Cardiorespiratory Fitness: A Protective Factor Against Alzheimer's Disease and Related Dementias

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Outline

- The problem of ADRD
- Potential solutions
- One potential partial solution
  - Spoiler alert: Take home message: Cardiorespiratory fitness has a graded, incremental inverse relationship to onset of ADRD
- Work to be done

The Problem

Alzheimer’s Disease and Related Dementias

- Over 55 million people with ADRD worldwide
- Anticipated to reach 78 million by 2030, 139 million by 2050
- Annual global cost US$1.3 Trillion
- Expected to reach US$2.8 Trillion by 2030
- Life expectancy: 3-11+ years

Possible Solutions

Management of ADRD is complicated

- Clinical
  - Pathology may be too advanced
  - BUT buying time may be a meaningful outcome
- Symptomatic
  - Even as you treat symptoms, disease progresses
- Pharmacological strategies

- Pre-Clinical
  - Variety of pathologies
  - How to detect? Enter biomarkers
- Disease Modifying Therapy
  - May not improve symptoms, but slow progression
- Non-Pharmacological strategies

For the greatest impact on long-term outcomes in ADRD, prevention strategies are key

Lancet Commission 2020 report, listed 12 risk factor life-course model of prevention.

Which is not a risk factor in the Lancet Commission list?

Less education,

Hearing impairment,

Diabetes,

Light walking,

Air pollution,

Updated 12 risk factor life-course model of dementia prevention

- less education,
- hypertension,
- hearing impairment,
- smoking,
- obesity,
- depression,
- physical inactivity,
- diabetes,
- low social contact,
- excessive alcohol consumption,
- traumatic brain injury, and
- air pollution

Livingston, Lancet 2020; 396: 413–46

AHRQ has identified XXXXXXXXXXXX as the only lifestyle intervention with plausible mechanistic evidence of dementia risk reduction: XXXXXXXXXXXX = Which item from the list below?

- less education,
- hypertension,
- hearing impairment,
- smoking,
- obesity,
- depression,
- physical inactivity,
- diabetes,
- low social contact,
- excessive alcohol consumption,
- traumatic brain injury, and
- air pollution

The AHRQ has identified physical activity as the only lifestyle intervention with strong evidence of mechanistic plausibility to prevent ADRD.

- Longitudinal neuroimaging studies: the volume of prefrontal and hippocampal brain areas are larger in individuals who engaged in more physical activity earlier in life. (Erickson, 2012 and 2019)
- In a population-based case-control study of 1324 subjects, moderate exercise performed in midlife or late life was associated with a reduced odds of having MCI. (Geda, 2010)
- Accelerometer-measured physical activity was associated with greater total gray matter volume in a population based cohort of 2550 participants. (Fox, 2022)
- In a study of 6104 veterans, followed for 10.3±5.5 years each 1-metabolic equivalent increase in exercise capacity conferred a nearly 8% reduction in the incidence of cognitive impairment. (Muller, 2016)

Which statement is True?

- Everyone can obtain the same benefit from the same amount of exercise.
- Mild, moderate, or intense exercise are equally beneficial.
- Genetics have no bearing on exercise capacity.
- Cardiorespiratory fitness (capacity of O_2 utilization) influences exercise capacity.
- Benefits of exercise are greater late in life.

Pitfalls of measuring exercise

- Unless an objective measure is used, it is difficult to precisely quantitate exercise duration, intensity, regularity, and effectiveness.
- Even accelerometer-derived measures do not factor in genetic variation.

- Precisely quantifying modifiable risk factors is critical to designing individualized actionable preventive care plans.

Potential advantages of measuring CRF

- Cardio-Respiratory Fitness (CRF) refers to the capacity of the circulatory and respiratory systems to supply oxygen to skeletal muscle mitochondria for energy production needed during physical activity. (1)
- CRF is assessed objectively by an exercise treadmill test (ETT) and expressed in metabolic equivalents (METs; 1 MET=3.5 ml of oxygen/kg of body weight/minute).
- CRF is a robust objective measure of health that can be tracked over time and compared across age groups, populations, fitness levels. (1)
- Physical activity and CRF have an established role in reducing risk of cardiovascular disease, cancer, other morbidities, and mortality.(2)

Potential advantages of measuring CRF

- The American Heart Association recommends adding CRF as a clinical vital sign. (Ross, 2016)
- CRF is a potentially stronger predictor of mortality than established risk factors such as smoking, hypertension, high cholesterol, and type 2 diabetes mellitus.
- Insufficient data on role of CRF and ADRD.
- We assessed the association of CRF with incident ADRD in a large clinical population.

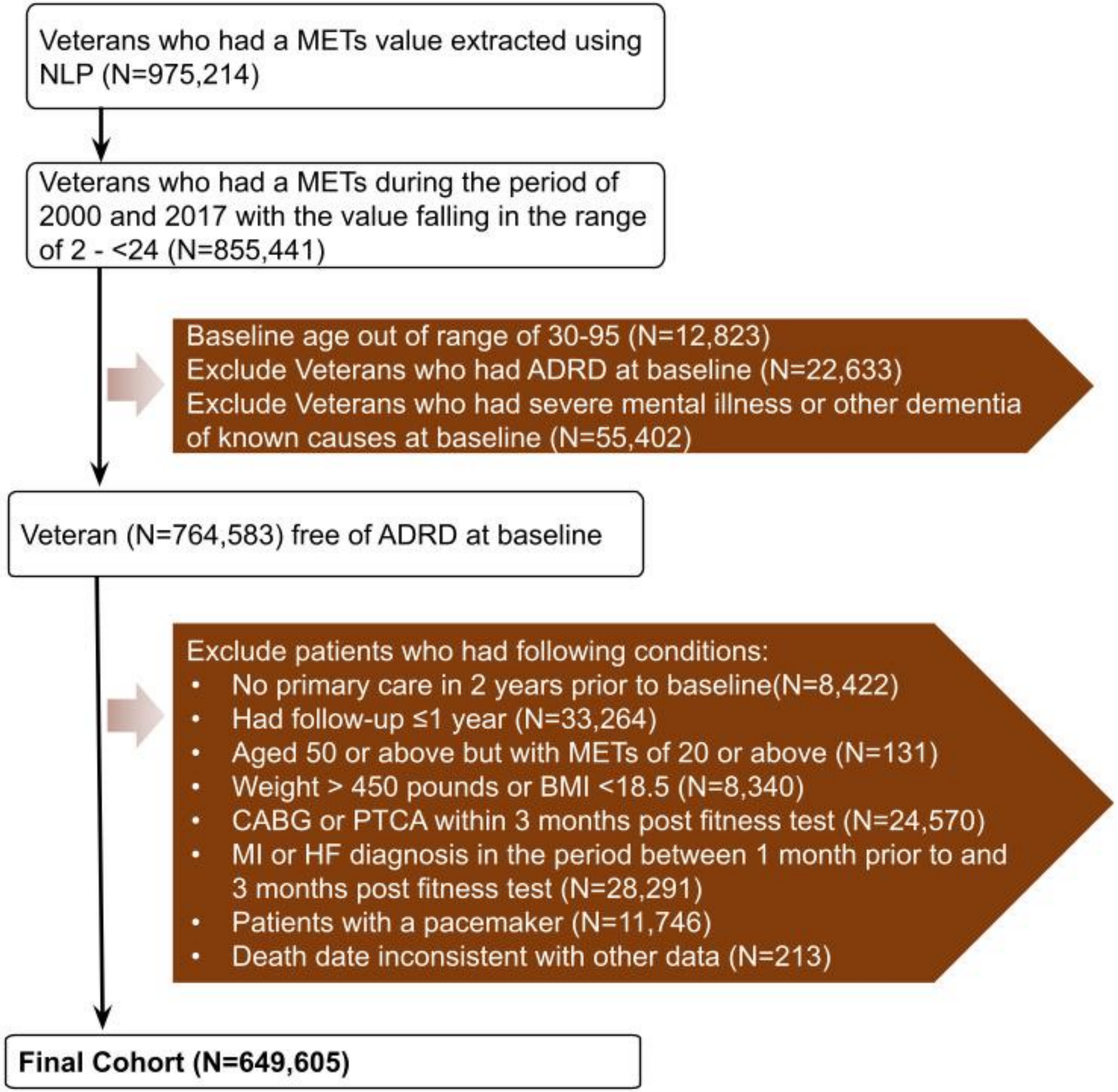


Figure 1 Flow chart displaying assembly of veteran cohort of METs and ADRD study

- We identified 649,605 Veterans (mean age 61 years old; 5.7% women; 16.6% African-Americans) free of ADRD who completed a standardized exercise tolerance test between 2000-2017, with no ischemia.
- We formed five age-and-gender-specific fitness categories based on peak metabolic equivalents (METs) achieved:
  - Least-fit (METs=3.8±0.6),
  - Low-fit (METs=5.8±1.4),
  - Moderately-fit (METs=7.5±1.5),
  - Fit (METs=9.2±1.7), and
  - High-fit (METs=11.7±2.1).
- We used multivariate Cox regression models and propensity score-matching to estimate the association.

RESULTS

- During up to 20 (ave 8.8) y. follow-up 44,105 (6.8%) participants developed ADRD (average rate 7.7/1,000 person-years).
- ADRD Incidence rate for Least-fit to High-fit categories was: 9.5, 8.5, 7.4, 7.2 and 6.4 /1000 person-years, respectively ($p<0.0001$).
- Compared to the Least-fit category, multivariable-adjusted hazard ratios (95% CI) for incident ADRD were: 0.87 (0.85–0.90), 0.80 (0.78-0.83), 0.74 (0.72-0.76), and 0.67 (0.65–0.70) respectively.

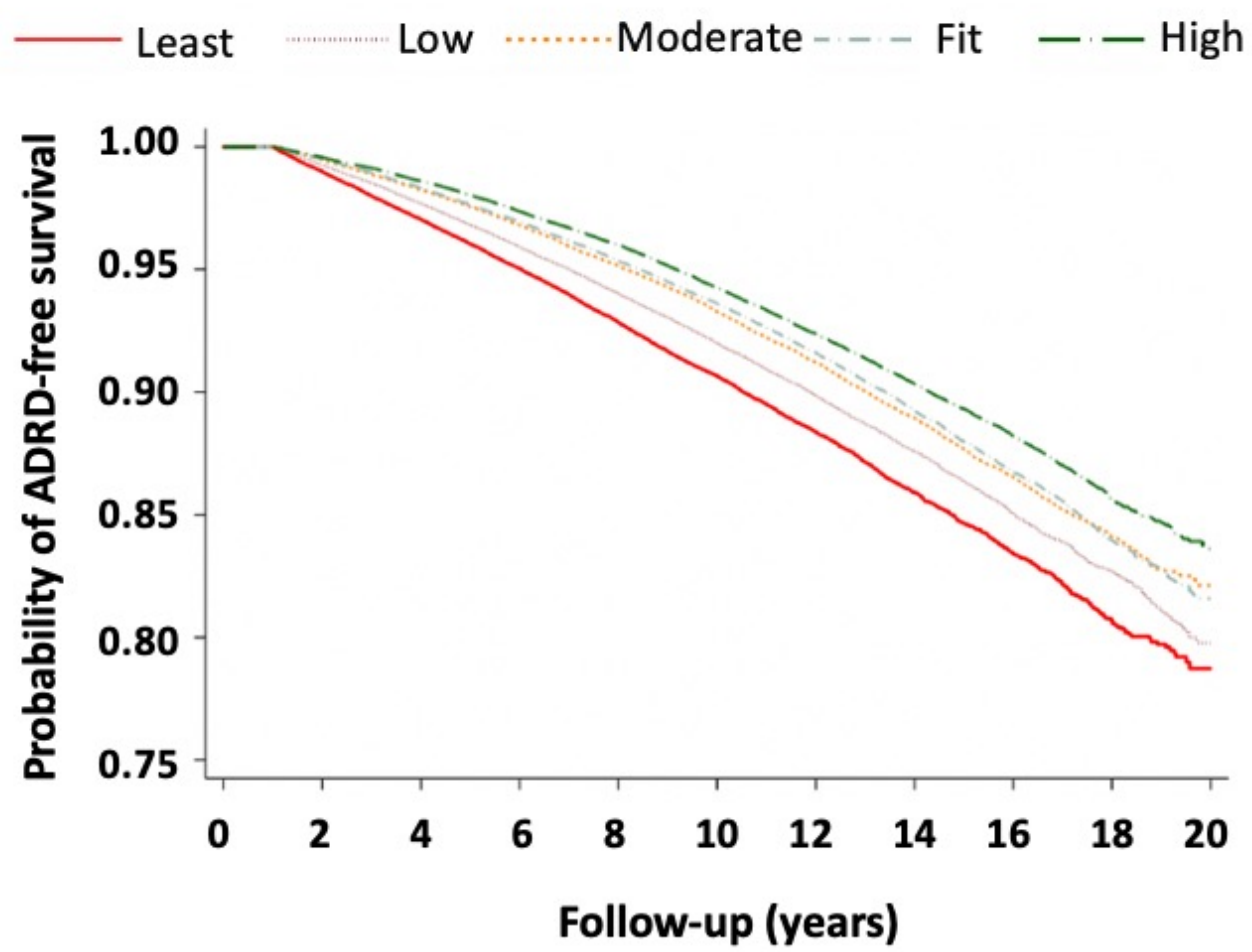
Cohort (N=649,605)

Fitness level	Rate per 1,000 person-years (events/person-years)	Hazard ratio (95% confidence interval)		
		Unadjusted	Age-sex-race-adjusted	Multivariable*-adjusted
Least-fit (N=132,634)	9.5 (9160/966178)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Low fit (N=129,493)	8.5 (9332/1103713)	0.84 (0.81-0.86): p<0.0001	0.81 (0.78-0.83): p<0.0001	0.87 (0.85-0.90): p<0.0001
Moderate fit (N=120,988)	7.4 (8132/1105981)	0.71 (0.69-0.73): p<0.0001	0.72 (0.70-0.74): p<0.0001	0.80 (0.78-0.83): p<0.0001
Fit (N=137,122)	7.2 (9430/1304546)	0.69 (0.67-0.71): p<0.0001	0.65 (0.63-0.67): p<0.0001	0.74 (0.72-0.76): p<0.0001
High-Fit (N=129,368)	6.4 (8051/1253071)	0.61 (0.59-0.63): p<0.0001	0.58 (0.56-0.59): p<0.0001	0.67 (0.65-0.70): p<0.0001
p Trend	<0.0001	<0.0001	<0.0001	<0.0001

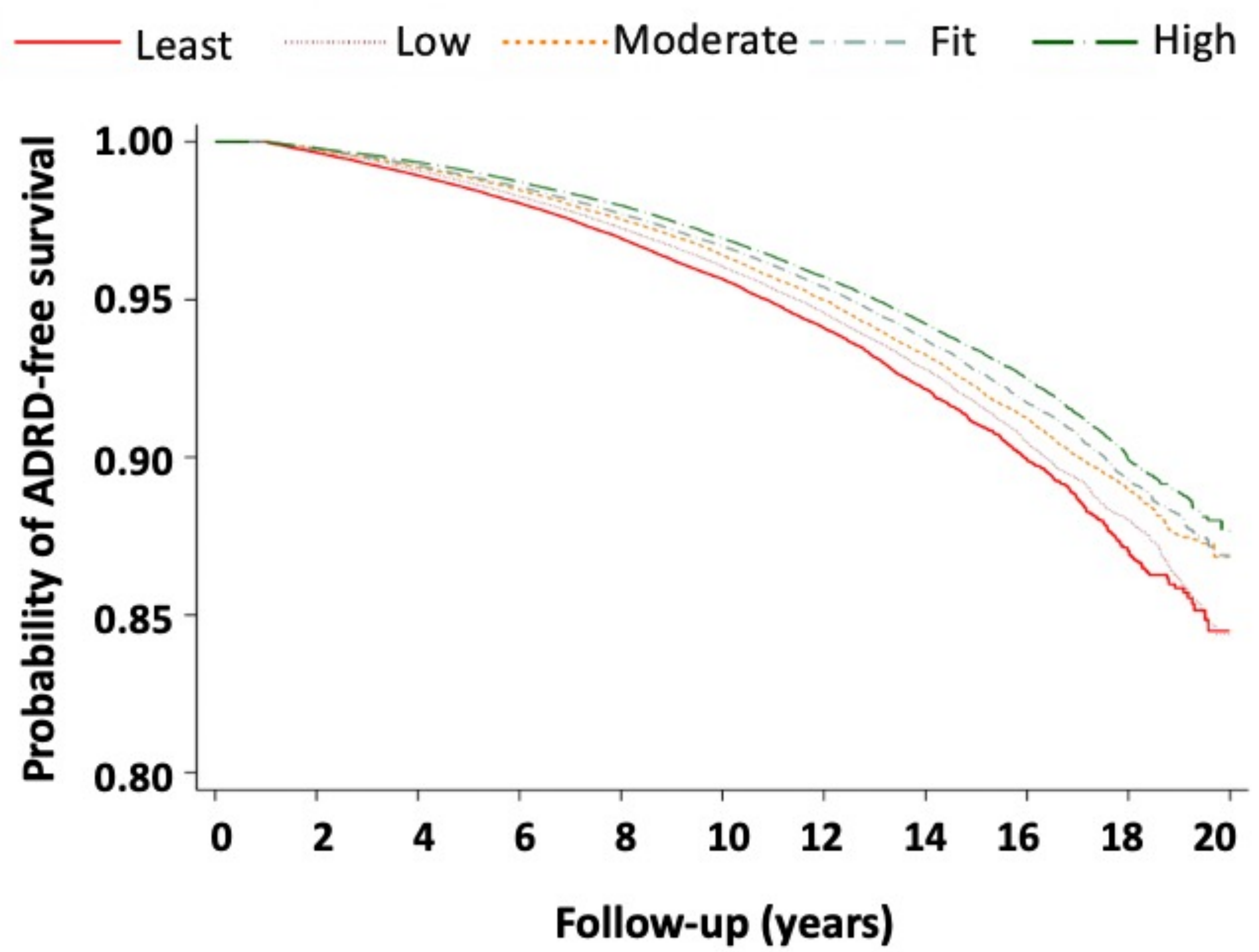
*Adjusting for age (continuous variable), gender, race, ethnicity, marital status, region, living area median income category, BMI category and comorbid conditions, and medications

Cohort (N=649,605)

Unadjusted KM Curve

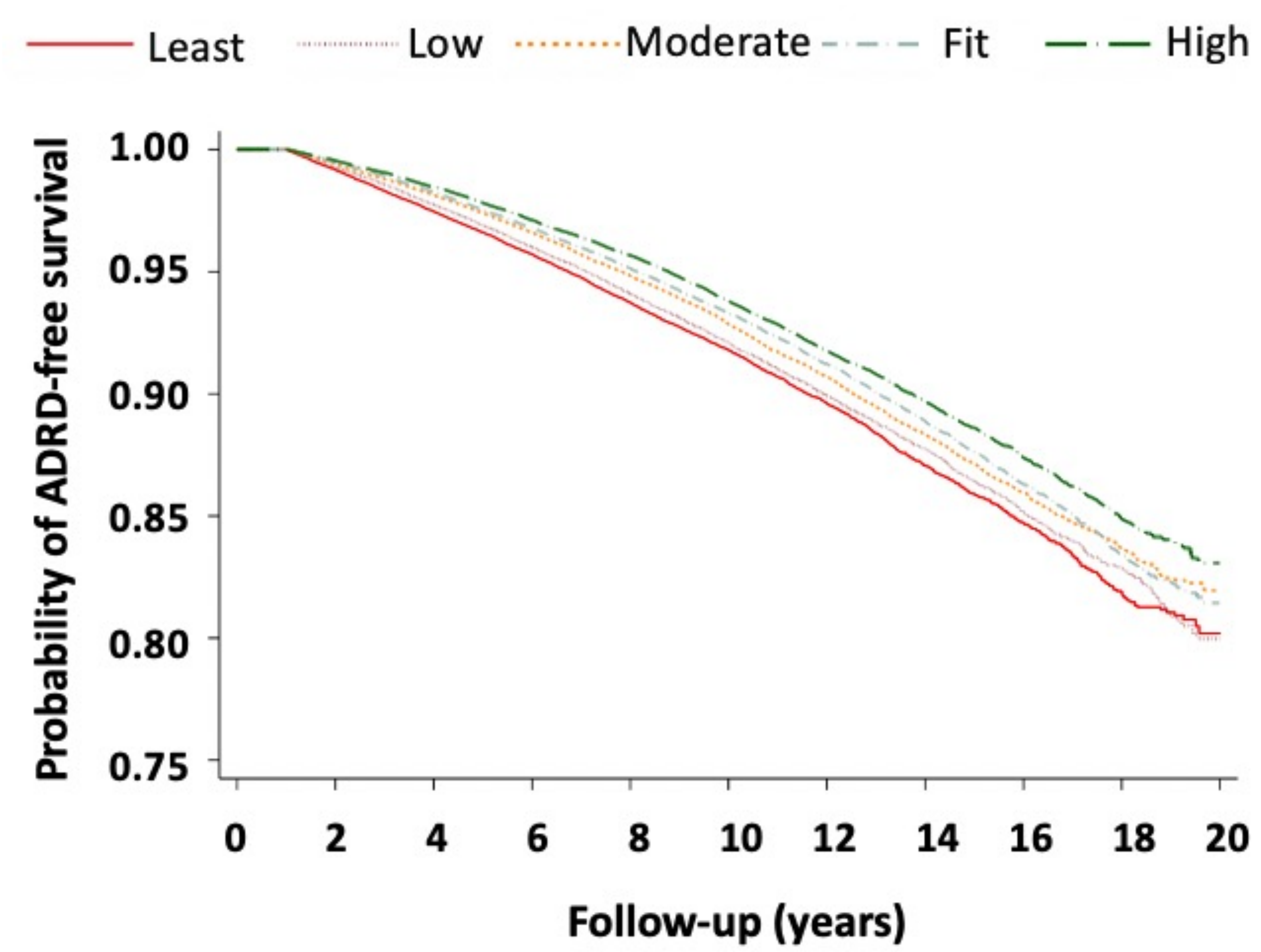


Multivariate-adjusted KM Curve



Propensity Score Matched Cohort (N=393,625)

Fitness Level	HR (95% Conference Interval)
Least-fit	1.00 (reference)
Low-fit	0.94 (0.91-0.98): p=0.0012
Moderate-fit	0.85 (0.82-0.89): p<0.0001
Fit	0.82 (0.79-0.85): p<0.0001
High-fit	0.75 (0.72-0.78): p<0.0001



Fitness	Age 50-59	Age 60-69	Age 70-79	Age 80+
Low vs Least	0.93 (0.86-0.99); p=0.0365	0.85 (0.81-0.90); p<0.0001	0.81 (0.77-0.86); p<0.0001	0.84 (0.78-0.91); p<0.0001
Moderate vs Least	0.80 (0.74-0.87); p<0.0001	0.76 (0.74-0.81); p<0.0001	0.78 (0.74-0.82); p<0.0001	0.78 (0.71-0.86); p<0.0001
Fit vs Least	0.74 (0.68-0.80); p<0.0001	0.71 (0.67-0.74); p<0.0001	0.71 (0.68-0.75); p<0.0001	0.77 (0.71-0.84); p<0.0001
High vs Least	0.67 (0.62-0.73); p<0.0001	0.61 (0.57-0.64); p<0.0001	0.67 (0.64-0.71); p<0.0001	0.72 (0.66-0.78); p<0.0001

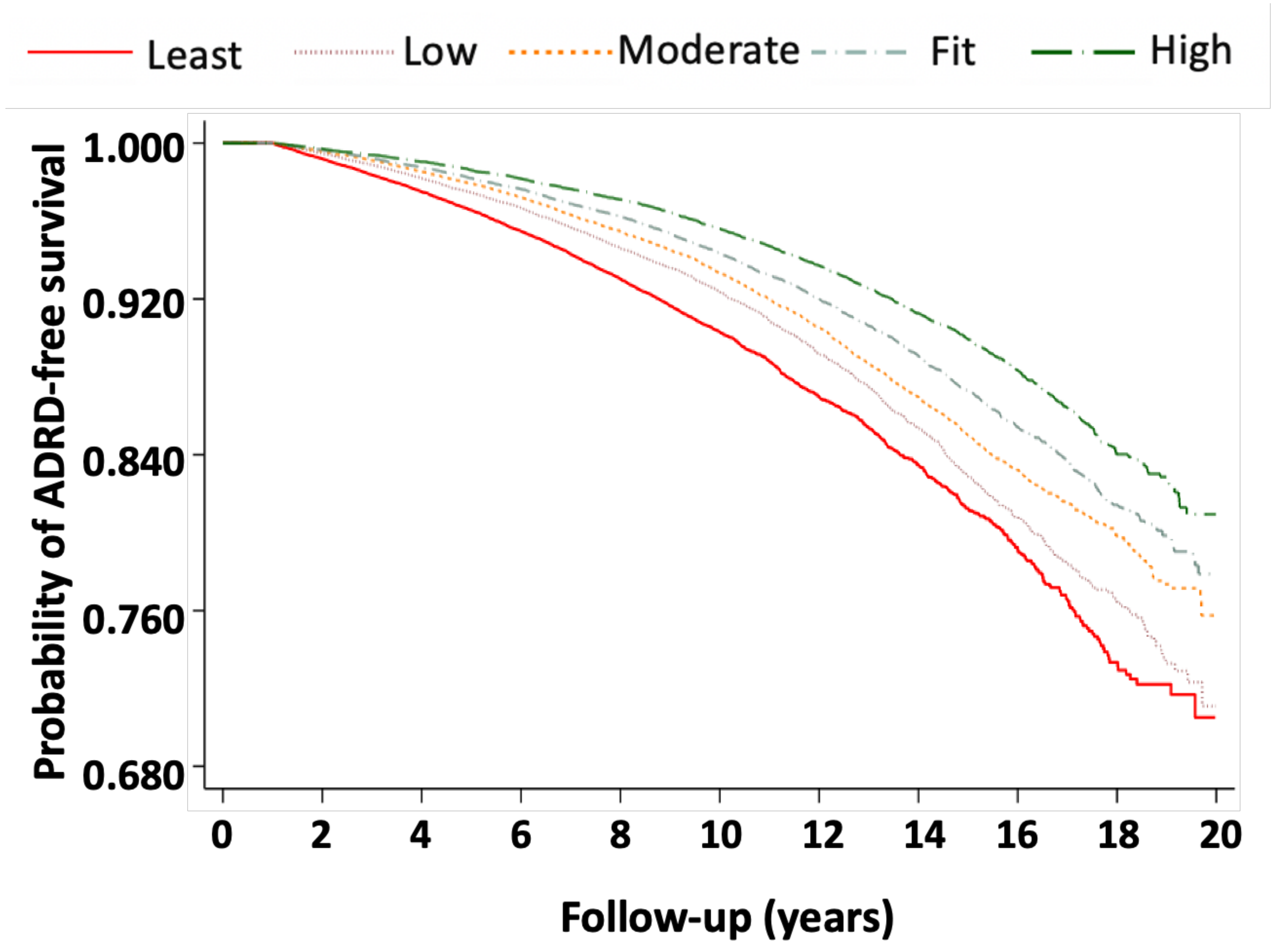


Figure e) Kaplan Meier plots of CRF in patients aged 60-69 (N=244469)

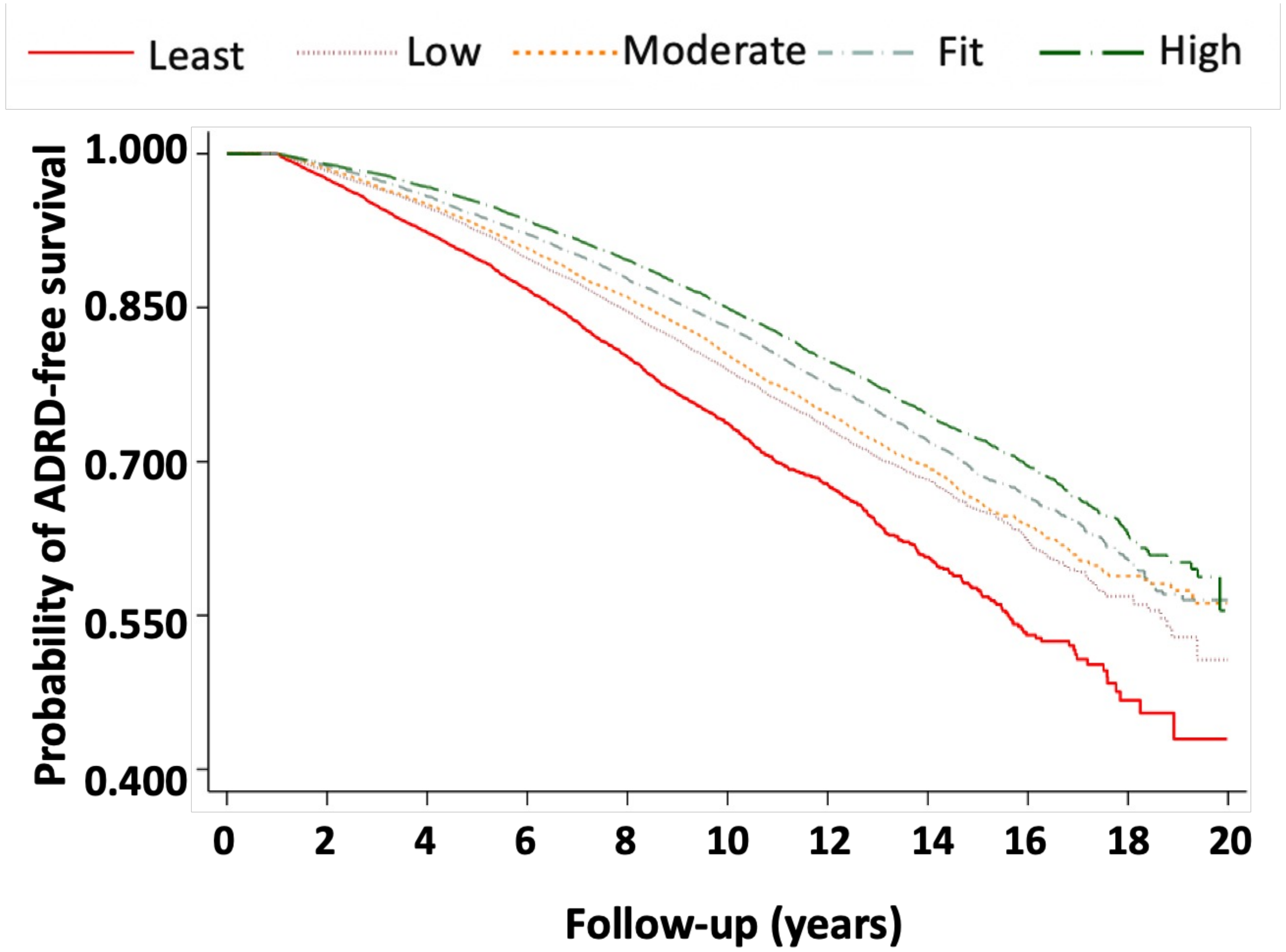


Figure f) Kaplan Meier plots of CRF in patients aged 70-79 (N=95082)

CONCLUSIONS:

- This is the largest study that examines the association between objectively determined CRF and incident ADRD in up to two decades of follow-up.
- Our finding of an independent, inverse, and graded association supports considering improving physical activities and CRF as an ADRD prevention strategy.

LIMITATIONS:

- Veterans may not be representative of the general population
- Differences between standard care and specialty dementia clinic care/ research work-up.
  - Lack of biomarkers. Biomarkers are not yet part of standard care.
  - ADRD typically underdiagnosed, but results in the diagnosed cases can still be informative.
  - AD and ADRD. Future studies can sort out biomarker-supported diagnosis and be more specific for AD vs other neurodegenerative conditions.

NEXT STEPS

- Reproduce our findings in a cohort that represents general population
- Correlate CRF with ADRD biomarkers including biofluid biomarkers, cognitive test results, imaging biomarkers, and autopsy.
- Correlate CRF with ADRD biomarkers over time in a longitudinal study.
- Identify optimal values of CRF by age that are linked to the lowest risk of AD/ADRD
- Develop and validate a deep learning-based risk prediction model to determine the optimal CRF level for individuals to achieve the lowest risk of AD/ADRD

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