflecting temporary rather than sustained changes in physical activity. To avoid reverse causation, i.e. frailty development near the end of follow-up precluding physical activity in wave 4 (2022), lifestyle patterns observed during wave 4 were not included in the defined trajectories of the main analysis. However, due to the possibility of substantial uncaptured changes in physical activity during this 10-year temporal lag, we also performed a sensitivity analysis using 20-year physical activity trajectories (see *Statistical Analysis* below).

In exploratory analyses, similar longitudinal trajectories were developed for smoking habits and adherence to the Mediterranean diet to examine whether the observed associations extended to other major modifiable lifestyle factors. For the trajectories of smoking habits, groups (ii) and (iii) were merged into one group that defined those who smoked for some period of follow-up.

2.3.6. Frailty and pre-frailty assessment

Frailty and pre-frailty were assessed using the FRAIL (Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight) scale, a simple 5-point self-report instrument based on the Fried phenotype and incorporating multimorbidity, which has been validated for frailty screening and prediction of disability, functional decline, and mortality [3,46]. The scale consists of five domains, each scored dichotomously (0 or 1 point), yielding a total score ranging from 0 to 5, with higher scores indicating greater frailty. Fatigue was evaluated according to the frequency of tiredness experienced during the previous four weeks and was scored positively when participants reported feeling tired all or most of the time. Resistance and ambulation were assessed based on self-reported difficulty climbing 10 stairs and walking several hundred yards without assistance, respectively. One point was assigned for the illnesses component when participants reported at least five of the predefined chronic conditions, whereas the weight-loss component was scored positively when an unintentional body weight reduction of 5% or more had occurred during the preceding year. Based on the total FRAIL score, participants were classified as robust (0 points), pre-frail (1–2 points), or frail (3–5 points). Detailed scoring criteria for each FRAIL component are provided in Additional File 2. A Greek translation and validation of the FRAIL scale has been undertaken by our group in a different community-based cohort from the same region (unpublished data).

2.4. Statistical analysis

Continuous variables were evaluated for normality using P-P plots and are presented as mean values with standard deviations for the normally distributed and as median values with interquartile ranges (IQR) for the non-normally distributed. Categorical variables are expressed as frequencies. The chi-squared test was used to examine the associations between categorical variables. The one-way analysis of variance (ANOVA) was used to compare the mean values of normally distributed variables. For non-normally distributed continuous variables, median values were compared using the non-parametric K-sample test on the equality of medians with continuity correction. The primary endpoint, the 22-year cumulative incidence of prefrail/frail cases, was calculated as the ratio of incident cases to the total number of participants at follow-up. Due to the limited number of frail cases, the prefrail and frail cases were summed. As the exact time of onset of pre-frailty/

frailty during follow-up was not available, time-to-event analysis using Cox proportional hazards regression could not be appropriately performed. Therefore, multivariable logistic regression was used to evaluate the association between physical activity trajectories and pre-frailty/frailty status at the 22-year follow-up. To assess if a persistently physical active lifestyle decreases the odds of prefrailty/frailty in older age beyond potential confounding effects, we fitted multivariable logistic regression models using prefrailty/frailty as the outcome variable, physical activity trajectories as an independent 4-level categorical variable, adjusted for age (continuous), sex, baseline BMI (continuous), baseline formal education years (continuous), baseline hypertension (binary), baseline hypercholesterolemia (binary), and baseline diabetes mellitus (binary). Covariates were selected based on preliminary univariate logistic regression models evaluated against the prefrailty/frailty outcome. Variables that demonstrated statistical significance ($p < 0.05$) in these univariate models were included in the final multivariable model (specifically: age [$p < 0.001$], sex [$p = 0.003$], education [$p = 0.001$], BMI [$p < 0.001$], hypertension [$p < 0.001$], diabetes [$p = 0.016$], and hypercholesterolemia [$p = 0.014$]). Smoking and MedDietScore were not included as covariates because their univariate associations with pre-frailty/ frailty were not statistically significant ($p > 0.05$), while Smoking and Mediterranean diet trajectories were excluded to avoid potential overadjustment, as these lifestyle factors may lie on the casual pathway between physical activity and frailty development. Post-baseline measurements of BMI, hypertension, hypercholesterolemia, and diabetes were not included as covariates, as these factors may lie on the causal pathway between physical activity and frailty. Additionally, weight loss is part of the frailty phenotype, and inclusion of follow-up BMI could therefore overlap with the outcome measure. As a sensitivity analysis, the multivariable logistic regression analysis was repeated using physical activity trajectories based on the 20-year follow-up assessment (wave 4), in which we defined seven trajectories: never active, early decliners, very late incliners, fluctuating PA patterns, late incliners, early incliners, and persistently active participants.

Inverse probability of censoring weighting (IPCW) was used to account for potential non-response bias. First, we employed logistic regression to estimate the probability of response (propensity score) for each participant given their baseline characteristics (i.e., age, sex, physical activity, education, smoking, BMI, obesity, hypertension, systolic blood pressure, diastolic blood pressure, diabetes, hypercholesterolemia, total cholesterol levels). Weights were calculated as the inverse of the propensity score and integrated into the fully adjusted logistic regression outcome model to derive adjusted effect estimates. Robust variance estimates were used to calculate confidence intervals.

Population Attributable fractions (PAF) were calculated to estimate the proportion of prefrailty/frailty cases theoretically attributable to unhealthy physical activity trajectories. PAF estimates were derived from multivariable models adjusted for age, sex, obesity, hypertension, diabetes, hypercholesterolemia, and educational status, using the punaf package in Stata [47,48].

All analyses were carried out using STATA 18 [49], and statistical significance was set at a two-sided p-value of < 0.05.

3. Results

3.1. Baseline characteristics and frailty status at the 22-year follow-up

Baseline descriptive characteristics of participants by frailty status at the follow-up are presented in Table 1. Briefly, 50% of participants were male, and the cohort's age range was 32-73 at wave 1 (baseline), 37-78 at wave 2 and 42-83 at wave 3.

At 22 years of follow-up, of the 574 participants, 6% were found to be frail (n = 34), 29% prefrail (n = 165), and 65% robust (n = 375), using the FRAIL scale. No clinically meaningful differences in baseline characteristics were observed between participants included in the analysis and the remainder of the baseline cohort (non-participants) [41]. Compared to pre-frail and frail individuals, participants classified as robust were predominantly male (55% vs 41%–44% across pre-frail and frail groups, $p = 0.010$), younger (mean age 47 years vs 49–56 years across pre-frail and frail groups, $p < 0.001$), with lower BMI (mean BMI 26.0 vs 27.4–27.6 across pre-frail and frail groups, $p < 0.001$), and lower prevalence of diabetes (4% vs 7%–18%, p=0.003), hypertension (29% vs 45%–50%, p<0.001), and hypercholesterolemia (44% vs 54%–59%, $p = 0.043$) at the baseline visit. Furthermore, a higher proportion of these individuals had completed more than twelve years of formal education.

Table 1
Baseline demographic, clinical and lifestyle characteristics of participants and their associations with frailty status at the 22-year follow-up, as classified by the FRAIL scale.

Baseline characteristics	Overall (n=574)	Robust (n=375)	Pre-frail (n=165)	Frail (n=34)	p-value
Age at baseline, mean ± SD	48 ± 8	47 ± 7	49 ± 9	56 ± 9	<0.001
Male sex, %	50	55	41	44	0.010
Age Categories					<0.001
≤40 y (%)	19	21	18	9	
41-50 y (%)	47	52	41	15	
51-60 y (%)	26	23	29	47	
>60 y (%)	8	4	12	29	
Marital status					0.822
Married, %	83	82	84	91	
Divorced, %	4	5	3	3	
Single, %	11	11	11	6	
Widowed, %	2	2	2	-	
Education ≥12 years, %	81	84	77	69	0.028
Smoking (ever), %	56	58	51	50	0.236
BMI (kg/m^2), mean ± SD	26.5 ± 4.4	26.0 ± 4.0	27.6 ± 4.9	27.4 ± 5.0	<0.001
High adherence to the Mediterranean diet, %	32	34	31	21	0.241
Physical activity level (sedentary), %	60	59	65	56	0.346
Hypertension, %	35	29	45	50	<0.001
Diabetes, %	6	4	7	18	0.003
Hypercholesterolemia, %	48	44	54	59	0.043

Continuous variables are presented as mean values (± standard deviation) for normally distributed variablesand as medians (inter-quartile-range, IQR) for non-normally distributed variables, while categorical are presented as relative frequencies (percentages). P-values referring to differences between the groups werederived using chi-square test for the categorical variables, one-way ANOVA for the normally distributed continuous variables and nonparametric K-sample test on the equality of medians with continuity correction for the rest.

3.2. Trajectories of lifestyle parameters

Among the 574 participants, 237 (41%) had persistently low levels of physical activity throughout waves 1-3 and an additional 68 (12%) decreased from a previously higher level of activity, while 106 (19%) maintained moderate or high physical activity throughout waves 1-3 and an additional 163 (28%) had increasing levels of physical activity (*Table 2*).

3.3. Physical activity trajectories and prefrailty/frailty risk after 22 years

Prefrailty or frailty was found in 199 persons, of whom 78% were persistently inactive or had declining physical activity (Fig. 1). As shown in *Table 3*, both persistent and inclining physical activity were associated with an 80% and 79% respective decrease in the odds of developing prefrailty/frailty as classified by the FRAIL scale during 22-year follow-up, compared withpersistent inactivity, after adjusting for age, sex, years of education, as well as baseline BMI, hypertension, diabetes, and hypercholesterolemia. Upon multivariable adjustment (i.e., age, sex, years of education, as well as baseline BMI, hypertension, diabetes, and hypercholesterolemia), the association between baseline physical activity levels and long-term frailty development did not reach statistical significance (OR: 0.741, 95%CI: 0.496-1.107, p=0.143).

In the sensitivity analysis including the physical activity assessment at the 20-year follow-up, seven PA trajectories were identified. The persistently active and the three inclining trajectories were associated with significantly lower odds of pre-frailty/ frailty compared with the persistently inactive trajectory, whereas the fluctuating and declining trajectories were not significantly associated with pre-frailty/frailty (Additional File 3).

Using IPCW to re-evaluate estimates accounting for non-response bias based on baseline clinical and demographic characteristics, the results were consistent with the primary analysis (OR for declining activity: 1.54, 95% CI: 0.76-3.12, $p = 0.229$; OR for inclining activity: 0.20, 95%CI: 0.11-0.35, $p < 0.001$; OR for persistently active: 0.24, 95%CI: 0.13-0.45, $p < 0.001$).

Table 2
Distribution of lifestyle trajectories according to pre-frailty and frailty status at the 22-year follow-up, as classified by the FRAIL scale.

Lifestyle trajectories	Overall	Frailty status at 22-year follow-up			p-value
		Robust	Pre-frail	Frail	
Smoking habits (2002-2012)*					0.315
No smoking throughout follow-up, %	55	53	60	64	
Smoking for some of the follow-up time (smokers who then quit or non-smokers who at some point started), %	16	16	13	18	
Persistent smoking throughout the entire follow-up, %	29	31	27	18	
Adherence to Med Diet (2002-2012)					0.561
Never adherent, %	23	24	23	21	
Declining adherence, %	50	50	50	44	
Inclining adherence, %	11	9	12	20	
Always adherent, %	16	17	15	15	
Physical Activity (2002-2012)					<0.001
Persistently inactive, %	41	32	57	65	
Declining activity, %	12	8	18	26	
Inclining activity, %	28	37	14	9	
Persistently active, %	19	23	11	-**	

Categorical variables are presented as relative frequencies (percentages). P-values referring to differences between the groups, derived using chi-square test.
* Former smokers were defined as participants who had quit smoking ≥1 year before assessment; participants who had quit within the previous year were classified as current smokers.
** No participants belonged to this category.

3.4. Population-attributable fractions (PAF)

The PAF of 22-year prefrailty/frailty status attributable to unhealthy physical activity trajectories (i.e., never active and declining activity) throughout follow-up was 49.5% (95% CI, 36.3 to 59.9). Collectively, for other modifiable risk factors (e.g. hypertension, diabetes mellitus, hypercholesterolemia, obesity), PAF was 20.8% (95% CI, 6.3 to 33.1). However, when considering both unhealthy physical activity trajectories and other modifiable risk factors, the PAF reached 64.8% (95% CI, 49.6 to 75.4).

4. Discussion

In this longitudinal study of a representative sample of community-dwelling middle-aged adults in the greater area of Athens, Greece, we found that the odds of physical pre-frailty/frailty at the 22-year follow-up were approximately 80% lower among individuals who either maintained or increased physical activity to a level of at least 600 MET-minutes/week during follow-up. Importantly, these associations remained robust after adjustment for major confounders, such as age, sex, BMI, educational level, and the presence of hypertension or diabetes at baseline; in fact, the observed association of longitudinally low physical activity on pre-frailty and frailty was greater than the collective impact of other cardiometabolic risk factors known to be associated with frailty risk. By contrast, our data did not reveal a significant association between baseline physical activity levels and long-term development of frailty, highlighting the importance of sustained lifestyle choices throughout midlife, rather than “snapshot” achievements, on clinically meaningful outcomes in older age.

Data analysis revealed that nearly 50% of prefrail/frail events over the 22-year period were attributable to unhealthy physical activity trajectories. Unhealthy physical activity trajectories along with traditional modifiable risk factors explained nearly 65% of cases, elucidating an additional 55% of previously unexplained 22-year prefrailty/frailty risk. Although the interpretation of attributable risk is contingent upon the assumption of a causal relationship between exposure and the outcome, which cannot be inferred given the observational nature of this study, our data supports the hypothesis that adequate physical activity levels earlier in the life course may be highly impactful for frailty risk reduction.

In order to minimize the possibility of reverse causation which is inherent to observational studies of the relationship between physical activity and frailty, whereby preclinical frailty may lead to lower activity levels instead of the reverse, we introduced a 12-year lag period between the final assessment of physical activity and the evaluation of frailty. At the same time, this lag introduces a potential disconnection between remote PA trajectories and frailty development, which we minimized through confirmation of our findings with the sensitivity analysis including 20-year PA trajectories. This 12-year interval also limits our ability to account for changes in physical activity occurring between the final physical activity assessment and frailty evaluation.

The impact of physical activity on frailty development has been previously examined in longitudinal cohort studies across Europe, Asia, and the United States. Earlier studies primarily relied on single baseline assessments of physical activity [25–32] or relatively short follow-up periods (≤5 years) [34,36], whereas more recent longitudinal studies incorporate repeated assessments of physical activity or trajectory-based approaches, and have extended follow-up periods ranging from 16 to 24 years [35,37–39], similar to our methodology. Among those, Lin et al. [39],Fung et al [38]., and Wang et al [35] also examined physical activity trajectories over 20-year periods and found a protective effect of persistent and inclining physical activity on future frailty development, but contrary to our study focused on an older population with a mean age of 66, 60, and 58 years, respectively. Jung et al. assessed physical

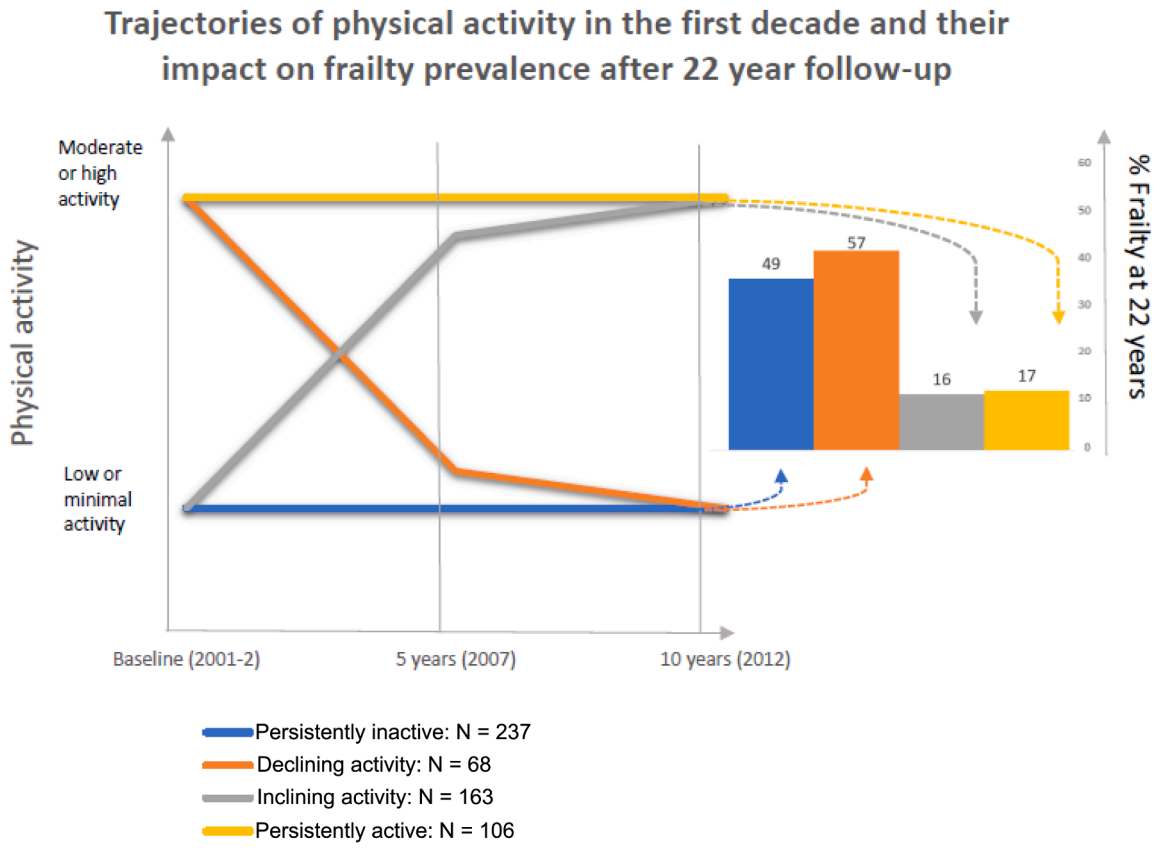


Fig. 1. Physical activity trajectories of participants at baseline, 5 years, and 10 years of follow-up, and the relevant prevalence of frailty or prefrailty at 22 years for each of the following trajectory groups: persistently inactive (blue, low or minimal activity at baseline, 5 years, and 10 years), declining activity (orange, moderate/high activity at baseline but low/minimal activity at 5 and 10 years), inclining activity (grey, low/minimal activity at baseline and moderate/high activity at 5 and 10 years), and persistently active (yellow, moderate/high activity at baseline, 5 years, and 10 years). 9 of participants exhibited transient fluctuating physical activity patterns between assessments and were classified according to their predominant long-term activity pattern (persistently active or persistently inactive).

Table 3
Results from multi-adjusted logistic regression model (Odds Ratio and 95% Confidence Intervals) for the association between exercise trajectories and pre-frailty/frailty status at 22-year follow-up, based on FRAIL scale score.

Variable	Odds ratio	95% Confidence Interval	p-value
	Pre-frailty/frailty (Frail score ≥ 1)		
Physical activity trajectory			
Persistently inactive	Reference		
Declining activity	1.28	0.69-2.38	0.432
Inclining activity	0.21	0.12-0.36	<0.001
Persistently active	0.20	0.11-0.37	<0.001

Odds Ratios (95% confidence interval) were estimated using logistic regression models with adjustment for age (continuous), sex, baseline BMI (continuous), baseline formal education years (continuous), baseline hypertension (binary), baseline hypercholesterolemia (binary), and baseline diabetes mellitus (binary).

activity as a binary response to the question "do you exercise at least once a week", rather than through a validated questionnaire such as the IPAQ, and included the self-reported physical activity at the end of follow-up in the exposure trajectory, raising concerns of reverse causation [37].

The present study contributes to the above literature in several important ways. We found that persistently active and increasing physical activity trajectories are associated with significantly lower odds of pre-frailty/frailty in a population approximately a decade younger than examined in previous trajectory-based studies. This addresses the limited evidence on long-term physical activity trajectories in populations younger than 60 years at baseline [35] and allows the investigation of physical activity patterns earlier in the life course, when reverse causation and underlying subclinical frailty are less likely to influence lifestyle choices. Additionally, the inclusion of population attributable fraction analyses complemented the individual-level associations by providing an estimate of the potential public health relevance of maintaining healthy physical activity across midlife.

Considering that the pathological processes associated with frailty may initiate several decades before its onset [20], preventive strategies at the public health level should prioritize younger, healthier populations, rather than those at close temporal proximity or already in the process of frailty development. While the molecular mechanisms of frailty remain elusive, accumulating evidence links frailty to chronic inflammation [20,50], oxidative stress [51], and DNA damage [52]. These biological pathways provide a plausible explanation for our findings, suggesting that maintaining healthy PA throughout midlife may help delay the biological processes that contribute to frailty later in life. This interpretation is further supported by evidence showing that persistent PA represents a lifestyle pattern shown to decrease levels of inflammatory markers of middle-aged adults on long-term follow-up [21,53,54].

One of our study's major strengths is a representative sample of the regional population, supporting generalizability of our results to similar Mediterranean urban populations. Other strengths include long-term follow-up spanning over two decades, and longitudinal assessment of physical activity allowing to investigate the impact of lifestyle trajectories, while controlling for other significant confounders. The main limitation of our study is the absence of formal frailty status assessment at baseline, which precludes calculations of incident frailty and clinically meaningful outcome differences in this cohort. However, participants were apparently healthy without conditions precluding physical

activity at baseline, minimizing the possibility of pre-existing frailty or pre-frailty. Furthermore, physical activity trajectories were predefined using clinically meaningful categories following the 600 MET-min/week threshold established in the WHO physical activity recommendations [23], rather than derived using data-driven trajectory modelling; this approach minimizes the effect of cohort-related biases on our conclusions, but it may have limited the identification of more complex longitudinal patterns and more efficient cut-offs of physical activity for the prevention of frailty. Moreover, frail and pre-frail cases were combined to preserve statistical power, as only 6% of participants were classified as frail, with 29% classified as pre-frail at follow-up. Consequently, our findings predominantly represent pre-frail individuals and should be generalized to frailty prevention with caution. Furthermore, this grouping precluded the investigation of whether physical activity trajectories were differently associated with the transition from robust to pre-frail status and from pre-frail to frail status.

Another potential limitation of this study is the possibility of reverse causation, which cannot be entirely ruled out in observational analyses of physical activity and frailty. Individuals exhibiting early manifestations of frailty may already experience declining mobility, leading to reduced engagement in physical activity and, consequently, an accelerated trajectory towards frailty. Additional limitations include a relatively small sample, owing to the long-term follow-up and resultant loss to follow-up, as well as a high number of participants refusing to participate to the additional interviewing of frailty assessment. Although selection bias has been addressed through reassuring results of baseline comparisons between participants and non-participants, as well as IPCW analysis, healthy volunteer bias cannot be completely ruled out. Furthermore, our results relied on self-reported measurements of frailty, which introduce subjectivity in functional status assessment. In order to mitigate this limitation, an individual assessment of functional deficits was performed on a case-by-case basis via a personalized interview by an experienced geriatric physical therapist, thus minimizing inaccuracies in reporting and avoiding shortcomings of electronic record-based approaches. However, social desirability bias, recall bias, and subjectivity in self-reported outcomes cannot be entirely ruled out. Finally, although we accounted for several important confounders associated with frailty, our study did not include data on sleep duration and sleep quality, and therefore could not investigate their interplay in the association between physical activity and development of frailty.

5. Conclusion

Long-term physical activity throughout middle age was strongly associated with maintaining robustness and functional independence in older age, with protective associations that potentially exceed those of other cardiometabolic factors. These findings support the need for public health strategies promoting physical activity in younger populations and strengthen the basis for counseling adults in primary care on the multifaceted benefits a physically active lifestyle. Future research should focus on revealing barriers to healthful lifestyle modification for middle-aged adults and investigate the optimal timing, frequency, duration, and type of midlife physical activity recommendations for prevention of physical frailty in older age. Such targeted physical activity interventions may help reduce the burden of frailty in ageing societies, representing a feasible and potentially cost-effective strategy.

Abbreviations

ATTICA – Attica Epidemiological Study
BMI – Body Mass Index
DM – Diabetes Mellitus
DNA – Deoxyribonucleic Acid
ELSA – English Longitudinal Study of Aging
FRAIL – Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight scale
IPAQ – International Physical Activity Questionnaire
MET – Metabolic Equivalent of Task
PA – Physical Activity
SBP – Systolic Blood Pressure
STATA – Stata Statistical Software
TLSA – Taiwan Longitudinal Study of Aging
UK – United Kingdom
UN – United Nations
USA – United States of America
WHO – World Health Organization

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Data of availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The ATTICA study adheres to the ethical guidelines of the Declaration of Helsinki and has been approved by the Ethics Committee of the First Cardiology Department of the National and Kapodistrian University of Athens (#017/01.05.2001), and the Ethics Committee of the Harokopio University (#38/29.03.2022). All participants were informed about the objectives and procedures of the study, and they provided written consent in order to participate.

Consent for publication

Not applicable.

Declaration of the use of generative AI and AI-assisted technologies in scientific writing and in Fig., images and artwork

The authors declare that no generative AI or AI-assisted technologies were used in the preparation of this manuscript or in the creation of Fig. s, images, or artwork.

CRediT authorship contribution statement

Danai Sgouropoulou: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Sofia-Panagiota Giannakopoulou:** Writing – review & editing, Investigation, Formal analysis. **Evangelia Damigou:** Writing – review & editing, Resources, Methodology, Investigation, Formal analysis, Data curation. **Fotios Barkas:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Evangelos Liberopoulos:** Supervision, Methodology, Conceptualization. **Demosthenes B Panagiotakos:** Supervision, Resources, Project administration, Methodology. **Petros P Sfikakis:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Conceptualization. **Evrydiki Kravvariti:** Writing – review & editing, Visualization, Supervision, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjfa.2026.100217.

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