The Journal of Prevention of Alzheimer's Disease 12 (2025) 100222

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Original Article

Trajectories of Cardiorespiratory Fitness Measured by Metabolic Equivalents and the Risk of Alzheimer's and Related Dementias

Edward Zamrini[a,b,c,**], Yan Cheng[a,b], Peter Kokkinos[a,b], Charity J Morgan[d], Charles Faselis[a,b], Helen M Sheriff[a,b], Yijun Shao[a,b], Xuemei Sui[e], Ali Ahmed[a,b], Qing Zeng[a,b,**,*]

[a] Washington DC VA Medical Center, Washington, DC, USA
[b] George Washington University, Washington, DC, USA
[c] Irvine Clinical Research, Irvine, CA, USA
[d] University of Alabama at Birmingham, Birmingham, AL, USA
[e] University of South Carolina, Columbia, SC, USA

ARTICLE INFO

Keywords:
Cardiorespiratory fitness
Alzheimer's and related dementias
Trajectory
Cluster
Analysis

ABSTRACT

Background: Higher fitness levels have been reported to protect against Alzheimer's Disease and Related Dementias (ADRD). However, the association between changes in fitness over time and ADRD risk remains unknown. This study aims to identify clusters of metabolic equivalents (METs) trajectories and examine their correlation with incident ADRD.

Methods: A retrospective cohort study was conducted among Veterans with ≥3 standardized exercise treadmill tests (ETT) between 2000 and 2017. The exposure was change in fitness expressed in metabolic equivalents (METs). METs are based on treadmill speed, grade, and time. One MET is equivalent to 3.5 ml per kg of body weight per minute. The outcome was incident ADRD after the final ETT test, identified by diagnosis codes. Standardized METs scores were generated using mean and standard deviation for each age and sex stratum. Latent class growth analysis (LCGA) identified trajectory clusters. We assessed the association between clusters and ADRD using unadjusted Kaplan-Meier curves (overall and by age groups) and a multivariate Cox regression model adjusted for baseline characteristics at the first ETT.

Results: A total of 75,851 veterans were included. The average number of ETTs was 4.0 ± 1.8, with the average time gap of 6.5 ± 3.8 years between first and last test. We identified five trajectory clusters: Group 1 (n = 22,485), Group 2 (n = 22,694), Group 3 (n = 6691), Group 4 (n = 19,386), and Group 5 (n = 4595). All groups, except for Group 3, showed a stable and slight improvement or decline over time, differing only in their initial standardized METs scores: Group 5 had the highest initial score, Group 1 had the lowest initial score, while Group 3 started out with a score almost as high as Group 4 and dropped to as low as Group 1. Compared to Group 1, Group 3 had a 12 % reduced risk of developing ADRD (HR = 0.88; 95 % CI: 0.77 – 1.01; p = 0.0660), with a greater reduction than Group 2 (10 %) but less than Group 4 (17 %) or Group 5 (24 %).

Discussion: Our findings underscore the potential benefits of maintaining fitness to reduce the risk of ADRD with age. Although declining fitness levels are associated with an increased risk, the initial higher baseline fitness provides a degree of ongoing protection against ADRD.

1. Introduction

Alzheimer's Disease and Related Dementias (ADRD) affect millions of patients globally and are a major public health concern [1]. ADRD not only cause decline in cognitive and functional abilities of the individuals affected but also place considerable emotional and financial strain on their families and caregivers [2,3]. Given the widespread impact of ADRD, there is a pressing need to explore preventive strategies.

The Lancet Commission identified 14 potential risk factors [4]. The National Institute on Aging has identified physical activity as the only lifestyle intervention with strong evidence of mechanistic plausibility to prevent ADRD [5]. Extensive research aimed at understanding and preventing ADRD has revealed a promising link between cardiorespiratory fitness and a reduced incidence of dementia [6–9]. These studies suggest that higher fitness levels may be protective against the onset of ADRD. However, there is a lack of studies on the association between changes

* Correspondence: Qing Zeng-Treitler, PhD, Professor & Director, George Washington University Biomedical Informatics Center, 2600 Virginia Ave NW, Suite 300, Washington, DC 20037.
E-mail address: zengq@gwu.edu (Q. Zeng).
** Qing Zeng-Treitler and Edward Zamrini are senior authors and contributed equally.

https://doi.org/10.1016/j.tjpad.2025.100222
Received 11 February 2025; Received in revised form 25 May 2025; Accepted 31 May 2025

in the trajectory of an individual's cardiorespiratory fitness (CRF) over time and the risk of developing ADRD. CRF refers to the ability of the circulatory and respiratory systems to supply oxygen to skeletal muscles during sustained physical activity. VO2 max is the gold standard for assessing cardiorespiratory fitness. However, directly assessing VO2 max is labor-intensive and cost prohibitive to use in large populations such as hospital/clinical settings. Thus, cardiorespiratory fitness is estimated by standardized exercise treadmill protocols using treadmill speed, elevation and time and is expressed in peak metabolic equivalents (METs; 1 MET=3.5 ml/kg of body weight/minute) [10].

In examining the relationship between CRF and ADRD, it is important to utilize accurate and objective measures. Many existing studies focus on exercise and depend on self-reported data [11–13]. These are prone to multiple biases including variations in exercise patterns, effort expended, and recollection. In this study we used METs obtained from rigorous stress tests as an objective, precise measure of cardiorespiratory fitness. For our research, we analyzed the trajectories of METs from a longitudinal database to capture changes in fitness levels.

The methodology of trajectory analysis involves categorizing METs changes into patterns that can be analyzed statistically [14]. Traditionally, these patterns are often predefined by experts and might include linear increases or decreases, or more complex U-shaped or non-linear trends over time [15,16]. However, our study adopts a machine learning unsupervised clustering approach which allows the use of data only, without expert knowledge, to determine the most natural grouping of trajectories based on inherent similarities among individual patterns [17]. This technique enhances the objectivity of the analysis by minimizing potential biases that might arise from imposing preconceived categories.

The primary objective of our study is to identify distinct clusters of individuals based on their MET trajectories and to investigate how these clusters correlate with the risk of developing ADRD. By understanding these relationships, we aim to pinpoint specific trajectory patterns associated with higher risks. The goal is to leverage these insights to develop targeted interventions that can modify MET levels and potentially reduce the incidence of ADRD, thereby alleviating its burden on patients, families, and healthcare systems worldwide.

2. Methods

2.1. Study design and population

We conducted a retrospective cohort study using the Veterans Health Administration (VHA) Clinical Data Warehouse (CDW) database, which contains US national electronic health records of Veterans. The study received VHA's Central Institutional Review Board approval (IRBNET#1576,748–1). This study focused on Veterans who completed at least one ETT during 2000–2017 with results of valid METs values between 2 and 24 from the unstructured clinical notes. Veterans were excluded if they were under 30 or over 95 years old, had baseline of ADRD or severe mental illness, or were not VA health care users. While ADRD is typically diagnosed after age 50, early onset can occur in a person's 30 s [16,18]. Given the considerable number of younger patients in the database, we used age 30 as the cutoff for cohort selection. We also excluded those with follow-up of 1 year or less, conditions such as ≥20 METs at age of ≥50 years, weight >450 pounds, body mass index (BMI) <18.5 kg/m^2, coronary revascularization, myocardial infarction, heart failure, pacemaker use, and/or inconsistent death dates. The final cohort included Veterans ≥3 exercise treadmill tests (ETTs) between 2000 and 2017, with each test separated by at least one year.

2.2. Exposure and outcome

Longitudinal METs were the exposure, which were extracted from ETT data via a validated Natural Language Processing (NLP) tool [7]. Because METs were highly related to and influenced by age and sex, we generated standard METs scores within each age and sex stratum to remove heterogeneity caused by aging and sexual difference, using the formula as below:

$$standardized\,METs = \frac{METs - Mean\,METs\,of\,Correponding\,Age\,Group\,and\,Sex}{Standard\,Deviation\,of\,METs\,of\,Correponding\,Age\,Group\,and\,Sex} + 2.4$$

The mean and standard deviation (SD) of METs by age group and sex are shown in (Table 1).

Table 1
Mean and standard deviation (SD) of METs by age group and sex.

Age (years)	Mean METs	SD METs
Female (N = 3057)		
30–39 (n = 266)	8.2	3.2
40–49 (n = 882)	7.8	2.8
50–59 (n = 1237)	7.1	2.6
60–69 (n = 506)	6.4	2.3
70–79 (n = 121)	5.6	2.1
80+ (n = 45)	4.7	1.6
Male (N = 72,794)		
30–39 (n = 1578)	10.0	3.5
40–49 (n = 6970)	9.4	3.2
50–59 (n = 23,871)	8.3	3.0
60–69 (n = 28,055)	7.3	2.7
70–79 (n = 10,109)	6.6	2.5
80+ (n = 2211)	5.8	2.3

Incident ADRD diagnoses were the outcome identified using International Classification of Diseases 9/10-Clinical Modification (ICD-9/10-CM) codes. At least two encounters with ADRD diagnosis codes were required to confirm the ADRD diagnoses [7]. To guarantee there was no time overlapping between exposure and outcome, we only used historical METs measures which occurred at least one year before the outcome or censoring date to generate the trajectory of standardized METs. Time to event was calculated from the first ETT to the first diagnosis of ADRD. The follow-up began with the first ETT, as our hypothesis was that not only the METs trajectory but also the initial METs level would be associated with the outcome. Patients who did not develop ADRD were censored at death, last encounter date, or December 31, 2018, whichever occurred first.

2.3. Covariates

Baseline covariates included demographics, chronic comorbid conditions, and concurrent medications. Demographics were self-reported data recorded in the VHA databases. Chronic comorbid conditions were confirmed using ICD-9/10-CM codes from outpatient and inpatient records. Concurrent medications were identified from the data of prescription history within 1 year before the first ETT test (including the first ETT test). All data were at the individual level, except for the income data, which was median income data at the zip code level based on the census data [19]. For variables that have missing values, we used 'unknown' as a category instead of simply excluding observations.

2.4. Statistical analysis

Latent class growth analysis (LCGA) is a semiparametric technique to identify distinct clusters of individuals who are similar in terms of their trajectory of a time-repeated measure [20,21]. LCGA models were fitted on historical METs from the first ETT test up to the test at least one-year before the outcome date. Although we may have the maximum of 19 years follow-up between the first and last ETT test of the specified period, we used the METs data up to the 15th year after the first METs because we didn't have enough sample size after that, which may otherwise render the estimates inaccurate and unreliable. Since no individuals had a complete METs history of 15 years or METs measure every

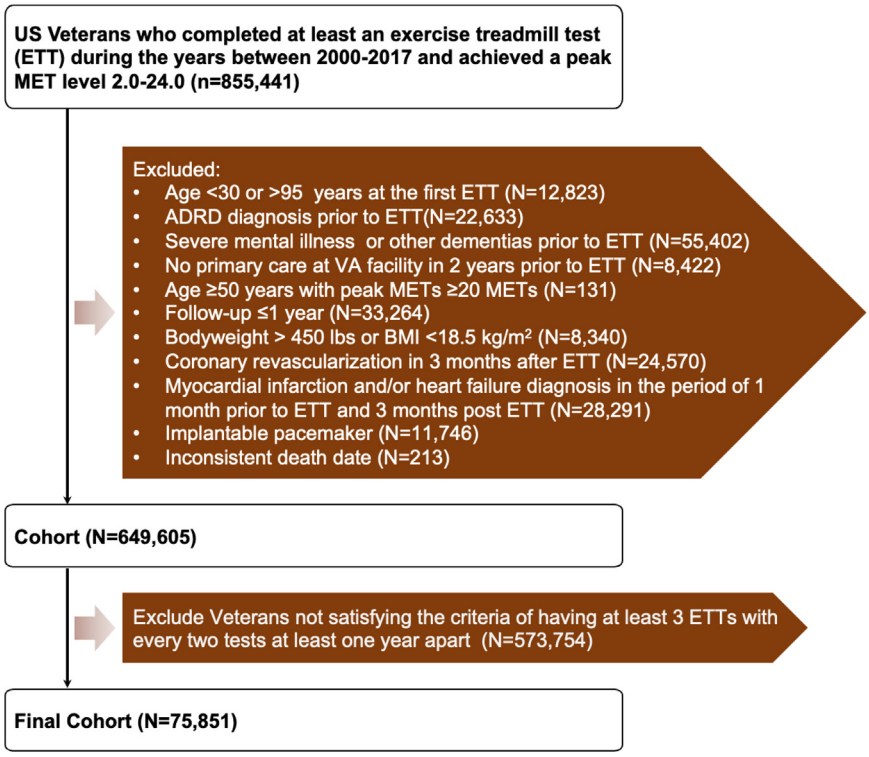

Fig. 1. Flowchart of Cohort Selection.

year, and the LCGA method tolerates incomplete longitudinal data, we used only available METs measures. We then classified individuals into joint trajectory groups of standardized METs over time.

We fit models with an increasing number of clusters from 1 to n, and selected the optimal number of clusters satisfying two conditions: 1) Bayesian Information Criterion (BIC) with lower values indicating a better fitting model; [22] and 2) the estimated average posterior probabilities of cluster membership in each trajectory class >0.7 [23]. After selecting the optimal number of clusters, an individual was assigned to the trajectory cluster to which they were most likely to belong based on the posterior membership probabilities given their observed METs history.

We compared the patient characteristics at the first ETT test across trajectory clusters. Means and SDs were reported for continuous variables, and numbers and proportions were reported for categorical variables. We evaluated the association between clusters and ADRD by unadjusted Kaplan-Meier curves. Similarly, we also plotted Kaplan-Meier curves in subgroups by age to evaluate the robustness of the association. Finally, we fit a multivariate Cox regression model of ADRD using cluster membership as an exposure with adjusting for all other covariates including demographics, chronic comorbid conditions, and concurrent medications.

We set two-tailed p-value at 0.05. All analyses were conducted in SAS 9.2. All VHA data are saved in the VA Informatics and Computing Infrastructure (VINCI) system, which is not sharable for public use.

3. Results

3.1. Baseline characteristics

We initially identified 855,441 Veterans who completed at least one ETT during 2000–2017 with results of valid METs value between 2.0 and 24.0. After executing the inclusion/exclusion criteria, we obtained a final cohort of 75,851 veterans who had at least 3 ETTs with every two tests at least one year apart. (Fig. 1)

A total of 75,851 Veterans were included in the study. The average follow-up duration was 11.3±4.1 years, with a median follow-up of 11.0 years and first quartile to third quartile the range of 8.1–14.6 years. Average number of ETTs was 4.0±1.8, with the mean gap between first and last tests of 6.5±3.8 years. We identified five trajectory clusters (Group 1: n = 22,485; Group 2: n = 22,694, Group 3: n = 6691; Group 4: n = 19,386; Group 5: n = 4595) in LCGA models according to the specified selection rule. As shown in Fig. 2, x-axis indicates years from the first ETT, y-axis indicates standardized METs, and trajectories indicate the mean of standardized METs of each cluster. All groups except for Group 3 shared a similar trajectory pattern, stable with slight improvement or decline over time, with the only difference being in the first standardized METs value at Year 0. However, Group 3 declined substantially from a relatively high to low METs.

We compared patient characteristics at the first ETT between the five groups (Table 2). The average METs scores were 4.7±1.5, 7.2±1.7, 10.1±1.8, 10.3±1.8, and 12.9±2.0 for Groups 1 through 5, respectively. Group 1 were oldest with mean age of 61 years, followed by Group 2 and 5 with mean age around 60 years, and Group 3 and 4 with mean age of 59 years. Except for more Hispanics in Group 3, the sex and race distribution in the 5 groups were similar. A higher proportion of patients living in rural areas was in Group 4, while it was lower in Groups 1 and 5. From Group 1 to Group 5, there was a trend of increasing proportion of patients who were married, had higher income, demonstrated higher CRF level, lower BMI value, and had fewer comorbid conditions or were under medicine treatment.

3.2. Incidence of ADRD

Among 75,851 Veterans, 5736 (7.6 %; 6.7 per 1000 person-years) developed ADRD during the follow-up period: Group 1 (8.3 %; 8.0 per 1000 person-years), Group 2 (8.0 %; 7.1 per 1000 person-years), Group 3 (7.6 %; 6.1 per 1000 person-years), Group 4 (6.5 %; 5.4 per 1000 person-years), and Group 5 (6.1 %; 5.1 per 1000 person-years).

3.3. Kaplan Meier curves

Compared to group 4 with similar baseline standardized METs as Group 3, the probability of ADRD-free survival was significantly lower

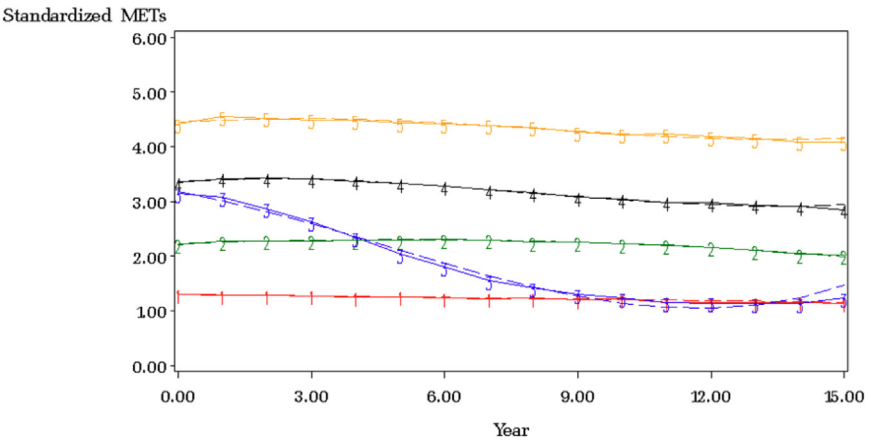

Fig. 2. Joint Trajectory Clusters.

Table 2
Patient Characteristics at the First ETT.

		Group 1		Group 2		Group 3		Group 4		Group 5	
		n = 22,485		*n* = 22,694		*n* = 6691		*n* = 19,386		*n* = 4595	
		Mean/N	SD/ %	Mean/N	SD/ %	Mean/N	SD/ %	Mean/N	SD/ %	Mean/N	SD/ %
Original METs		4.7	1.5	7.2	1.7	10.1	1.8	10.3	1.8	12.9	2.0
Standardized METs		1.3	0.5	2.2	0.6	3.3	0.6	3.4	0.6	4.5	0.7
Age		61.2	10.0	60.7	10.0	59.0	9.4	59.1	9.7	60.4	9.7
Sex	F	930	4.1 %	953	4.2 %	255	3.8 %	711	3.7 %	208	4.5 %
	M	21,555	95.9 %	21,741	95.8 %	6436	96.2 %	18,675	96.3 %	4387	95.5 %
Race	White	17,203	76.5 %	17,171	75.7 %	5156	77.1 %	14,639	75.5 %	3501	76.2 %
	Black	3630	16.1 %	3679	16.2 %	1045	15.6 %	3026	15.6 %	558	12.1 %
	Others	540	2.4 %	560	2.5 %	174	2.6 %	529	2.7 %	154	3.4 %
	Unknown	1112	4.9 %	1284	5.7 %	316	4.7 %	1192	6.1 %	382	8.3 %
Ethnicity	Non-Hispanics	20,623	91.7 %	20,669	91.1 %	6023	90.0 %	17,492	90.2 %	4102	89.3 %
	Hispanics	1100	4.9 %	1073	4.7 %	451	6.7 %	1046	5.4 %	256	5.6 %
	Unknown	762	3.4 %	952	4.2 %	217	3.2 %	848	4.4 %	237	5.2 %
Marital Status	Married	10,977	48.8 %	12,074	53.2 %	3627	54.2 %	11,356	58.6 %	2754	59.9 %
	Divorced\Single\Widowed	11,499	51.1 %	10,594	46.7 %	3063	45.8 %	7971	41.1 %	1824	39.7 %
	Unknown	9	0.0 %	26	0.1 %	1	0.0 %	59	0.3 %	17	0.4 %
Living Area	Urban	16,708	74.3 %	15,784	69.6 %	4590	68.6 %	13,084	67.5 %	3325	72.4 %
	Rural	3172	14.1 %	4074	18.0 %	1206	18.0 %	3875	20.0 %	697	15.2 %
	Unknown	2605	11.6 %	2836	12.5 %	895	13.4 %	2427	12.5 %	573	12.5 %
Income	1st Quartile	5144	22.9 %	5129	22.6 %	1555	23.2 %	4264	22.0 %	866	18.8 %
	2nd Quartile	5323	23.7 %	5385	23.7 %	1620	24.2 %	4477	23.1 %	894	19.5 %
	3rd Quartile	5670	25.2 %	5608	24.7 %	1687	25.2 %	4654	24.0 %	1104	24.0 %
	4th Quartile	6183	27.5 %	6359	28.0 %	1777	26.6 %	5834	30.1 %	1697	36.9 %
	Unknown	165	0.7 %	213	0.9 %	52	0.8 %	157	0.8 %	34	0.7 %
Age-sex-specific CRF	Lowest	12,395	55.1 %	1775	7.8 %	25	0.4 %	149	0.8 %	15	0.3 %
	Low	7561	33.6 %	5515	24.3 %	87	1.3 %	373	1.9 %	16	0.3 %
	Moderate	1978	8.8 %	9796	43.2 %	825	12.3 %	1340	6.9 %	38	0.8 %
	High	502	2.2 %	5105	22.5 %	3182	47.6 %	8277	42.7 %	123	2.7 %
	Highest	49	0.2 %	503	2.2 %	2572	38.4 %	9247	47.7 %	4403	95.8 %
BMI		30.0	6.1	29.6	5.1	28.8	4.5	28.4	4.2	26.9	3.5
Comorbidities	Anemia	4033	17.9 %	2821	12.4 %	625	9.3 %	1723	8.9 %	383	8.3 %
	Arthritis	8977	39.9 %	7874	34.7 %	2185	32.7 %	5779	29.8 %	1348	29.3 %
	Cancer	6019	26.8 %	5055	22.3 %	1192	17.8 %	3301	17.0 %	850	18.5 %
	Chronic Kidney disease	1864	8.3 %	1171	5.2 %	290	4.3 %	645	3.3 %	123	2.7 %
	Depression	7106	31.6 %	6518	28.7 %	1884	28.2 %	4955	25.6 %	1081	23.5 %
	Diabetes	8174	36.4 %	7283	32.1 %	1908	28.5 %	4449	22.9 %	700	15.2 %
	Hypertension	17,181	76.4 %	17,151	75.6 %	4816	72.0 %	13,192	68.0 %	2792	60.8 %
	Hyperlipidemia	15,293	68.0 %	16,103	71.0 %	4588	68.6 %	13,365	68.9 %	3117	67.8 %
	TBI	296	1.3 %	212	0.9 %	56	0.8 %	171	0.9 %	42	0.9 %
	Asthma/COPD	6144	27.3 %	4507	19.9 %	1153	17.2 %	2674	13.8 %	573	12.5 %
	Cardiovascular Diseases	10,794	48.0 %	11,745	51.8 %	3423	51.2 %	9592	49.5 %	2149	46.8 %
Medicines	Statins	12,498	55.6 %	13,250	58.4 %	3754	56.1 %	10,526	54.3 %	2354	51.2 %
	Hypoglycemics	6767	30.1 %	5768	25.4 %	1461	21.8 %	3193	16.5 %	455	9.9 %
	Cardiac/antihypertensives	16,956	75.4 %	17,554	77.4 %	5096	76.2 %	13,718	70.8 %	2903	63.2 %

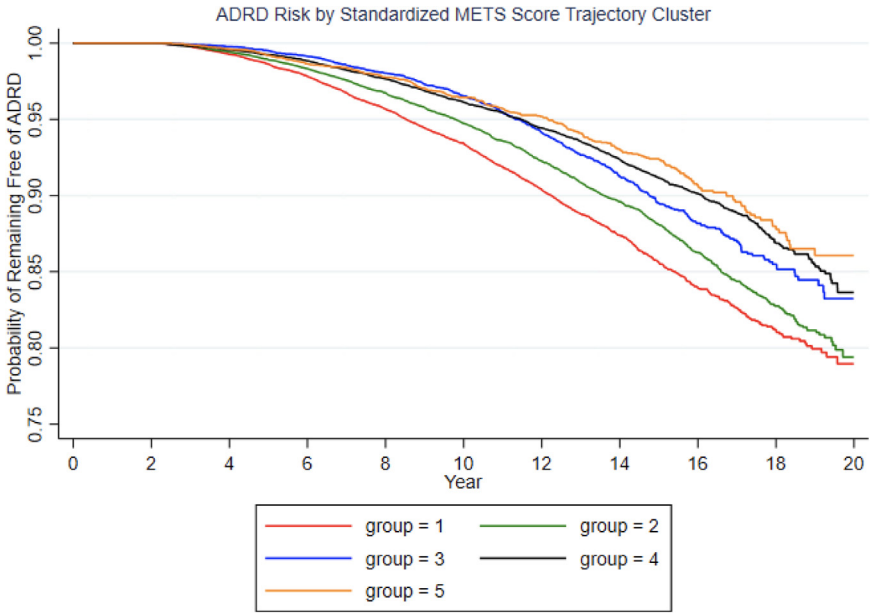

Fig. 3. Unadjusted Kaplan Meier in the Overall.

for those in Group 3. However, Group 3 continued to perform better than the groups (Group 1 and 2) that had lower baseline and equivalent endpoint standardized METs. This pattern was consistent in both overall and age-specific subgroups (Fig. 3 and 4).

3.4. Unadjusted and multivariable adjusted cox regression models

In both unadjusted and adjusted Cox Regression models, the results confirmed what we observed from the Kaplan Meier curves (Fig. 5). Using Group 1 as the reference group, Group 3 had a 12 % lower risk of developing ADRD (HR = 0.88; 95 % CI: 0.77 – 1.01; $p = 0.0660$) after adjusting for all other covariates. In comparison, Group 2 reduced the risk by 10 %, Group 4 by 17 %, and Group 5 by 24 %.

4. Discussion

4.1. Significance

Prevention and management of ADRD remain challenging, as neurodegenerative conditions are inexorably progressive. Any measures that may slow cognitive decline are welcome. Up until recently, only symptomatic medications were approved for Alzheimer's disease – the most common cause of dementia within the ADRD spectrum [24]. Currently, three disease-modifying anti-amyloid monoclonal antibodies have been approved by the United States Food and Drug Administration [25,26]. Their benefit, though welcome, is limited, and they carry a notable risk of severe complications requiring close monitoring and management. Non-pharmacological strategies have been proposed with mixed results [27,28]. Nonetheless exercise is believed to have the strongest supportive data [29]. However, accurately measuring the impact of exercise in epidemiological studies is challenging. Even when performed under controlled conditions in randomized controlled trials, the level of effort expended in any session can vary from day to day. Measuring cardiorespiratory fitness using METs can provide a reliable common currency of health level and risk of ADRD across locations and populations.

Several studies have explored the potential benefits of CRF for health in general and against ADRD specifically [7,30]. CRF is "one of the most important correlates of overall health status and a potent predictor of an individual's future risk of cardiovascular disease."[31] CRF more powerfully predicts risk for adverse health outcomes than traditional risk factors such as hypertension, smoking, obesity, and lipid abnormalities. CRF is also associated with reduced mortality [32].

Several factors affect CRF including genetics, sex, and age. Exercise is the only modifiable factor that can improve CRF. In a prior study, we demonstrated a graded inverse relationship of incidence of ADRD with CRF level in a large population of veterans followed up to 20 years [7]. Our goal in this study was to determine if a decline in CRF to a lower fitness group resulted in acquisition of the same ADRD risk as the lower fitness group or maintained some level of protection.

In this study we applied LCGA, an unsupervised machine learning approach, to identify trajectory clusters of standardized METs changes. Identifying these clusters may help clinicians understand the course of fitness change and its relation to ADRD risk, which can be used to develop more targeted interventions for delaying the onset of ADRD. We identified five distinct trajectory patterns of standardized METs. Among these, four patterns exhibited little change over time, indicating that, after adjusting for age and sex, these groups maintained consistent fitness levels—whether relatively high or low. Conversely, only one group (Group 3), accounting for 8.8 % of the total study population, demonstrated a noticeable decline in fitness levels over the years, even with adjustments for age and sex.

Consistent with previous research, the groups that maintained higher fitness levels were associated with a lower incidence of ADRD [7]. The group with declining fitness levels showed a higher risk of developing ADRD compared to those with similar baseline levels who maintained consistent fitness levels. Importantly, this group still exhibited a lower risk than those with both lower baseline and equivalent endpoints.

4.2. Implications

Our findings underscore the potential benefits of sustaining one's fitness level to mitigate the risk of ADRD as one ages. Additionally, having a higher level of fitness in middle to older ages (the average baseline age in the groups ranged from 59–61 years old) appears to offer protective benefits. While a decline in fitness level is linked with an increased risk, the initial higher baseline fitness provides a degree of ongoing protection against ADRD.

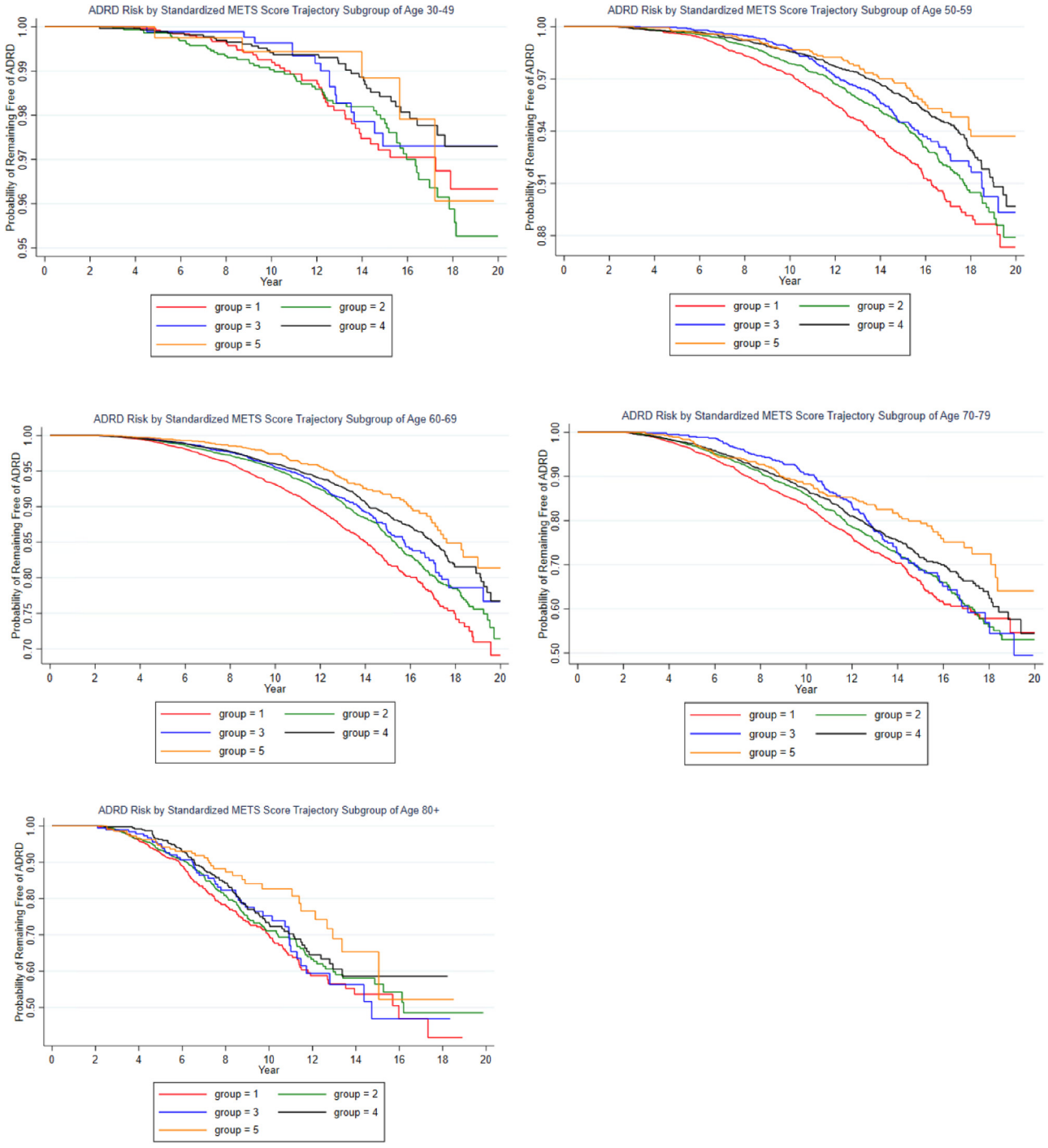

Fig. 4. Unadjusted Kaplan Meier in different age-specific subgroups.

4.3. Limitations

The majority of participants in our initial MET cohort were male and underwent fewer than three stress tests, which limited our sample size and may impact the generalizability of our findings. The performance of clustering can be evaluated by various metrics, which introduces challenges in standardizing and comparing outcomes across studies. While clustering analysis benefits from its unsupervised nature - reducing bias from predefined categories - it also lacks a reference standard. Calculating the amount of decline or the cut-off that determines an increased risk of dementia were outside the scope of this study. In addition, our study may have limited generalizability, as Veterans in our cohort are predominantly male.

4.4. Future work

In future research, we aim to incorporate social determinants of health and genetic markers to enhance our analyses. Additionally, we plan to utilize biomarkers of ADRD to refine the phenotyping process. By integrating these factors, we hope to better understand the complex interactions that contribute to ADRD risk and develop more targeted prevention strategies.

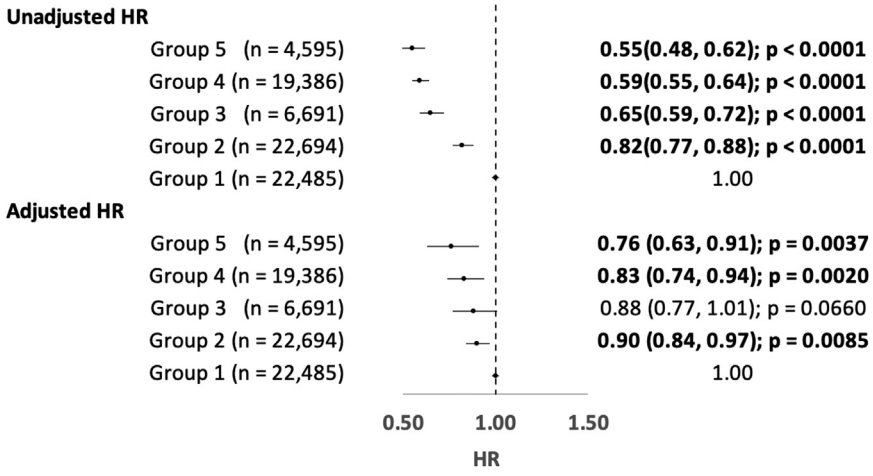

Fig. 5. Unadjusted and Adjusted Hazard Ratio for Risk of ADRD.

5. Conclusion

These findings indicate that a decrease in CRF increases risk of ADRD and starting at a higher CRF offers protection, even if CRF subsequently declines. Prospective, longitudinal, biomarker-based studies are needed to validate our findings.

Authorship

All authors had access to data output and roles in the writing of the manuscript.

Declaration of generative AI and AI-assisted technologies in the writing process

I confirm that I have not used any AI in the writing process.

Declaration of competing interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Qing Zeng-Treitler reports financial support was provided by National Institute on Aging. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Edward Zamrini: Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization. **Yan Cheng:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Peter Kokkinos:** Supervision, Investigation, Funding acquisition, Conceptualization. **Charity J Morgan:** Validation, Resources. **Charles Faselis:** Resources. **Helen M Sheriff:** Project administration. **Yijun Shao:** Data curation. **Xuemei Sui:** Writing – review & editing. **Ali Ahmed:** Writing – review & editing. **Qing Zeng:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization.

Acknowledgement

The authors thank the US Department of Veteran Affairs for providing data and analytical software support. This work was supported by the grant of NIA 3RF1AG069121–01S1. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Veterans Health Administration.

References

[1] Mortality 2018-2021 on CDC WONDER Online Database. Centers for Disease Control and Prevention, National Center for Health Statistics. National Vital Statistics System. Accessed December 13, 2023. http://wonder.cdc.gov/ucd-icd10expanded.html.

[2] Goren A, Montgomery W, Kahle-Wrobleski K, Nakamura T, Ueda K. Impact of caring for persons with Alzheimer's disease or dementia on caregivers' health outcomes: findings from a community based survey in Japan. BMC Geriatr 2016;16:122 Jun 10. doi:10.1186/s12877-016-0298-y.

[3] Rattinger GB, Schwartz S, Mullins CD, et al. Dementia severity and the longitudinal costs of informal care in the Cache County population. Alzheimers Dement 2015;11(8):946–54 Aug. doi:10.1016/j.jalz.2014.11.004.

[4] Livingston G, Huntley J, Liu KY, Costafreda SG, Selbæk G, Alladi S, Ames D, Banerjee S, Burns A, Brayne C, Fox NC, Ferri CP, Gitlin LN, Howard R, Kales HC, Kivimäki M, Larson EB, Nakasujja N, Rockwood K, Samus Q, Shirai K, Singh-Manoux A, Schneider LS, Walsh S, Yao Y, Sommerlad A, Mukadam N. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. Lancet. 2024;404(10452):572–628 Aug 10Epub 2024 Jul 31. PMID: 39096926. doi:10.1016/S0140-6736(24)01296-0.

[5] Kane RL, Butler M, Fink HA, et al. Interventions to prevent age-related cognitive decline, mild cognitive impairment, and clinical Alzheimer's-Type dementia, Rockville (MD): Agency for Healthcare Research and Quality (US); 2017. Report No.: 17-EHC008-EF.

[6] Tari AR, Nauman J, Zisko N, et al. Temporal changes in cardiorespiratory fitness and risk of dementia incidence and mortality: a population-based prospective cohort study. Lancet Public Health 2019;4(11):e565–74 Nov. doi:10.1016/S2468-2667(19)30183-5.

[7] Cheng Y, Zamrini E, Faselis C, et al. Cardiorespiratory fitness and risk of Alzheimer's disease and related dementias among American veterans. Alzheimers Dement 2023;19(10):4325–34 Oct. doi:10.1002/alz.12998.

[8] Liu R, Sui X, Laditka JN, et al. Cardiorespiratory fitness as a predictor of dementia mortality in men and women. Med Sci Sports Exerc. 2012;44(2):253–9 Feb. doi:10.1249/MSS.0b013e31822cf717.

[9] Demurtas J, Schoene D, Torbahn G, et al. Physical activity and exercise in mild cognitive impairment and dementia: an Umbrella Review of Intervention and observational studies. J Am Med Dir Assoc. Oct 2020;21(10):1415–1422.e6. doi:10.1016/j.jamda.2020.08.031.

[10] Jette M, Sidney K, Blumchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. Clin Cardiol. 1990;13(8):555–65 Aug. doi:10.1002/clc.4960130809.

[11] Meng Q, Lin MS, Tzeng IS. Relationship between exercise and Alzheimer's Disease: a narrative literature review. Front Neurosci 2020;14:131. doi:10.3389/fnins.2020.00131.

[12] Smith PJ. Pathways of prevention: a scoping review of dietary and exercise interventions for neurocognition. Brain Plast 2019;5(1):3–38 Dec 26. doi:10.3233/BPL-190083.

[13] IC T-B, Iliffe S, Cerga-Pashoja A, Lowery D, Warner J. The effect of exercise on behavioral and psychological symptoms of dementia: towards a research agenda. Int Psychogeriatr Jul 2012;24(7):1046–57. doi:10.1017/S1041610211002365.

[14] HL NN, Page MG, Katz J, et al. Trajectory modelling techniques useful to epidemiological research: a comparative narrative review of approaches. Clin Epidemiol 2020;12:1205–22. doi:10.2147/CLEP.S265287.

[15] Lee CL, Liu WJ, Chen CH, Wang JS. Associations of long-term physical activity trajectories with all-cause mortality in a general population. Int J Public Health 2023;68:1605332. doi:10.3389/ijph.2023.1605332.
[16] Washington DL, Gray K, Hoerster KD, et al. Trajectories in physical activity and sedentary time among Women Veterans in the Women's Health Initiative. Gerontologist 2016;56(Suppl 1):S27–39 Feb. doi:10.1093/geront/gnv676.
[17] Berlin KS, Parra GR, Williams NA. An introduction to latent variable mixture modeling (part 2): longitudinal latent class growth analysis and growth mixture models. J Pediatr Psychol 2014;39(2):188–203 Mar. doi:10.1093/jpepsy/jst085.
[18] Early-Onset Alzheimer's Disease. Johns Hopkins Medicine. Accessed July 23, 2024. https://www.hopkinsmedicine.org/health/conditions-and-diseases/alzheimers-disease/earlyonset-alzheimer-disease#:~:text=Alzheimer%20disease%20commonly%20affects%20older,in%20their%2030s%20or%2040s.
[19] Income Data. https://www.census.gov/topics/income-poverty/income/data.html.
[20] Buta E, Gordon KS, Gueorguieva R, et al. Joint longitudinal trajectories of pain intensity and opioid prescription in veterans with back pain. Pharmacoepidemiol Drug Saf 2022;31(12):1262–71 Dec. doi:10.1002/pds.5531.
[21] Andruff H, Carraro N, Thompson A, Gaudreau P. Latent class growth modelling: a tutorial. Tutor Quant Methods Psychol 2009;5(1):11–24.
[22] Stoica P, Selen Y. Model-order selection: a review of information criterion rules. IEEE Signal Process Mag 2004(July):36–47.
[23] Nagin D. Group-based modeling of development. Harvard University Press; 2009.
[24] Alzheimer's: medicines help manage symptoms and slow decline. Mayo Clinic; 2024. Accessed June 25 https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/in-depth/alzheimers/art-20048103.
[25] Wu W, Ji Y, Wang Z, et al. The FDA-approved anti-amyloid-beta monoclonal antibodies for the treatment of Alzheimer's disease: a systematic review and meta-analysis of randomized controlled trials. Eur J Med Res 2023;28(1):544 Nov 28. doi:10.1186/s40001-023-01512-w.
[26] Cummings J, Osse AML, Cammann D, Powell J, Chen J. Anti-amyloid monoclonal antibodies for the treatment of Alzheimer's disease. BioDrugs 2024;38(1):5–22 Jan. doi:10.1007/s40259-023-00633-2.
[27] Wang LY, Pei J, Zhan YJ, Cai YW. Overview of meta-analyses of five non-pharmacological interventions for Alzheimer's Disease. Front Aging Neurosci 2020;12:594432. doi:10.3389/fnagi.2020.594432.
[28] Li X, Ji M, Zhang H, et al. Non-drug therapies for Alzheimer's Disease: a review. Neurol Ther. 2023;12(1):39–72 Feb. doi:10.1007/s40120-022-00416-x.
[29] De la Rosa A, Olaso-Gonzalez G, Arc-Chagnaud C, et al. Physical exercise in the prevention and treatment of Alzheimer's disease. J Sport Health Sci. 2020;9(5):394–404 Sep. doi:10.1016/j.jshs.2020.01.004.
[30] Lee DC, Artero EG, Sui X, Blair SN. Mortality trends in the general population: the importance of cardiorespiratory fitness. J Psychopharmacol. 2010;24(4 Suppl):27–35 Nov. doi:10.1177/1359786810382057.
[31] Kaminsky LA, Arena R, Beckie TM, et al. The importance of cardiorespiratory fitness in the United States: the need for a national registry: a policy statement from the American Heart Association. Circulation 2013;127(5):652–62 Feb 5. doi:10.1161/CIR.0b013e31827ee100.
[32] Kokkinos P, Faselis C, Samuel IBH, et al. Changes in cardiorespiratory fitness and survival in patients with or without cardiovascular disease. J Am Coll Cardiol 2023;81(12):1137–47 Mar 28. doi:10.1016/j.jacc.2023.01.027.