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Objectively Measured Cardiorespiratory Fitness as a Potential Biomarker for Alzheimer Disease Risk in Older Adults: Evidence from the Generation 100 Study

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ABSTRACT

BRISSACH D. E., H. H. BERG, D. STENSVOLD, E. M. L. INGESTRÖM, T. L. WALKER, J. A. LAUKKANEN, T. VASANKARI, S. B. SANDO, A. R. TARI, and U. WISLØFF. Objectively Measured Cardiorespiratory Fitness as a Potential Biomarker for Alzheimer Disease Risk in Older Adults: Evidence from the Generation 100 Study. *Med. Sci. Sports Exerc.,* Vol. 58, No. 11, pp. 2423–2432, 2026. **Purpose:** Cardiorespiratory fitness is a modifiable physiological trait linked to dementia risk, but whether objectively measured peak oxygen uptake (VO_{2peak}) and short-term changes in fitness in older adults associate with Alzheimer disease (AD) remains unknown. We examined whether baseline levels and 1-yr changes in VO_{2peak} were associated with subsequent risk of AD in older adults. **Methods:** This prospective cohort study included participants from the Generation 100 study. VO_{2peak} was measured at baseline (2012–2013) and 1-yr follow-up. Participants were categorized as unfit (<80% of the sex-specific mean VO_{2peak}), moderately fit (80%–99%), or fit (≥100%). Incident AD was identified through national health registries, hospital records, and the Norwegian Prescribed Drug Registry. Cox proportional hazards models estimated associations between VO_{2peak} and incident AD. **Results:** A total of 1491 participants free from dementia, aged 70–77 yrs were included. Mean VO_{2peak} at baseline was 28.7 mL/kg/min. During a median follow-up of 8.7 yrs, 77 developed AD. Compared with unfit, moderately fit (adjusted hazard ratio 0.54, 95% confidence intervals [CI] 0.29–0.98) and fit (adjusted hazard ratio 0.52, 95% CI 0.29–0.93) participants had a lower AD risk. Each 1 mL/kg/min higher baseline VO_{2peak} was associated with a 4% lower risk of AD (HR 0.96, 95% CI 0.92–1.00). Staying above 80% of sex-specific mean VO_{2peak} (25.1 mL/kg/min for men and 20.9 mL/kg/min for women) was identified as a threshold of AD risk stratification of which below the risk increased substantially. Weaker associations were observed between 1-yr changes in VO_{2peak} and subsequent AD risk. **Conclusions:** Higher VO_{2peak} in older adults was associated with a substantially lower risk of developing AD, whereas short-term changes in fitness did not confer additional benefit. These findings suggest that entering older age with fitness >80% of sex-specific mean may be more important for reducing late-life AD risk than achieving short-term improvements after the age of 70. CRF emerged as a clinically relevant biomarker for AD that may help stratify risk and inform preventive strategies in aging populations. **Key Words:** AD PREVENTION, ALZHEIMER DISEASE, DEMENTIAS, FITNESS, OLDER ADULTS

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More than 55 million people are currently living with dementia worldwide, and this number is expected to triple by 2050 (1). Since age is the major nonmodifiable risk factor for dementia (2), the projected increase is largely due to a progressively aging population (3,4). Alzheimer disease (AD) is the most common cause of dementia, accounting for 60%–70% of all cases (2). It is a progressive neurodegenerative disorder characterized by amyloid-β plaques and tau-related neurofibrillary tangles, which together lead to synaptic dysfunction, neuronal loss, and brain atrophy (5,6). Clinically, AD presents with a gradual decline in memory and learning, accompanied by changes in thought and behavior, ultimately progressing to a loss of independence in daily life (7). The disease has profound implications for individuals, families, and health care systems. Despite major research efforts, the failure rate of AD drug development is higher than in any other disease area, and no curative or preventive treatment has yet proven effective (8). In the absence of effective AD treatment, prevention has become a public health priority (9,10). Importantly, interventions capable of delaying the onset and progression of AD by 1 yr can reduce the global prevalence of the disease by more than nine million cases in 2050 (11).

The Lancet Commission has estimated that addressing 14 modifiable risk factors, including physical inactivity, could prevent or delay nearly half of all dementia cases (10). Furthermore, observational studies suggest that cardiorespiratory fitness (CRF) is inversely associated with dementia risk. Studies show that a decline in CRF over time is linked to increased dementia risk (12,13), whereas improvements in CRF are associated with lower dementia incidence and mortality, delayed disease onset, and longer survival (14). A common limitation across these studies, however, is that CRF often was based on a single assessment (15–17), or estimated rather than objectively measured as maximal oxygen uptake (VO_{2max}) (12,14), and most have used all-cause dementia as the primary outcome (14–16). Moreover, much of the existing evidence is derived from mid- to late-life assessments (<60 yr at first assessment) (14,18). This leaves an important knowledge gap regarding whether the CRF level when entering older age and exercise interventions that improve CRF in older adults (>70 yr) can modify the risk of AD. Therefore, the aim of this study was to examine whether objectively measured CRF can be used as a biomarker for AD development, and whether 1-yr changes in CRF are associated with subsequent AD risk in older adults. Based on prior observational evidence, we hypothesized that CRF at baseline will predict future AD risk, and that improvements in CRF would be associated with a lower risk of developing AD. Furthermore, we hypothesize that a fitness threshold may exist that confers AD protection.

METHODS

Study Design and Population

This prospective cohort study is a substudy of the Generation 100 Study (ClinicalTrials.gov: NCT01666340; REC 2012/381), a randomized controlled trial that examined the effects of 5 yr supervised exercise training versus physical activity recommendations on morbidity and mortality in older adults. In 2012, all inhabitants of Trondheim, Norway, aged 70–77 yr (n = 6966) were invited to participate. A total of 1567 older adults (790 women) were included and randomized to exercise intervention or control group at baseline. Compared with invited individuals who declined to participate, those included in the study were younger, reported better overall health, and had a higher educational level (19). The study comprises clinical measurements, questionnaires on health and lifestyle, and repeated exercise testing at baseline, 1-, 3-, 5-, and 10-yrs follow-up. Detailed descriptions of study design, examination protocols, and inclusion and exclusion criteria have been published (19).

In this substudy, 1491 participants without AD or dementia were included. In total, 76 participants were excluded before analyses due to dementia related disease or death before 1-yr exercise testing (Fig. 1). We chose to use baseline and 1-yr VO_{2peak} assessments for two reasons: first, the largest changes in VO_{2peak} occurred between baseline and the 1-yr follow-up (20); and second, anchoring follow-up at the 1-yr assessment ensured sufficient observation time to achieve adequate statistical power for detecting incident AD cases. Participants were categorized as unfit (<80% of the sex-specific mean peak oxygen uptake; VO_{2peak}), moderately fit (80%–99% of the sex-specific mean VO_{2peak}) or fit (>100% of the sex-specific mean VO_{2peak}) according to VO_{2peak} at baseline, independent of randomized exercise intervention. This substudy obtained separate ethical approval (REC #183708), and all participants provided written informed consent before inclusion in the Generation 100 study.

Outcome

The primary outcome was incident AD, and the secondary outcome was incident all-cause dementia. Cases with AD and other dementia disease cases were identified by a neurologist through systematic review of hospital records from April 2021 to the end of follow-up, set at August 11, 2022. A second neurologist was conferred in uncertain cases. In addition, complete case identification was ensured by linkage to the Norwegian Cause of Death Registry and to the Norwegian Prescribed Drug Registry for dementia related deaths and dispensed antidementia medications (ATC code N06D) between January 1, 2011 and June 30, 2024. Individuals with AD or dementia related deaths or antidementia prescriptions not

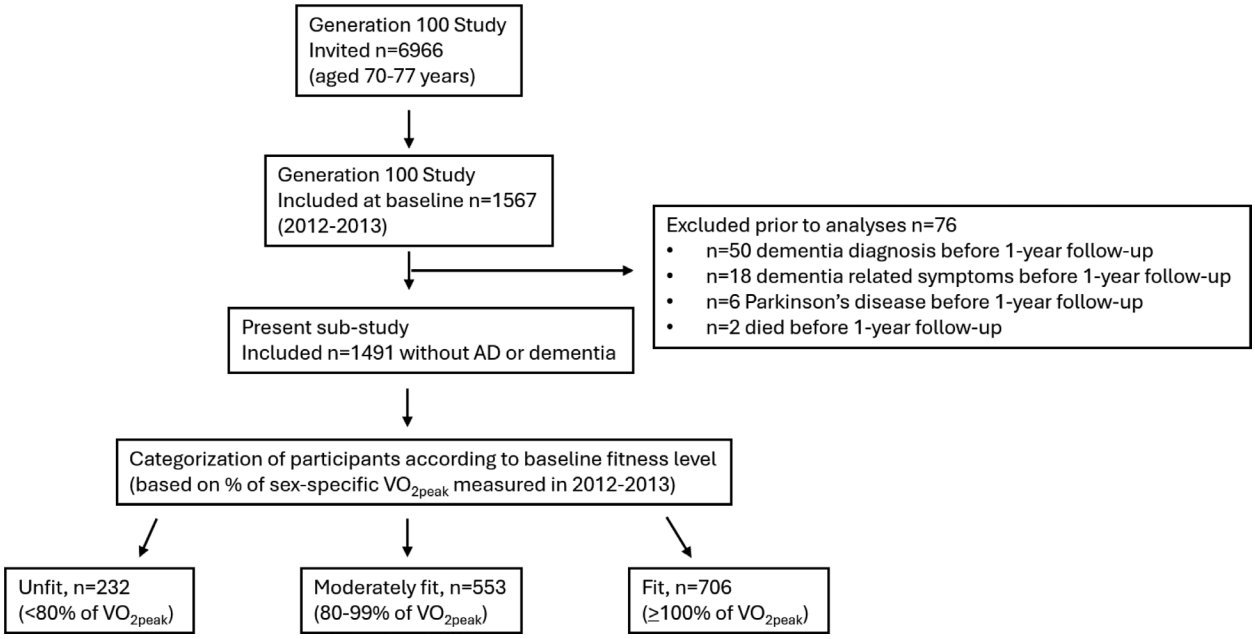


FIGURE 1—Study flowchart. Flow of participants from invitation to final analytic sample, including exclusions before the 1-yr baseline for analyses of VO_{2peak} and incident Alzheimer disease.

identified during the initial hospital record review underwent a second diagnostic validation by the neurologist. AD cases were classified as mild cognitive impairment or dementia in accordance with validated clinical criteria for AD (21,22). Non-AD dementia cases were classified using validated diagnostic criteria for Vascular cognitive disorder, Dementia with Lewy Bodies, Parkinson disease dementia and Progressive supranuclear palsy (23–26). Cases with Amyotrophic lateral sclerosis, Parkinson disease without dementia, and dementia cases with uncertain etiology were classified according to the International Classification of Disease, 10th revision.

Questionnaires and Clinical Examinations

Participants completed questionnaires on health, lifestyle, and socioeconomic factors and underwent standardized clinical measurements including height, weight, blood pressure, and venous blood sampling. Smoking exposure was quantified in pack-years, defined as the number of cigarettes per day multiplied by the number of years smoking, and categorized as never, formerly, or currently smoking. Hypertension was defined as resting systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or self-reported/register-based use of antihypertensive medication. Educational attainment was categorized as higher education, defined as college or university, yes or no.

Cardiorespiratory Fitness Assessment

VO_{2max} was measured using a cardiopulmonary exercise test on either a treadmill (primary modality) or cycle ergometer ($n = 43$; 4.7% of tests) using a Cortex Metamax II (Leipzig, Germany) for treadmill tests and Oxycon Pro ergospirometry system (Erich Jaeger, Hoechberg, Germany) for cycle tests. After a standardized warm-up, workload increased every ~1.5 min or when VO_2 reached steady state. Tests continued until volitional exhaustion or the achievement of VO_{2max}, defined as a respiratory exchange ratio ≥1.05 and a plateau in VO_2 (<2 mL/kg/min increase over two 30-s epochs). As 39% at baseline and 36% at the 1-yr test did not reach a true VO_{2max}, VO_{2peak} is used throughout. The same modality (treadmill vs cycle) was used at follow-up when feasible; one baseline and eight follow-up cycle-ergometer tests were excluded for modality consistency before imputation (19).

Physical Activity Levels

Self-reported physical activity was assessed at baseline and at 1-yr follow-up using a standardized questionnaire capturing exercise frequency, duration and perceived intensity (19). Perceived intensity was rated using the Borg Rating of Perceived Exertion scale (6–20,27) and categorized as low intensity (ratings from 6 to 10), moderate intensity (11–14) and high intensity (15–20,28).

Statistical Analysis

Descriptive data are presented as mean (standard deviation) for continuous variables and frequency (%) for categorical variables. Absolute risk of AD was calculated as the number of AD events in each fitness category, divided by the number of participants in that category. Incidence rates of AD and all-cause dementia

were calculated as incident AD or all-cause dementia per 1000 person-years of follow-up. Kaplan–Meier survival analysis was used to estimate the cumulative probability of remaining free from AD during follow-up. Cox proportional hazards regression models were used to examine the association between VO_{2peak} and incident AD. The date of the 1-yr testing served as baseline for follow-up in the time-to-event analyses. The date of AD or other dementia diagnosis was defined as the date that came first of diagnosis in hospital, diagnosis by general practitioner, or first dispensation of prescribed antidementia medication according to the Norwegian Prescribed Drug registry. The date of symptom debut was the first date of reported AD- or dementia related symptoms by next-of-kin in hospital records. Participants were followed until AD diagnosis, all-cause dementia diagnosis, Parkinson disease diagnosis without dementia, amyotrophic lateral sclerosis, death, or end of follow-up on August 11, 2022, whichever came first. All analyses were repeated using all-cause dementia as the outcome. The proportional hazard assumption was satisfied through visual inspection of Schoenfeld residuals. All Cox proportional hazard analyses are reported as adjusted hazard ratio (aHR), adjusted for age, sex, education, and smoking exposure with 95% confidence intervals (CI). Covariates were prespecified before outcome analyses based on established risk factors for AD and their potential confounding role in the association between CRF and AD. Given the number of AD events (n = 77), we restricted the number of covariates to minimize model overfitting, in accordance with established guidance on events per variable in survival models (29). All analyses were two-sided with α = 0.05, conducted in Stata/SE 19.5 (StataCorp, College Station, TX).

Baseline VO_{2peak} was analyzed both continuously (mL/kg/min) and across three sex-specific fitness categories: unfit (<80% of the sex-specific mean VO_{2peak}; reference group), moderately fit (80%–99% of the sex-specific mean VO_{2peak}), and fit (≥100% of the sex-specific mean VO_{2peak}) as recommended (14,30,31). Changes in VO_{2peak} from baseline to 1 yr were examined as absolute change, and across four categorical trajectories reflecting transitions above and below a threshold of 80% of the sex-specific mean VO_{2peak}. The threshold was selected based on the primary analyses. Analyses including the 1-yr change in VO_{2peak} were also adjusted for baseline VO_{2peak}. We also evaluated continuous VO_{2peak} within strata defined by the threshold (unfit vs fit at baseline). To explore the independent and joint association between CRF and self-reported exercise intensity with incident AD, we fitted two additional Cox proportional hazards models. The first model included both baseline CRF (fit [≥80% of sex-specific mean $VO_{2peak]}$ vs unfit [<80%]) and self-reported exercise intensity (high [Borg ≥15] vs low/moderate [Borg <15]) as predictors. The second model used a four-category variable crossclassifying CRF and exercise intensity, with the unfit + low/moderate intensity group as the reference.

Missing values for VO_{2peak} (baseline: n = 28; 1-yr: n = 350), education (n = 52), and smoking pack-years (n = 240) were imputed using multiple imputation by chained equations with 100 imputations and 10 iterations. The imputation model included all variables in the analysis models, with the addition of three competing-event indicators (death, Parkinson disease without dementia, and non-AD dementia), and up to 13 auxiliaries (body mass index, self-reported health, self-reported exercise intensity for the last week and last year, hypertension at baseline and 1-yr, and smoking status at baseline). All 13 auxiliaries were added to the imputation model for VO_{2peak} at 1-yr, whereas the imputation model for VO_{2peak}, education, and smoking pack-years at baseline only included the seven baseline auxiliaries. The auxiliaries were selected from 53 candidates from questionnaires and clinical measurements in the Generation 100 study based on whether they were correlated with or predictive of missingness in the variables to be imputed (Supplemental data, Supplemental Digital Content, https://links.lww.com/MSS/D434).

Sensitivity Analyses

We conducted the following sensitivity analyses to examine the robustness of our primary findings: (1 a complete-case analysis to assess whether missing data influenced the results; (2 exclusion of the first 3 yr of follow-up to reduce potential reverse causality; (3 redefinition of the event time using onset of symptom instead of date of diagnosis among AD cases; and (4 a competing risk analysis using the Fine–Gray subdistribution hazards model, treating death and non-AD dementia as competing events. All sensitivity analyses were adjusted for the same covariates as the main model.

RESULTS

Baseline Characteristics of Participants

Table 1 presents the baseline characteristics of the participants across fitness categories. The study included 1491 older adults (760 [51%] women) with a mean age of 72.8 (2.1) yr and BMI of 26.0 (3.6). Nearly half (47.3%) of participants were categorized as fit. Compared with the moderately fit and fit groups, the unfit group had higher BMI, lower self-rated health, and higher prevalence of AD risk factors, including lower physical activity level, a history of smoking, hypertension, and cardiovascular disease. However, educational attainment and family history of dementia were similar across fitness categories. Median follow-up time was 8.7 (interquartile range [IQR] 8.4–8.9) yr.

TABLE 1. Baseline characteristics of participants by fitness category.

	Total	Unfit (<80% of VO_{2peak})	Moderately Fit (80%–99% of VO_{2peak})	Fit (≥100% of VO_{2peak})
Participants, *n* (%)	1491	232 (15.6%)	553 (37.1%)	706 (47.3%)
Sex	51.0%			
Male	731 (49.0%)	123 (53.0%)	266 (48.1%)	342 (48.4%)
Female	760 (51.0%)	109 (47.0%)	287 (51.9%)	364 (51.6%)
Age, years	72.8 (2.1)	73.3 (2.1)	72.9 (2.1)	72.6 (2.0)
VO_{2peak}, mL/kg/min	28.7 (6.5)	20.5 (2.8)	26.0 (2.9)	33.5 (5.3)
BMI, kg/m^2	26.0 (3.6)	28.6 (4.2)	26.8 (3.3)	24.5 (2.7)
Smoking, pack years	8.9 (13.6)	16.1 (18.0)	10.1 (14.1)	5.6 (10.3)
Higher education				
Yes	728 (48.8%)	110 (47.4%)	251 (45.4%)	367 (52.0%)
No	711 (47.7%)	110 (47.4%)	280 (50.6%)	321 (45.5%)
Missing	52 (3.5%)	12 (5.2%)	22 (4.0%)	18 (2.5%)
Hypertension				
Yes	897 (60.2%)	171 (73.7%)	363 (65.6%)	363 (51.4%)
No	583 (39.1%)	58 (25.0%)	184 (33.3%)	341 (48.3%)
Missing	11 (0.7%)	3 (1.3%)	6 (1.1%)	2 (0.3%)
Family history of dementia				
Yes	221 (14.8%)	28 (12.1%)	76 (13.7%)	117 (16.6%)
No	1101 (73.8%)	178 (76.7%)	410 (74.1%)	513 (72.7%)
Missing	169 (11.4%)	26 (11.2%)	67 (12.2%)	76 (10.8%)
History of CVD				
Yes	280 (18.8%)	72 (31.0%)	108 (19.5%)	100 (14.2%)
No	1201 (80.5%)	158 (68.1%)	441 (79.8%)	602 (85.3%)
Missing	10 (0.7%)	2 (0.9%)	4 (0.7%)	4 (0.6%)
Self-reported good health				
Yes	1252 (84.0%)	149 (64.3%)	468 (84.6%)	635 (89.9%)
No	168 (11.2%)	70 (30.1%)	55 (10.0%)	43 (6.1%)
Missing	71 (4.8%)	13 (5.6%)	30 (5.4%)	28 (4.0%)

Data are presented as mean (standard deviation) for continuous variables and *n* (%) for categorical variables. % of VO_{2peak} represents the percentage of sex-specific mean at baseline. Pack-years represent estimated lifetime cigarette exposure. Higher education defined as college/university; Hypertension defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or taking blood pressure medications.

BMI, body mass index; CVD, cardiovascular disease; VO_{2peak}, peak oxygen uptake.

Mean time between baseline and follow-up VO_{2peak} testing was 13 (1.4) months. Mean VO_{2peak} at baseline was 28.7 (6.5) mL/kg/min. Men had significantly higher VO_{2peak} than women, with mean values of 31.4 (6.7) and 26.1 (5.0) mL/kg/min, respectively ($P < 0.001$). Overall, mean VO_{2peak} increased by 1.7 (3.4) mL/kg/min from baseline to 1-yr follow-up, corresponding to a 6% improvement.

Alzheimer Disease and Dementia Disease Incidence

During follow-up, 128 (8.6%) all-cause dementia cases were identified. Of these, 77 (60.2%) (31 men and 46 women) were classified as AD cases and 51 (39.8%) as non-AD cases. Among the non-AD cases, 18 (35.3%) had a validated diagnosis of vascular cognitive disorder, Parkinson disease dementia, Lewy body dementia, or progressive supranuclear palsy. Only four cases (5.8%) were attributed to other nonneurodegenerative causes, while the remaining 29 (56.9%) were classified as having uncertain etiology due to insufficient diagnostic information in the hospital records (details shown in Supplemental Table 8, Supplemental Digital Content, https://links.lww.com/MSS/D434).

During the study period, total person-years of follow-up was 12,080. The incidence rate of AD was 6.4 per 1000 person-years of follow-up (95% CI 5.0–7.8). The incidence rate of all-cause dementia was 10.6 per 1000 person-years of follow-up (95% CI 8.8–12.5).

VO_{2peak} at Baseline and Risk of Alzheimer Disease

Baseline VO_{2peak} was lower among participants who later developed AD (27.2 [6.4] mL/kg/min) than among those who did not (28.8 [6.5] mL/kg/min; $P = 0.040$). The absolute risk of developing AD was 8.2% among unfit participants compared with 4.7% and 4.5% absolute risk among those classified as moderately fit and fit. Also, the incidence rate of AD was higher in the unfit participants, compared with the moderately fit and fit participants (Table 2). Both moderately fit and fit participants had a lower risk of AD compared with those classified as unfit (Fig. 2). Specifically, the moderately fit group had a 46% lower risk (aHR 0.54, 95% CI 0.29–0.98), and the fit group had a 48% lower risk (aHR 0.52, 95% CI 0.29–0.93). When VO_{2peak} was analyzed as a continuous variable, each 1 mL/kg/min higher VO_{2peak} at baseline was associated with a 4% lower risk of AD (aHR 0.96, 95% CI 0.92–1.00; Table 2).

TABLE 2. Risk of AD by fitness category and per unit higher VO_{2peak} at baseline.

	VO_{2peak}, mL/kg/min	*n*	AD Events (*n*)	IR (95% CI)	HR (95% CI)
Unfit	<25.1 (men). <20.9 (women)	232	19	10.8 (5.9–15.6)	1.00 (Reference)
Moderately fit	25.1–31.4 (men). 20.9–26.1 (women)	553	26	6.0 (3.7–8.3)	0.54 (0.29–0.98)
Fit	≥31.4 (men). ≥26.1 (women)	706	32	5.6 (3.7–7.5)	0.52 (0.29–0.93)
Moderately fit and fit combined	≥25.1 (men). ≥20.9 (women)	1259	58	5.7 (4.3–7.2)	0.56 (0.32–0.97)
VO_{2peak} (continuous)	Per 1 mL/kg/min	1491	–	–	0.96 (0.92–1.00)

Adjusted for age, sex, education and smoking exposure. Participants were classified as unfit (<80% of sex-specific mean VO_{2peak} at baseline), moderately fit (80%–99% of sex-specific mean VO_{2peak} at baseline) and fit (≥100% of sex-specific mean VO_{2peak} at baseline). IR is Incidence rate per 1000 person-years.
AD, Alzheimer disease; CI, confidence intervals; HR, hazard ratio; IR, incidence rate; $VO_{2peak,}$ peak oxygen uptake.

VO_{2peak} thresholds for preclinical AD risk stratification. Based on previous literature, 80% of the sex-specific mean VO_{2peak} (25.1 mL/kg/min for men and 20.9 mL/kg/min for women) was tested as a threshold of AD risk stratification, combining the moderately fit and fit groups, and comparing them with the unfit group. In the unfit group, 19 (8.2%) participants developed AD, compared with 58 (4.6%) among those classified as fit. Participants above this threshold had a 44% lower risk of developing AD (aHR 0.56, 95% CI 0.32–0.97) compared with those categorized as unfit.

Among participants who were unfit at baseline, mean VO_{2peak} was similar between those who later developed AD (19.5 mL/kg/min) and those who remained free from AD (20.6 mL/kg/min; P = 0.136). Consistently, baseline VO_{2peak} as a continuous variable was not associated with AD risk within the unfit group (aHR 0.86, 95% CI 0.72–1.02).

When using all-cause dementia instead of AD as the outcome, the association between fitness category and dementia risk was similar in direction but weaker than in the main analysis (aHR 0.67, 95% CI 0.43–1.05; Supplemental Table 1, Supplemental Digital Content, https://links.lww.com/MSS/D434).

Change in VO_{2peak} and Risk of Alzheimer Disease

Participants who maintained fitness levels at or above 80% of the sex-specific mean VO_{2peak} at both baseline and the 1-yr follow-up had a 58% lower risk of developing AD compared with the reference group, which consisted of participants who remained unfit at both assessment time points (<80%) (aHR 0.42, 95% CI 0.20–0.89; Fig. 3). Participants who changed fitness category—from fit to unfit or from unfit to fit—did not differ significantly in AD risk compared with the reference group (aHR 0.53, 95% CI 0.12–2.46 and aHR 0.59, 95% CI 0.20–1.17, respectively; Fig. 3).

When VO_{2peak} was analyzed as a continuous variable, each 1 mL/kg/min increase in VO_{2peak} from baseline to 1-yr, were not associated with the risk of developing AD (aHR 1.06, 95% CI 0.99–1.14), nor when baseline VO_{2peak} was included in the model (aHR 1.04, 95% CI 0.97–1.12). Within the subgroup of participants who were unfit at baseline, the 1-yr change in VO_{2peak} did not show any association with later AD risk. Estimates were similar in the main model (aHR 0.94, 95% CI 0.80–1.11) and after additional adjustment for baseline VO_{2peak} (aHR 0.97, 95% CI 0.83–1.13).

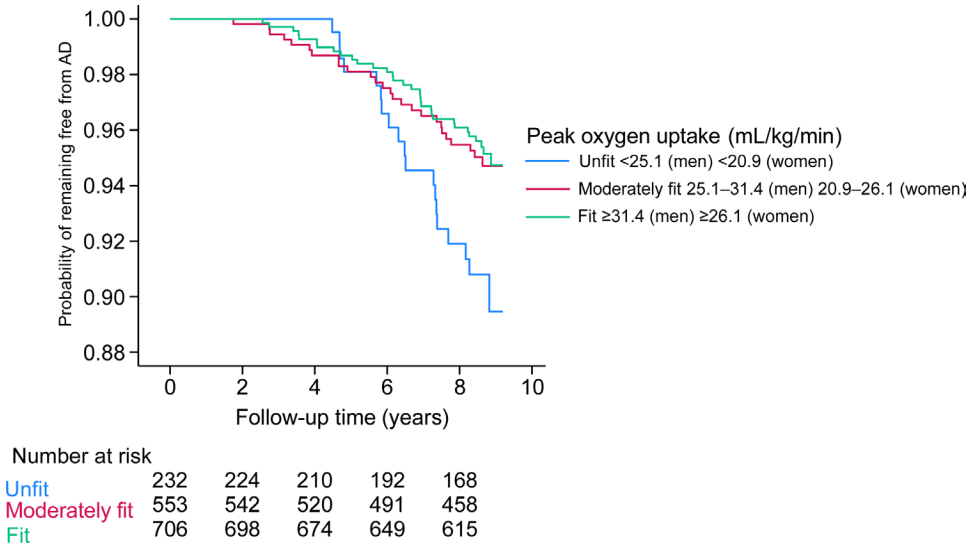


FIGURE 2—Kaplan–Meier curves showing the cumulative probability of remaining free from Alzheimer disease during follow-up according fitness category. Participants were classified as unfit (<80% of the sex-specific mean VO_{2peak}), moderately fit (80%–99%), or fit (≥100%).

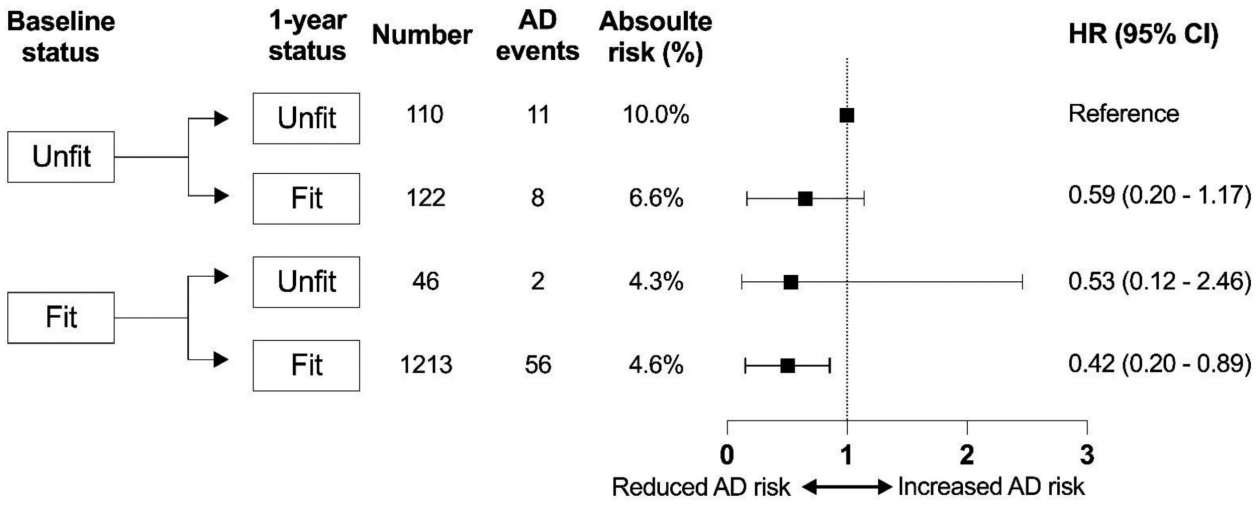


FIGURE 3—Relative risk of AD by changes in fitness category from baseline to 1-yr testing. Four fitness-change trajectories were defined based on transitions above or below 80% of the sex-specific mean VO_{2peak} from baseline to 1-yr testing. Adjusted for age, sex, education, and smoking exposure (pack-years). AD, Alzheimer disease; CI, confidence intervals; HR, hazard ratio; $VO_{2peak,}$ peak oxygen uptake.

When using all-cause dementia instead of AD as the outcome, the association between change in VO_{2peak} and dementia risk was similar in direction but weaker than in the main analysis (Supplemental Table 1, Supplemental Digital Content, https://links.lww.com/MSS/D434).

Physical Activity Levels by Fitness Category and Changes From Baseline to 1-Yr

At baseline, participants classified as fit reported higher physical activity levels than those classified as unfit, exercising more frequently, for longer durations, and at higher intensities (Supplemental Table 2, Supplemental Digital Content, https://links.lww.com/MSS/D434). One quarter of the fit group (25.3%) reported high-intensity activity (Borg ≥15), compared with 13.6% in the unfit group. From baseline to 1-yr, the overall physical activity level increased modestly, with more participants reporting almost daily activity (20.7% to 23.5%) and a higher proportion exercising at high intensity (23.5% to 27.3%). At the 1-yr follow-up, the same pattern remained: those who were classified as fit reported higher physical activity levels, including more frequent exercise, longer durations, and a higher proportion training at high intensity compared with the unfit group.

In the joint analysis of CRF and self-reported exercise intensity (Supplemental Table 3, Supplemental Digital Content, https://links.lww.com/MSS/D434), the protective association between fitness and AD risk was largely unchanged after adjustment for self-reported exercise intensity (aHR 0.51, 95% CI 0.29–0.87), whereas self-reported high-intensity exercise was not independently associated with AD risk (aHR 0.77, 95% CI 0.42–1.41). In the crossclassified analysis, both the fit + low/moderate intensity group (aHR 0.47, 95% CI 0.26–0.83) and the fit + high intensity group (aHR 0.40, 95% CI 0.19–0.84) had substantially lower AD risk than the unfit + low/moderate intensity reference group.

Sensitivity Analysis

We conducted several sensitivity analyses to assess the robustness of the association between being fit (≥80% of the sex-specific mean VO_{2peak}) versus unfit, examining whether the results were affected by missing data, outcome definition, reverse causality, and when the event was defined (Supplemental Tables 4–6, Supplemental Digital Content, https://links.lww.com/MSS/D434). Specifically, in the complete-case analysis, participants classified as fit had a lower risk of AD, with HRs similar in magnitude to the main model, although not statistically significant (Supplemental Table 4, Supplemental Digital Content, https://links.lww.com/MSS/D434). Excluding the first 3 yrs of follow-up (leaving 72 AD cases for analysis) to minimize potential reverse causality yielded similar results, with fit participants again showing a lower risk of AD (aHR 0.51, 95% CI 0.29–0.88; Supplemental Table 5, Supplemental Digital Content, https://links.lww.com/MSS/D434). Finally, using symptom debut in AD cases instead of diagnosis date as the event time produced an estimate closely aligned with the main analysis (aHR 0.56, 95% CI 0.32–0.97; Supplemental Table 6, Supplemental Digital Content, https://links.lww.com/MSS/D434) and did not alter the median follow-up time (8.7 yrs, IQR 8.4–8.9). Finally, a competing risk analysis treating death and non-AD dementia as competing events yielded subdistribution hazard ratios comparable in magnitude to the primary Cox regression estimates (Supplemental Table 7, Supplemental Digital Content, https://links.lww.com/MSS/D434), indicating that the association between VO_{2peak} and incident AD was not materially altered.

DISCUSSION

In this prospective cohort study of almost 1500 community-dwelling older adults, we found that higher CRF, assessed objectively as VO_{2peak} at baseline, was associated with a substantially lower risk of developing AD over almost 9 yrs of follow-up. Participants with VO_{2peak} levels at or above 80% of the sex-specific mean had approximately a 45% lower risk of AD compared with those classified as unfit (<80% of the sex-specific mean). These findings were consistent across sensitivity analyses using symptom debut, extended lag periods, and alternative dementia definitions. In contrast, 1-yr changes in $VO_{2peak,}$ whether modeled as a continuous variable or categorized according to fitness thresholds, were not associated with later AD risk. Together, these findings suggest that habitually higher fitness, rather than short-term changes in fitness, may be most relevant for AD risk reduction in late life.

Comparison With Previous Studies

Our results align with previous observational research demonstrating an inverse association between CRF and dementia risk, including studies showing 30%–50% lower incidence among individuals with higher fitness levels (18,32). Most earlier studies, however, relied on estimated CRF from nonexercise models, single assessments, or mid-life exposures—factors that may underestimate true associations due to measurement error or reverse causality. By using objectively measured VO_{2peak} and restricting analyses to incident AD, our study extends this evidence base and provides more robust support for the role of late-life CRF in neurodegenerative disease risk. Our joint analysis of CRF and self-reported exercise intensity showed that CRF remained the dominant prognostic marker for AD risk, while perceived intensity added limited independent information. This aligns with previous evidence that objectively measured CRF is a stronger predictor of long-term health outcomes than self-reported physical activity alone (30,33).

The observation that baseline fitness—but not 1-yr CRF change—was associated with AD risk contrasts with studies reporting benefits of improved fitness for cognitive outcomes or mortality (34,35). This discrepancy may reflect the long preclinical phase of AD development, during which pathophysiological changes accumulate over decades. Short-term improvements in fitness at age ≥70 may therefore be insufficient to alter long-established disease trajectories, or the follow-up period may have been too short to detect effects of recent changes in physiological reserve. Another possibility is that participants who increased fitness were already on a declining health trajectory, partly obscuring benefits of short-term improvement. A third explanation is that participants in this cohort were already relatively fit for their age compared with populations in previous studies (36), which may have limited the potential for additional benefit.

Notably, incidence rates of AD and dementia in our cohort were low (10.6 dementia cases per 1000 person-years) compared with recently reported rates among 70–74-yr-olds from the same county in Norway as the Generation 100 Study population (24.6 cases per 1000 person-years) (37). This supports that our cohort consisted of fit and healthy older adults with a low AD risk already at inclusion. This notion is supported by the presence of a clear threshold effect: individuals with VO_{2peak} levels ≥80% of the sex-specific mean (25.1 mL/kg/min for men and 20.9 mL/kg/min for women) had a ~45% lower risk of AD, yet no additional reduction in risk was observed among those classified as fit (≥100%) compared with those who were moderately fit (80%–99%). These findings raise the possibility of an L-shaped association between CRF and AD risk, where the largest risk reduction occurs up to ~80% of the sex-specific mean VO_{2peak}, with little additional benefit above this threshold. Another contributing factor is the very small proportion of participants who transitioned from unfit to fit (n = 122), compared with the far larger group who remained fit throughout follow-up (n = 1213). This imbalance limited the number of AD events within specific trajectory strata. Indeed, three of the four strata included few events (range, 2–11), resulting in wide confidence intervals and limited precision of the hazard ratio estimates. Under these conditions, only large differences in risk would be expected to reach statistical significance. These considerations are relevant when interpreting the null findings for certain transition categories. Longitudinal analyses with more repeated CRF measurements across longer time intervals may help clarify these associations.

Potential Mechanisms

Several mechanisms may explain the association between higher CRF and reduced AD risk. Greater fitness is linked to improved cerebrovascular health, enhanced cerebral perfusion, reduced systemic inflammation, improved metabolic function, and increased neurotrophic support—all of which may mitigate neurodegenerative processes (33). CRF also reflects genetics and long-term physical activity behavior and overall physiological resilience, which may protect against vascular and nonvascular pathways leading to AD (38). Meanwhile, improvements in CRF over only 1 yr may not produce sufficient biological change to influence these mechanisms in older adults, particularly if significant neuropathology is already present.

Strengths and Limitations

Key strengths of this study include the use of objectively measured VO_{2peak} in a large and well-characterized

cohort of older adults. Further, the validation of AD and dementia diagnoses through health registries and thorough hospital record review represents a significant strength because they ensure that diagnostic information is both accurate and consistent. In addition, multiple sensitivity analyses addressing reverse causality and misclassification. The current study focused on AD rather than all-cause dementia, which further enhances interpretability, given heterogeneity across various dementia etiologies. However, several limitations merit consideration. First, although extensive validation was performed, some AD cases may have been misclassified or missed, particularly in the earliest preclinical stages. Secondly, residual confounding by unmeasured lifestyle, genetic, or socioeconomic factors cannot be excluded. Third, the limited number of events did not allow separate analyses of the CRF–AD association in important subgroups, such as those defined by sex, APOE ε4 status, age, or family history of dementia. Finally, the cohort consisted of relatively healthy, motivated older adults, which may limit generalizability to frailer populations or those with greater comorbidity.

Implications and Future Directions

These findings highlight CRF as a promising late-life marker for identifying individuals at elevated risk of AD. The proposed threshold of ~80% of the sex-specific mean VO_{2peak} may have practical value for risk stratification in clinical or public-health settings. When direct measurement of VO_{2peak} is not feasible, CRF can be estimated using validated nonexercise prediction models (39), which may offer a practical alternative for risk stratification in older adults. Future studies should examine long-term fitness trajectories, incorporate biomarkers of AD pathology, and test whether targeted exercise interventions can slow clinical and biological progression among individuals at risk.

CONCLUSIONS

In summary, high objectively measured CRF when entering the 70s was associated with a lower risk of developing AD over nearly 9 yrs of follow-up, whereas 1-yr changes in CRF were not. These findings suggest that entering older age with high fitness may be more important for reducing late-life AD risk than achieving short-term improvements after the age of 70. Moreover, CRF emerged as a clinically relevant marker for AD that may help stratify risk and inform preventive strategies in aging populations.

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