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# Frequency, intensity and duration of physical activity is associated with frailty in older adults with cardiac aging

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**While cardiovascular aging and frailty are strongly associated in older adults, their mechanistic relationship and how physical activity, through its frequency, intensity, and duration, may influence their association remains unclear. A prospective community cohort of older adults without cardiovascular disease were studied cross-sectionally for cardiac structure and function via echocardiogram, dynamometer-derived handgrip strength, skeletal muscle measurements and physical activity questionnaires. Based on handgrip strength and cardiac aging, we derived four phenotypic groups:[1] Normal[2], Physical frailty without cardiac aging[3], Cardiac aging without physical frailty, and[4] Physical frailty and cardiac aging. Multinomial logistic regression was used to examine factors associated with cardiac frailty phenotypes, adjusting for physical activity characteristics, physical measurements, demographics, and cardiovascular risk factors. Amongst 592 participants, the prevalence in the four groups were 44.9%, 20.6%, 18.8%, and 15.7% respectively. Participants in group 1 were the youngest (64, IQR 22), while those in group 4 were the oldest (75, IQR 4.7). Higher frequencies of physical activity (once a week: RRR = 8.922, 95%CI 1.799, 44.250, *p* = 0.007; and 2–3 times a week: RRR = 3.873, 95%CI 1.036, 14.478, *p* = 0.044) were associated with Group 4 category. Higher intensity of physical activity indicated by heavy breath and sweat or near exhaustion (RRR = 0.081, 95%CI 0.017, 0.380, *p* = 0.001), and longer duration (> 1 h: RRR = 0.261, 95%CI 0.079, 0.869, *p* = 0.029) were associated with Group 4 category as well. More than half of community older adults had physical frailty with or without cardiac aging. Higher intensity and longer physical activity duration were associated with lower risks of cardiac aging in the presence of physical frailty, although frequency of once and two to three times a week was associated with higher odds. Physical activity frequency showed no significant association with risks of isolated cardiac aging or physical frailty. These results highlight the importance of tailoring physical activity characteristics based on cardiac frailty phenotypes for developing individualized preventive interventions. Trial registration: ClinicalTrials.gov Identifier: NCT02791139 (06/06/2016).**

**Keywords** Frailty, Cardiovascular aging, Preventive cardiology, Physical activity

Almost half of the world's older population is at risk of becoming frail[1]. At the same time, the risk of cardiovascular disease (CVD) increases significantly, affecting 70–80% of older adults[2]. As frailty and cardiovascular (CV) aging

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symptoms, such as weakness and reduced effort tolerance, are similar, these symptoms should not be viewed in isolation[3]. They are interrelated across a spectrum with interactions in skeletal muscle, CV systems, and lifestyle factors[4]. Those with CVD, including subclinical disease, are more susceptible to frailty[4,5]. Whether modifying factors related to frailty may reduce CV aging in community-dwelling adults is unclear.

Frailty prevention, comparable to the treatment of chronic conditions, is most effective when undertaken early on while still reversible. Identifying this substantial proportion of individuals at risk for frailty is crucial for targeting preventative measures. Frailty syndrome results from an interplay of the aging process, chronic disease, lifestyle, and environmental factors, causing a loss of functional reserve. This leads to poor endurance, a higher risk of falls, impairment, hospitalization, institutionalization, and death[1]. Methods of identifying frailty range from the commonly used Fried phenotype scoring criteria to screening tools such as the handgrip strength test and short physical performance battery test[4]. While there are many ways to diagnose frailty objectively, identifying the pre-frail adults in the community is less well-defined. Several studies define pre-frailty as the presence of at least one Fried's phenotypic feature, a frailty index between 0.09 and 0.24, or the use of various biomarkers[6].

Understanding CV aging in the context of frailty is essential. Cardiac function and structural abnormalities are independently associated with frailty, even in subclinical CVD, and have the strongest correlation with frailty compared to other organ systems[5]. However, while many studies demonstrate the clinical implications of frailty in patients with CVD[7,8] less is understood about frailty and CV aging before the onset of overt CVD, and there is still no clear approach to understanding frailty in CV health, also known as cardiac frailty. Echocardiographic markers of CV aging include increased left ventricular (LV) wall thickness, decrease in peak early diastolic filling (E ), increased atrial contraction wave (A) resulting in a decline in E/A ratio, and diastolic dysfunction, which may contribute to symptoms of frailty among the geriatric population[9]. Thus, testing approaches to phenotype cardiac aging with frailty based on objective markers (such as by echocardiogram) may be a way forward.

As a broad concept, physical activity counteracts some of the effects of frailty by maintaining or improving physiological functions, leading to increased well-being and improved quality of life. More structured activities such as exercise programs have shown how exercise can improve cardiorespiratory fitness, muscle strength and functional status in sedentary older adults who are frail or pre-frail[10,11]. However, outside of structured exercise studies, data regarding frequency, intensity and duration of physical activity that are associated with baseline frailty and cardiovascular health state in older adults are less prevalent.

In this research, we propose to tease out the complex relationship between physical frailty, aging-related deteriorations in cardiovascular health and physical activity, in a real-world community setting. Additionally, we aim to understand the descriptive characteristics and underlying factors of cardiovascular aging and frailty within the community. Among phenotypic groups classified as (1) Normal, (2) Physical frailty without cardiac aging, (3) Cardiac aging without physical frailty, and (4) Physical frailty and cardiac aging, we will examine the association between physical activity characteristics and physical and cardiovascular health in aging.

## Methods

### Study population

Asymptomatic community adults with no prior history of CVD underwent transthoracic echocardiography as part of the Cardiac Aging Study (CAS), a prospective study that examined characteristics and determinants of cardiac structural and functional changes with aging[12]. CAS participants were community older adults who had participated in a large population-based prospective cohort throughout Singapore as well as directly from the community[13,14]. The cohort included individuals who consented for the study. Those with prior history of coronary heart disease, stroke, chronic kidney disease, cancer, or established CVD, including known atrial fibrillation or valvular heart disease were excluded. Written informed consent was obtained from participants upon enrolment. The Singhealth Institutional Review Board (2014/628/C) approved the study protocol. All methods were performed in accordance with the relevant guidelines and regulations.

### Data acquisition

All participants were examined and interviewed on one study visit by trained study coordinators. CV risk factors of diabetes mellitus, hypertension and dyslipidemia, were established based on previous physician diagnosis or use of relevant medications. Smoking history was classified as "Yes" for current or previous smokers and "No" for those who had never smoked. Physical activity frequency, intensity, and duration were categorically determined from self-administered structured questionnaires. Frequency was categorized as inactive, once a week, 2–3 times/week, or almost every day. Intensity was classified as mild ('take it easy'), moderate ('heavy breath and sweat'), or intense ('near exhaustion'). The duration was categorised as short < 15 min, average 16- <30 min, long 30-<60 min, and very long as > 60 min. To estimate peak oxygen consumption, $VO_2$ peak (ml/kg/min), we used a validated prediction model based on a physical activity questionnaire[15] that has been estimated for this cohort[16]. The questionnaire captured basic anthropometric and exercise metrics including demographic data, body measurements, heart rate, and physical activity parameters. This calculator is accessible at worldfitnesslevel.org.

Body composition analysis was obtained using a multifrequency bioimpedance analyser (In Body 270, Biospace Company. Appendicular lean mass (ALM) (in kilograms) was calculated as the sum of skeletal muscle mass for the bilateral upper and lower limbs and adjusted for body size as follows: ALM (kg)/height ($m^2$).

Handgrip strength (HGS) was used to assess the weakness domain in the Cardiovascular Health Study Frailty Phenotype[17,18]. HGS has been linked structurally to LV mass[19], CVD mortality and morbidity[20]. In this study, HGS was measured with a dynamometer (Takei Model TKK5401 Grip D). Participants were instructed to grip with full force. Measurements were recorded to the nearest 0.1 kg. The procedure was repeated twice for each hand, and the highest value was used. Overall HGS was calculated as the average of left-hand and right-hand grip strength measurements. The cutoffs for HGS were defined based on the Asian Working Group for Sarcopenia

(AWGS) 2019 consensus[21,22] which corresponded to < 28 kg for men and < 18 kg for women. These cut-offs used to define the presence of frailty have been recommended for clinical use in our study population and were previously used to define sarcopenia in association with cardiac function[19,23]. Therefore, participants identified as having low HGS would score at least 1 (pre-frail) based on Cardiovascular Health Study Frailty Phenotype[17].

### Transthoracic echocardiography

Two-dimensional (2D), colour, pulsed and continuous wave Doppler images were obtained from the parasternal and apical views according to current recommendations[24] (details in Supplementary data). An E/A ratio cut-off of ≤ 0.8 indicated impaired myocardial relaxation in cardiac aging[25]. All measurements were measured by the same operator and the measurements were averaged over three cardiac cycles and adjusted by the RR interval.

### Classification of clinical phenotypes: 'cardiac frailty' phenotypes

Participants were classified into 4 clinical phenotypes of cardiac frailty using dynamometer-assessed HGS and echocardiogram-based assessment of cardiac function. The four phenotypic groups were: Group 1 "Normal": normal grip strength and E/A > 0/8; Group 2 "Physical frailty without cardiac aging": low grip strength and E/A > 0.8; Group 3 "Cardiac aging without physical frailty": normal grip strength and E/A < 0.8; Group 4 "physical frailty and cardiac aging": low grip strength and low cardiac function.

### Statistics

Baseline characteristics, CV risk factors, exercise levels, and measures of muscle mass were summarized using median (interquartile range (IQR) for continuous data and frequency and percentages (%) for categorical data). Comparisons among the groups were made using chi-square and Kruskal–Wallis rank test as appropriate.

To determine the factors associated with cardiac frailty phenotypes, we used multinomial logistic regression, with group 1 "normal" as the reference category. Model was built using a fixed set of covariates comprising physical activity characteristics and physical measurements and adjusted for participants' baseline demographics and risk factors. Physical activity characteristics included frequency, intensity, and duration of activity. Due to low counts in 'Intensity' variable for 'near exhaustion', responses for 'near exhaustion' was combined with 'heavy breath and sweat' during regression analyses.

Physical measures comprised of height, heart rate, systolic blood pressure, diastolic pressure, and ALM. Baseline demographics and risk factors included age, sex, smoking history, diabetes mellitus, hypertension, and dyslipidemia. Subsequently, sensitivity analyses model 2.1-2.X were done for other commonly used echocardiographic markers seen with cardiac aging, such as LV mass, left atrium size, E/e', and PASP[26,27]. These echocardiographic markers were added one by one to the multinomial logistic regression. A two-sided p-value of < 0.05 was considered statistically significant. Statistical analysis was conducted using STATA version 17.

## Results

### Baseline characteristics

The baseline characteristics of the participants are presented in Table 1. Out of 592 participants, 44.9% ($n$ = 266) were in group 1, 20.6% ($n$ = 122) in group 2, 18.8% ($n$ = 111) in group 3, and 15.7% ($n$ = 93) in group 4. The median age of the cohort was 71 (IQR 11.6) years. Participants in group 1 were the youngest (median 64 years), while those in group 4 were the oldest (median 75 years). The distribution of men and women in all the 4 groups was almost equal. Hypertension, dyslipidemia, diabetes mellitus and anthropometric factors like waist circumference were significantly different between the groups.

Physical activity characteristics differed significantly between the groups. For frequency of physical activity, almost half of the overall cohort (49.5%) had engaged in physical activity almost every day. Inactivity was least prevalent in Group 1 compared with the other groups (13.9% vs. 23.8% vs. 21.6% vs. 22.6%). For intensity of physical activity, a large majority of the cohort (77.4%) practiced low intensity 'take it easy' physical activity. Low intensity of physical activity was most prevalent in Group 4, followed by Group 3, Group 2 and Group 1 respectively (96.6% vs. 83.6% vs. 85.0% vs. 65.0%). Duration of physical activity was however more spread out amongst the groups. Durations of < 15 min, > 15-<30 min, > 30- <60 min and > 1 h were prevalent in all 4 Groups of participants. In contrast, the longest duration of physical activity beyond 1 h was most prevalent in Group 1, followed by Group 3, Group 2 and Group 4 respectively (35.0% vs. 27.3%, 26.7% vs. 15.7%) (Fig. 1). Calculated peak oxygen consumption (a measure of aerobic capacity) was significantly different between the groups; Group 3 and 4 had lower aerobic capacity as compared to Groups 1 and 2. (Fig. 2a). Both ALM and HGS were lower in Groups 2 and 4 with physical frailty, compared to Groups 1 and 3 without physical frailty.

### Cardiovascular measurements

Several of the left heart chamber echocardiographic measurements differed significantly among the groups. Groups 3 and 4, with cardiac aging, had greater wall thickness. However, LV mass was not significantly different among the groups and did not meet the criteria for LV.

hypertrophy[28]. Although measurements of left atrial volume differed significantly among the groups, left atrial size did not meet clinical thresholds for enlargement[28]. LV systolic function did not differ significantly among the groups. (Supplementary Table 1).

For diastolic parameters, Groups 1 and 2 had higher early E mitral inflow and systolic mitral annular tissue doppler velocities. Groups 3 and 4 had slower mitral deceleration time. Septal and lateral tissue doppler S' and e' velocities were highest in Group 1 and lowest in Group 4. The ratios of peak velocity flow in early diastole E to peak early diastolic septal and lateral mitral annular velocities——septal and lateral E/e', respectively——and PASP were higher in Groups 4 and 2 versus Groups 3 and 1, i.e., those with weaker HGS than those with normal HGS.

| | Overall ($N=592$) | Group 1: 'Normal' ($N=266$) | Group 2: 'Physical Frailty without cardiac aging' ($N=122$) | Group 3: 'Cardiac aging without physical frailty' ($N=111$) | Group 4: 'Physical frailty and cardiac aging' ($N=93$) | $p$-value |
|---|---|---|---|---|---|---|
| Clinical | | | | | | |
| Age, years | 71 (11.6) | 64 (22.0) | 73 (7.3) | 72 (6.7) | 75 (4.7) | 0.0001 |
| Weight, kilograms | 60 (14.3) | 61 (14.2) | 56 (14.2) | 62 (15.2) | 58 ± 13.8 | 0.0001 |
| Height, centimetres | 160 (12.0) | 163 (12.0) | 157 (13.0) | 161 (12.5) | 157 (13.5) | 0.0001 |
| Body mass index, kg/m$^2$ | 23 ± 4.3 | 23 (4.5) | 23 (4.5) | 24 (3.9) | 24 (3.8) | 0.0001 |
| Heart rate, beats per minute | 72 (15.5) | 71 (15.0) | 71 (17.0) | 75 (20.0) | 71 (13.0) | 0.0082 |
| Waist circumference, centimetres | 82 (14.0) | 80 (14.5) | 80 (11.0) | 86 (14.0) | 83 (12.0) | 0.0001 |
| Male | 287 (48.5%) | 124 (46.6%) | 61 (50.0%) | 52 (46.9%) | 50 (53.8%) | 0.65 |
| Systolic blood pressure, mmHg | 140 (26.0) | 134 (25.0) | 145 (23.0) | 144 (27.0) | 147 (25.0) | 0.0001 |
| Diastolic blood pressure, mmHg | 74 (14.5) | 74 (13.0) | 74 (16.0) | 75 (15.0) | 74 (13.0) | 0.62 |
| Hypertension | 264 (44.6%) | 87 (32.7%) | 62 (50.8%) | 58 (52.3%) | 57 (61.3%) | < 0.0001 |
| Dyslipidemia | 253 (42.7%) | 84 (31.6%) | 61 (50.0%) | 57 (51.4%) | 51 (54.8%) | < 0.0001 |
| Diabetes mellitus | 105 (17.7%) | 27 (10.2%) | 27 (22.1%) | 27 (24.3%) | 24 (25.8%) | < 0.0001 |
| Ever smoked | 112 (18.9%) | 44 (16.5%) | 23 (18.9%) | 22 (19.8%) | 23 (24.7%) | 0.38 |
| Physical activity | | | | | | |
| Frequency | | | | | | 0.017 |
| Inactive | 111 (18.8%) | 37 (13.9%) | 29 (23.8%) | 24 (21.6%) | 21 (22.6%) | |
| Once a week | 51 (8.6%) | 23 (8.7%) | 10 (8.2%) | 7 (6.3%) | 11 (11.8%) | |
| 2 to 3 times a week | 137 (23.1%) | 80 (30.1%) | 18 (14.8%) | 20 (18.0%) | 19 (20.4%) | |
| Almost everyday | 293 (49.5%) | 126 (47.4%) | 65 (53.3%) | 60 (54.1%) | 42 (45.2%) | |
| Intensity | | | | | | < 0.0001 |
| Take it easy | 452 (77.4%) | 173 (65.0%) | 102 (85.0%) | 92 (83.6%) | 85 (96.6%) | |
| Heavy breath and sweat | 124 (21.2%) | 89 (33.5%) | 17 (14.2%) | 16 (14.6%) | 2 (2.3%) | |
| Near exhaustion | 8 (1.4%) | 4 (1.5%) | 1 (0.8%) | 2 (1.8%) | 1 (1.1%) | |
| Duration | | | | | | 0.024 |
| < 15 min | 144 (24.6%) | 50 (18.8%) | 32 (26.7%) | 29 (26.4%) | 33 (37.1%) | |
| 16 to < 30 min | 118 (20.2%) | 51 (19.2%) | 25 (20.8%) | 22 (20.0%) | 20 (22.5%) | |
| 30 to 60 min | 154 (26.3%) | 72 (27.1%) | 31 (25.8%) | 29 (26.4%) | 22 (24.7%) | |
| > 1 h | 169 (28.9%) | 93 (35.0%) | 32 (26.7%) | 30 (27.3%) | 14 (15.7%) | |
| $VO_2$ (ml/kg/min) | 35.0 (10.0) | 37.5 (9.0) | 34.0 (9.0) | 31.0 (9.0) | 32.0 (7.5) | 0.0001 |

**Table 1**. Baseline characteristics stratified by 'cardiac frailty' phenotypes.

## Factors associated with cardiac frailty phenotypes

The results of the multinomial logistic regression are shown in Table 2. Group 1 was used as the reference group. Factors associated with a **Group 2** category of 'physical frailty without cardiac aging' were age (RRR = 1.064, 95%CI 1.027,1.102, $p=0.001$) and height (RRR = 0.927, 95%CI 0.874, 0.983, $p=0.011$). There was a non-significant trend for association with physical activity intensity (RRR = 0.560, 95%CI 0.283, 1.108, $p=0.096$). Factors associated with a **Group 3** category of 'cardiac aging without physical frailty' were age (RRR = 1.099, 95%CI 1.055,1.144, $p<0.0001$), heart rate (RRR = 1.048, 95%CI 1.026,1.071, $p<0.0001$), and waist circumference (RRR = 1.049, 95%CI 1.002,1.099, $p=0.042$), with a non-significant trend for ALM (RRR = 0.857, 95%CI 0.721, 1.018, $p=0.079$).

Factors associated with **Group 4** category of 'physical frailty and cardiac aging' were age (RRR = 1.204, 95%CI 1.125,1.289, $p<0.0001$), heart rate (RRR = 1.039, 95%CI 1.012, 1.064, $p=0.004$), waist circumference (RRR = 1.079, 95%CI 1.020,1.141, $p=0.008$) and ALM (RRR = 0.813, 95%CI 0.665, 0.994, $p=0.043$) as well as physical activity parameters. Higher frequencies of physical activity such as once a week (RRR = 8.922, 95%CI 1.799, 44.250, $p=0.007$) and 2 to 3 times a week (RRR = 3.873, 95%CI 1.036, 14.478, $p=0.044$) were factors associated with Group 4 category. Intensity of physical activity such as 'heavy breathing and sweating' or 'near exhaustion' (RRR = 0.081, 95%CI 0.017, 0.380, $p=0.001$), as well as > 1 h duration of physical activity (RRR = 0.261, 95%CI 0.079, 0.869, $p=0.029$) were factors that were associated with Group 4 category as well.

Across all 4 Groups, traditional risk factors of diabetes, hypertension, and dyslipidemia were not significant factors.

Sensitivity analyses adjusting for cardiac indices possibly related to aging such as LV mass, left atrial volume, and E/e' for each of the groups (Supplementary Tables 2 to 4) did not materially alter the overall results.

## Discussion

In this cohort of older adults living in the community, features of frailty and pre-frailty were not uncommon. Our proposed classification of clinical 'cardiac frailty' phenotypes, namely normal, either physical frailty or cardiac

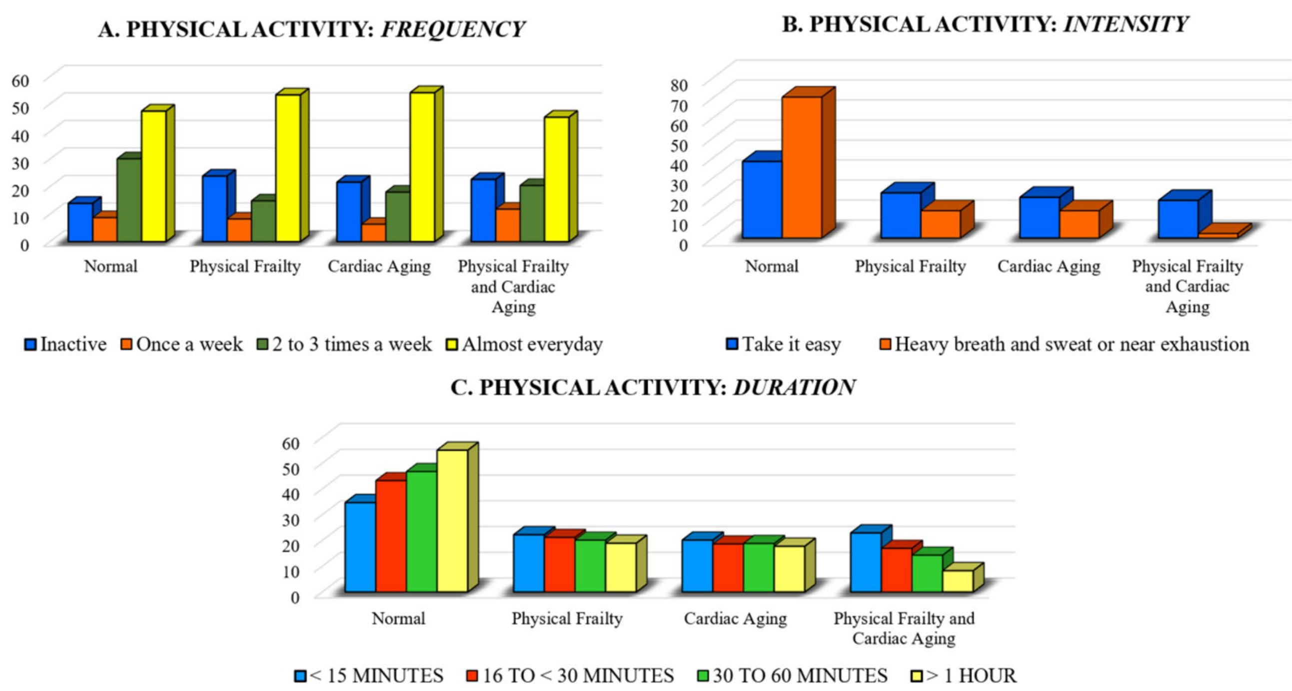


**Fig. 1**. Physical activity parameters between the groups (**A**) PA frequency, (**B**) PA duration, (**C**) PA intensity. *PA* physical activity. The bars represent the proportion of individuals within each PA parameter.

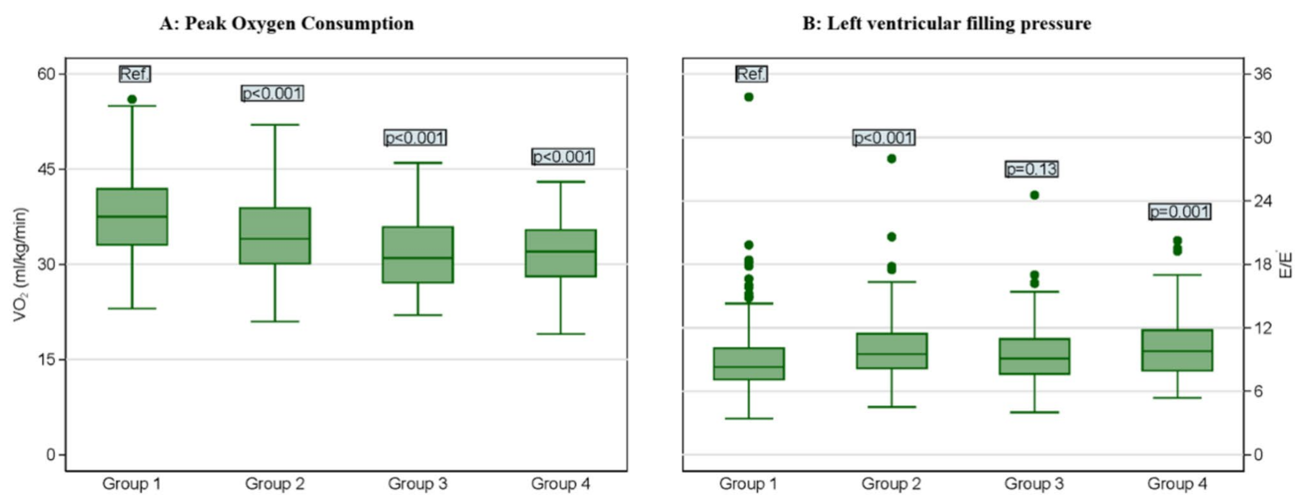


**Fig. 2**. Distribution of (**a**) Peak Oygen Consumption; (**b**) Left Ventricular Filling Pressures; across the groups. The boxes represent the 25th to 75th interquartile ranges, and the lines across the boxes represent the median. The round marker represents outliers. Group 1 was used as the reference category. $VO_2$ indicates peak oxygen consumption; .E/e' indicates left ventricular filling pressures.

aging, or both physical frailty and cardiac aging, is novel and useful for understanding factors that determine each category. By examining modifiable factors such as physical activity factors, this classification is targeted towards preventive interventions for frailty in communities. Analysis of physical activity patterns demonstrated that physical activity frequency showed no significant relationship with isolated cardiac aging or physical frailty. On the other hand, higher intensity and extended duration of exercise were inversely associated with concurrent cardiac aging and physical frailty risk, while higher intensity of physical activity was associated with higher odds.

In the Cardiovascular Health Study, the prevalence of frailty and pre-frailty in the community were 6.9% and 46.6%, respectively[17] and in a meta-analysis of low to middle-income countries, the pooled prevalence of frailty and pre-frailty were 17.4% and 49.3%[29] respectively. Frailty is manifestly higher among participants with established CVD and correlates to poorer functional status and higher morbidity and mortality. For instance, in an Asian cohort with congestive heart failure, 69% had frailty, and in the transcatheter aortic valve replacement

| Grouping | Relative risk ratio | *P* value | 95% confidence interval | |
|---|---|---|---|---|
| Group 1 | Base outcome | | Upper | Lower |
| Group 2: 'physical frailty without cardiac aging' | | | | |
| Age, years | 1.064 | **0.001** | 1.027 | 1.102 |
| Weight, kg | 0.975 | 0.347 | 0.925 | 1.028 |
| Height, cm | 0.927 | **0.011** | 0.875 | 0.983 |
| Heart rate, beats per minute | 1.008 | 0.494 | 0.986 | 1.030 |
| Systolic blood pressure, mmHg | 1.004 | 0.542 | 0.991 | 1.017 |
| Appendicular lean mass, kg | 1.018 | 0.777 | 0.902 | 1.151 |
| Waist Circumference, cm | 1.016 | 0.479 | 0.972 | 1.063 |
| Physical activity: frequency | | | | |
| Inactive | | | | |
| Once a week | 1.492 | 0.572 | 0.372 | 5.977 |
| 2 to 3 times a week | 0.506 | 0.279 | 0.147 | 1.739 |
| Almost everyday | 0.783 | 0.674 | 0.251 | 2.441 |
| Physical activity: intensity | | | | |
| Take it easy | | | | |
| Heavy breath and sweat/ near exhaustion | 0.560 | 0.096 | 0.283 | 1.108 |
| Physical activity: duration | | | | |
| < 15 min | | | | |
| 16 to < 30 min | 1.018 | 0.975 | 0.335 | 3.100 |
| 30 to 60 min | 0.971 | 0.958 | 0.320 | 2.944 |
| > 1 h | 1.053 | 0.926 | 0.353 | 3.134 |
| Hypertension | 1.020 | 0.949 | 0.562 | 1.852 |
| Dyslipidemia__ | 1.151 | 0.620 | 0.660 | 2.009 |
| Diabetes mellitus__ | 1.530 | 0.247 | 0.745 | 3.140 |
| Group 3: 'Cardiac aging without physical frailty' | | | | |
| Age, years | 1.099 | **< 0.0001** | 1.055 | 1.144 |
| Weight, kg | 1.044 | 0.137 | 0.986 | 1.105 |
| Height, cm | 0.987 | 0.703 | 0.923 | 1.056 |
| Heart rate, beats per minute | 1.048 | **< 0.0001** | 1.026 | 1.071 |
| Systolic blood pressure, mmHg | 1.006 | 0.388 | 0.993 | 1.019 |
| Appendicular lean mass, kg | 0.857 | 0.079 | 0.721 | 1.018 |
| Waist Circumference, cm | 1.049 | **0.042** | 1.002 | 1.099 |
| Physical activity: frequency | | | | |
| Inactive | | | | |
| Once a week | 1.983 | 0.371 | 0.442 | 8.890 |
| 2 to 3 times a week | 1.387 | 0.616 | 0.386 | 4.990 |
| Almost everyday | 1.136 | 0.837 | 0.336 | 3.845 |
| Physical activity: intensity | | | | |
| Take it easy | | | | |
| Heavy breath and sweat/ near exhaustion | 0.636 | 0.204 | 0.317 | 1.278 |
| Physical activity: duration | | | | |
| < 15 min | | | | |
| 16 to < 30 min | 0.813 | 0.732 | 0.250 | 2.651 |
| 30 to 60 min | 0.690 | 0.536 | 0.214 | 2.233 |
| > 1 h | 0.734 | 0.604 | 0.229 | 2.356 |
| Hypertension | 0.887 | 0.701 | 0.481 | 1.634 |
| Dyslipidemia | 1.273 | 0.411 | 0.716 | 2.266 |
| Diabetes_mellitus | 1.488 | 0.266 | 0.739 | 2.994 |
| Group 4: 'Physical frailty and cardiac aging' | | | | |
| Age, years | 1.204 | **< 0.0001** | 1.125 | 1.289 |
| Weight, kg | 0.991 | 0.794 | 0.925 | 1.061 |
| Height, cm | 1.009 | 0.814 | 0.934 | 1.091 |
| Heart rate, beats per minute | 1.039 | **0.004** | 1.012 | 1.064 |
| Systolic blood pressure, mmHg | 1.005 | 0.467 | 0.991 | 1.019 |
| Continued | | | | |

| Grouping | Relative risk ratio | *P* value | 95% confidence interval | |
|---|---|---|---|---|
| Appendicular lean mass, kg | 0.813 | **0.043** | 0.665 | 0.994 |
| Waist circumference, cm | 1.079 | **0.008** | 1.020 | 1.141 |
| Physical activity: frequency | | | | |
| Inactive | | | | |
| Once a week | 8.922 | **0.007** | 1.799 | 44.250 |
| 2 to 3 times a week | 3.873 | **0.044** | 1.036 | 14.478 |
| Almost everyday | 2.205 | 0.215 | 0.632 | 7.693 |
| Physical activity: intensity | | | | |
| Take it easy | | | | |
| Heavy breath and sweat/ near exhaustion | 0.081 | **0.001** | 0.017 | 0.380 |
| Physical activity: duration | | | | |
| < 15 min | | | | |
| 16 to < 30 min | 0.503 | 0.246 | 0.158 | 1.603 |
| 30 to 60 min | 0.418 | 0.139 | 0.132 | 1.325 |
| > 1 h | 0.261 | **0.029** | 0.079 | 0.869 |
| Hypertension | 1.325 | 0.442 | 0.647 | 2.710 |
| Dyslipidemia | 1.204 | 0.585 | 0.618 | 2.349 |
| Diabetes_mellitus | 1.340 | 0.471 | 0.605 | 2.967 |

**Table 2**. Multinomial logistic regression of factors that determine 'cardiac frailty' phenotypes.

population, the prevalence of frailty was as high as 86%[30,31]. While frailty is widespread in participants with established CVD, little is known regarding the prevalence of pre-cardiac frailty in the community. Our data demonstrates that physical frailty, as defined objectively using sex-based HGS thresholds, is prevalent in our community cohort, amounting to more than one third of the cohort, and can co-exist with cardiac dysfunction. Even though there was no clinically evident CVD, 34.5% of our cohort participants (Groups 3 and 4) had echocardiographic signs of cardiac aging and they had significantly lower aerobic capacity as compared to those with physical frailty but no cardiac aging. This is in keeping with previous studies showing that cardiac dysfunction (i.e., mitral annular velocities) correlated with peak $VO_2$ in participants with heart failure[32].

As individuals age, echocardiography reveals both structural and functional changes in the heart. Structural alterations include an increase in LV mass, LV hypertrophy, and enlarged left atrial volume. Functional changes manifest as diastolic dysfunction and reduced LV global longitudinal strain[27,33–35]. In this study, we used E/A ratio as a metric to define cardiac aging as it is one of the earliest signs of diastolic dysfunction and cardiac aging on echocardiography and which has been correlated with clinical outcomes[14]. Other cardiac structural and functional observations are supportive of overall features of cardiac aging in this cohort. Frailty has been associated with diastolic function, manifesting via higher E/e′ ratios and left atrial volume indexes[5]. Similarly, in our cohort, several of these changes were observed. Among participants in Groups 2 and 4 who had physical frailty, higher LV filling pressures (E/e') were observed which is in keeping with previous study findings of associations between diastolic dysfunction and frailty[33,36] (Fig. 2b).

Interestingly, we found that LV mass was not significantly different among the four cardiac frailty categories and that the mean values were far below echocardiographic criteria for LV hypertrophy[24]. This observation contrasts with the traditional notion that cardiac aging is associated with LV hypertrophy[37]. We hypothesize that prior to established CVD, a relationship represented by the cardiac-skeletal muscle axis exists such that skeletal muscle mass is closely related to LV mass particularly in older adults[19,38]. A positive relationship between skeletal muscle mass and LV mass exists such that LV mass is likely lower in frail older adults with low skeletal muscle mass. In these analyses, lower ALM was associated with cardiac aging where participants did not meet thresholds of increased LV mass (significantly in Group 4 and marginally in Group 3).

In terms of intensity and duration of physical activity, higher intensity and extended duration of exercise were inversely associated with concurrent cardiac aging and physical frailty risk. The observation that higher intensity of physical activity is associated with lower risks has also been observed in cohort of middle-aged adults with prevalent CVD[39]. Thus, our findings expand these notions that higher intensity physical activity may be beneficial to older community populations who are healthier before prevalent CVD. Importantly the effect of physical activity parameters was independent of traditional CVD risk factors such as hypertension, diabetes mellitus and dyslipidemia, when studied in association with cardiac frailty.

On the other hand, frequency of physical activity showed no significant correlation with isolated cardiac aging or physical frailty. Interestingly, low to moderate frequency physical activity was associated with higher risks of physical frailty and cardiac aging combined, but daily physical activity did not alter those risks. Given that the sample of participants in this frequency category was small and observed confidence intervals were wide, the observation should be interpreted with caution. The observed higher risks in frequency for this group may be due to factors (adjusted and unknown such as unmeasured behavioural factors) that are on the causal pathway, or overestimation of physical activities. However, increased physical activity intensity and extended duration demonstrated significant protective effects against participants with both cardiac aging and frailty. Regardless, our observations align with well-established benefits of physical activity intensity on mortality benefits[40] and on primary and secondary CVD prevention[41]. Notably, this work emphasizes that cardiorespiratory fitness (quantified by VO2 max), a robust independent predictor of mortality, improves more with higher intensity and duration of exercise rather than merely increasing exercise frequency[42,43].

Physical activity parameters of the isolated cardiac aging or physical frailty group did not differ significantly from those without any frailty. These findings contrast with studies that showed the benefit of exercise therapy in gain of lean mass and reduction of physical domains of frailty[44,45], or improvements in cardiac diastolic function[46]. On the other hand, those with cardiac aging, regardless of physical frailty status, had higher resting heart rates and larger waist circumference. It may be that a certain level of physical activity needs to be achieved to reduce central obesity and resting heart rate before the benefits in delaying cardiac aging can be realized. It is also possible that physical activity improves cardiac parameters in some participants while improving physical strength and functional status via peripheral mechanisms in others. For instance, in patients with heart failure with preserved ejection fraction, improvements in exercise capacity measured by $VO_2$ were found to be due to improvements in peripheral vascular and skeletal muscle function as evidenced by the increase in peripheral arterial-venous oxygen difference rather than changes in cardiac output or peak exercise stroke volume[47]. For community older adults without gross reductions in cardiac output to begin with (vs. CVD patients), habitual physical activity improves oxygen extraction at the muscular-vessel levels (despite no obvious incremental changes in cardiac output), which is functionally important for carrying out activities of daily living.

While some prospective studies address the effects of exercise training on cardiac aging, results have been conflicting[48–51]. As the association factors are similar, whether those with cardiac aging alone are individuals who would then develop cardiac aging with physical frailty later, is uncertain. More research is required to understand the underlying exercise-mediated physiological improvements in functional capacity in older adults to develop appropriate preventive strategies. Nevertheless, defining clinical phenotypes such as groups defined in this work, may represent a way forward in understanding complex evolutions in physical and cardiac aging. Our findings support the role of physical activity as primary prevention in community older adults with this cardiac frailty phenotype, emphasizing the relative importance of intensity and duration over frequency.

Our study has several limitations. Whether co-existing cardiac aging and physical frailty occurred due to lack of physical activity or whether both conditions together resulted in individuals being more sedentary is uncertain due to the cross-sectional design of this study, making causal inferences difficult. While participants were generally independent in their activities of daily living and could participate in the study procedures fully, our results likely reflect real-world physical activity behaviors in our older adult population. While relevant to our local population, our results may not reflect physical activity behaviors of other populations. Another limitation is the reliance on self-reporting of physical activity parameters which may be affected by recall and misclassification biases and the fact that the study did not capture the type of physical activity done. However, as a large community-based study, self-reported physical activity would be the most feasible method. Notably, the majority of the data obtained in this study were objective and extensive, such as CV examinations by established methods, measurement of handgrip strength and bio-impedance measurements, which are known to correlate with dual energy X-ray absorptiometry[52]. We acknowledge the limitations of using the echocardiography E/A ratio as the criterion for cardiac aging. The problem of pseudo-normal LV filling seen in advanced diastolic dysfunction, whereby trans-mitral flow pattern appears normal due to opposing increase in left atrial pressures, is unlikely in this community cohort, whose left atrial structures were generally normal. Although there are other potential diastolic dysfunction parameters that could have been used, this easily obtainable echocardiographic marker of myocardial relaxation state provides a practical clinical tool for documenting the progression and prognostic implications of cardiac aging. Furthermore, sensitivity analyses done using several other markers of diastolic dysfunction did not change our overall findings. Finally, while HGS strongly correlates with frailty and sarcopenia and has even been proposed to be used alone as a screening tool[53], the most commonly used criteria for detecting frailty is Fried's frailty phenotype which involves five areas: unintentional weight loss, self-reported exhaustion, weakness measured by HGS, slow walking speed, and low physical activity[17]. Individuals meeting three or more of these criteria are classified as frail, those with one or two criteria are considered pre-frail Thus, individuals categorised under the physical frailty phenotype in our cohort may not be as frail as those with established frailty based on Fried's phenotype.

Nonetheless, our study is consistent with earlier findings that physical activity may ameliorate some of the effects of frailty[54]. We also demonstrate that a single easily obtainable echocardiographic biomarker can be used to detect subclinical cardiac frailty. Our work also provides insight into why certain individuals may not respond as well to exercise interventions for reducing symptoms and frailty. As the global proportion of older persons steadily increases, the search for modifiable and individualized factors that might retain day-to-day functional capacity or improve physiological processes is vital for a higher quality of life and longer health span. Further longitudinal studies and exploratory research are necessary to determine whether exercise and other factors delay or reverse age-related myocardial changes and to develop tailored preventive interventions differentiated based on cardiac frailty phenotypic factors.

## Conclusion

More than half of community older adults had physical frailty with or without cardiac aging. Higher intensity and longer physical activity duration were associated with lower risks of cardiac aging in the presence of physical frailty. The lack of association between physical activity and certain aging phenotypes emphasises yet unknown mechanisms that determine the response to exercise. Exploratory research is needed to find other mechanisms that slow cardiac aging and develop individualized preventive interventions based on cardiac frailty phenotypes.

## Data availability

The datasets generated and/or analysed during the current study are not publicly available due to institutional restrictions but are available from the corresponding author on reasonable request.

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## Author contributions
ASK, FG, LYW, WSL, JMG contributed to the conception and design of the study, advised on all statistical aspects, and interpreted the data. RST, LLYT, SYT, CHO, ACWO, JPK, FG performed analyses. All authors critically reviewed previous drafts. All authors approved the final draft for submission.

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## Declarations

## Competing interests
The authors declare no competing interests.

## Ethics approval and consent to participate
Written informed consent was obtained from participants upon enrolment. The Institutional Review Board (2014/628/C) approved the study protocol.

## Additional information
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