

Collective effects of age, sex, genotype, and cognitive status on fitness outcomes

Jill K. Morris^{1,3} | Guanlin Zhang² | Ryan J Dougherty^{5,6} | Jonathan D. Mahnken^{2,3} |
 Casey S. John³ | Sarah R. Lose^{4,6} | Dane B. Cook^{5,7} | Jeffrey M. Burns^{1,3} |
 Eric D. Vidoni^{1,3} | Ozioma Okonkwo^{4,6}

¹ Department of Neurology, University of Kansas Medical Center, Kansas City, Kansas, USA

² Department of Biostatistics and Data Science, University of Kansas Medical Center, Kansas City, Kansas, USA

³ University of Kansas Alzheimer's Disease Research Center, Fairway, Kansas, USA

⁴ Department of Medicine, University of Wisconsin-Madison, Madison, Wisconsin, USA

⁵ Department of Kinesiology, University of Wisconsin-Madison, Madison, Wisconsin, USA

⁶ Wisconsin Alzheimer's Disease Research Center, Madison, Wisconsin, USA

⁷ William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin, USA

Correspondence

Jill K. Morris, Department of Neurology, KU Alzheimer's Disease Center, University of Kansas Medical Center, MS 6002, 4350 Shawnee Mission Pkwy, Fairway, KS 66205
 Email: jmorris2@kumc.edu

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Abstract

Introduction: Individuals with Alzheimer's disease (AD) broadly exhibit lower cardiorespiratory fitness (CRF) compared to cognitively healthy older adults. Other factors, such as increasing age and female sex, are also known to track with lower CRF levels. However, it is unclear how these factors together with AD diagnosis and genetic risk (apolipoprotein e4; *APOE4*) collectively affect CRF.

Methods: Our primary objective was to characterize the collective relationship of age, sex, *APOE4* carrier status, and cognitive status (nondemented or AD) with two commonly reported CRF outcomes, VO_2 max and oxygen uptake efficiency slope (OUES). To interrogate the unique and combined effect of age, sex, *APOE4*, and cognitive status on CRF, we pooled multiple datasets and tested several statistical models allowing all possible interactions.

Results: AD diagnosis was consistently associated with lower maximal CRF, which declined with increasing age. *APOE4* was also associated with lower maximal CRF (VO_{2max}), but only in male subjects. Submaximal CRF (OUES) was lower in *APOE4* carriers of both sexes, although this difference converged in male subjects with advancing age.

Discussion: This multi-cohort analysis ($n = 304$) suggests that *APOE4* carrier status and sex are important considerations for studies that evaluate maximal and submaximal CRF.

KEYWORDS

aging, Alzheimer's disease, apolipoprotein e4, cardiorespiratory fitness, oxygen uptake efficiency slope

1 | INTRODUCTION

Low cardiorespiratory fitness (CRF) and physical inactivity have been linked to Alzheimer's disease (AD),¹⁻⁴ and longitudinal studies have

shown a relationship between self-reported physical activity and exercise (planned repetitive physical activity for the purpose of health), and sustained cognitive function.⁵⁻¹⁰ Higher lifetime physical activity, which has been shown to contribute to greater CRF levels in later life¹¹

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is associated with reduced AD risk,^{12,13} and in individuals with elevated AD risk, higher CRF has been associated with greater brain volume and better cognitive performance.¹⁴ In two separate clinical trials, we have shown that aerobic exercise interventions designed to increase CRF improve cognitive function in nondemented older adults in a dose-dependent manner, and that exercise-induced improvement in CRF is positively associated with both memory and hippocampal volume in AD.^{15,16}

Despite these positive findings, it is clear that some individuals experience more brain benefit from physical activity and exercise than others, and this response is particularly variable in participants with AD.^{16,17} Age, sex, and AD status have all been individually linked to CRF, but it is unclear how these factors, collectively with AD genetic risk status, such as apolipoprotein E4 (*APOE4*) carrier status, relate to CRF responses in humans. We sought to further interrogate the independent and combined effects of these key factors to determine their relationships with two commonly used indices of CRF. The first measure, VO_2 max, is considered the “gold standard” measure of CRF in exercise trials but requires expertise to perform and is not feasible for all research participants. A less intensive measure that does not require achieving maximal effort, oxygen uptake efficiency slope (OUES), is more feasible and likely safer for some participants.^{18,19} Given the links between CRF and AD risk, as well as the heterogeneous nature of study subjects and observed CRF responses, we aimed to characterize the collective impacts of age, sex, *APOE4* carrier status, and cognitive status on commonly reported CRF outcomes.

2 | METHODS

2.1 | Participants

Participants were recruited as part of intervention and observational studies at the University of Kansas Alzheimer's Disease Center (KU) and the Wisconsin Alzheimer's Disease Research Center (UW). We have previously reported results from these investigations.^{15,16,20-22} Briefly, both sites are part of the U.S. network of Alzheimer's Disease Centers of Excellence that support research into brain aging and dementia. All work was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving human subjects. All human subjects provided informed consent.

The KU sample was drawn from the most recent individual graded exercise testing (GXT) from both intervention (pre-intervention timepoint only) and observational studies (ClinicalTrials.gov: NCT01129115, NCT02000583, NCT01128361, NCT00267124). The UW sample was drawn from participants enrolled in sub-studies of the Wisconsin Registry for Alzheimer's Prevention study.^{23,24} All individuals were evaluated using the Clinical Dementia Rating (CDR) and determined to have either nondemented (ND) or cognitive impairment due early-stage AD (CDR 0.5 or 1; AD). We included ND subjects 50 years and older and AD subjects of any age. We pooled GXT results from the baseline assessments for past exercise studies

RESEARCH IN CONTEXT

- 1. Systematic review:** A traditional literature review (PubMed) was performed to identify relevant studies. It has been shown that Alzheimer's disease (AD) subjects have lower cardiorespiratory fitness (CRF) levels compared to cognitively healthy individuals. However, CRF is also affected by a variety of other factors, including age and sex, and there is limited information regarding the effect of the primary AD risk gene, apolipoprotein E epsilon 4 (*APOE4*), on CRF.
- 2. Interpretation:** Here, we interrogated the independent and combined contributions of age, sex, cognitive diagnosis, and *APOE4* carrier status to examine the effects of these factors on both maximal (VO_2 max) and submaximal/functional fitness (oxygen uptake efficiency slope). *APOE4* was associated with lower maximal fitness only in male subjects, but was associated with lower functional fitness at younger ages regardless of sex.
- 3. Future directions:** This article suggests that *APOE4* genotype and sex should be a consideration factor for ongoing clinical trials examining CRF in aging and AD.

and clinical data from 510 individuals between our two sites. We then excluded 206 individuals who did not achieve a respiratory exchange ratio (RER) of ≥ 1.10 during the GXT, a well-accepted threshold for an excellent effort during an exercise test.²⁵ The remaining 304 individuals (219 ND, 85 AD) were included in our final analyses. For these individuals, we also assessed additional criteria that could impact our results, including the rating of perceived exertion (RPE) and use of beta-blockers. These data, along with clinical data, are included in Table 1.

2.2 | Assessment and measures

CRF was indexed as the maximal oxygen uptake during the GXT normalized to whole body mass ($mL \cdot kg^{-1} \cdot min^{-1}$). Treadmill speed and incline changes were preset and controlled by the metabolic analysis software. Expired gases were captured using a nose clip or mask, mouthpiece, and 2-way nonbreathing valve. Participants were oriented to the Borg Rating of RPE 6 to 20 scale before beginning the GXT. GXT outcome measures were obtained using the Balke protocol at UW and the modified Bruce protocol at KU. Both sites used American College of Sports Medicine recommendations for absolute and relative indications for terminating tests. Details can be found in the parent datasets.^{15,16,20,22} OUES, a valid estimate of cardiorespiratory efficiency, was calculated by regressing oxygen uptake on the log transformed total ventilation at each 15-second sampling period of the entire GXT.²⁶

TABLE 1 Demographics and graded exercise testing performance

	Female				Male			
	AD		ND		AD		ND	
	E4 Carrier	E4 Noncarrier	E4 Carrier	E4 Noncarrier	E4 Carrier	E4 Noncarrier	E4 Carrier	E4 Noncarrier
Number, n	30	9	53	82	22	24	26	58
Age (years)	73.1 (7.6)	73.8 (5.4)	66.6 (7.0)	70.4 (6.6)	72.6 (7.8)	72.3 (7.8)	70.1 (8.4)	72.5 (7.6)
RER	1.14 (0.06)	1.15 (0.05)	1.16 (0.05)	1.15 (0.06)	1.16 (0.07)	1.16 (0.05)	1.16 (0.05)	1.17 (0.8)
RPE	17.8 (1.7)	17.7 (1.5)	17.5 (1.7)	17.8 (1.3)	17.9 (1.6)	17.4 (1.8)	17.9 (1.2)	17.4 (1.9)
Beta-blocker (#,%)	3 (10%)	1 (11.1%)	3 (5.7%)	2 (2.4%)	2 (9.1%)	1 (4.2%)	1 (3.8%)	3 (5.2%)
VO _{2max} (mL/kg/min)	19.3 (3.0)	18.9 (3.1)	22.5 (4.5)	20.9 (4.5)	22.0 (4.0)	24.2 (5.1)	25.8 (5.8)	26.1 (5.2)
OUES	1348 (209)	1543 (219)	1715 (394)	1608 (399)	1987 (529)	2182 (641)	2436 (673)	2265 (555)

Notes: Characteristics of participants who met RER criteria for inclusion in our analysis (n = 304) broken down by categorical variables (sex, cognitive diagnosis, and E4 carrier status). Data are shown as means and SD.

Abbreviations: AD, Alzheimer's disease; ND, nondemented; E4, apolipoprotein e4; RER, respiratory exchange ratio; RPE, rating of perceived exertion; OUES, oxygen uptake efficiency slope.

2.3 | Statistical analyses

Participant characteristics were explored with standard descriptive statistics. We then performed a backward elimination for ordinary least squares regression modeling to predict VO₂ max and OUES. We included cognitive status (ND/AD), APOE4 status (E4 carrier/noncarrier), and sex (male/female) as dichotomous variables, as well as age in years as a continuous measure. We began our backward elimination with an inclusive model allowing for all possible interactions (ie, up to the 4-way interaction among diagnosis, APOE4 carrier status, sex, and age). Given the known strong effect of sex on CRF outcomes, and its significance in the full model, we then performed subgroup analyses separating males and females to explore the relationship of the remaining variables (age, APOE4, and cognitive status) on CRF. We iteratively tested these reduced models to identify the most parsimonious predictors of VO₂ max and OUES.

We used a threshold of $P = .2$ for backward elimination steps. We then assessed for multicollinearity. When condition indices exceeded 100, we reduced backward elimination to a lower P value ($P = .15$) and reassessed condition indices.²⁷ Adjusted R-square values were estimated from these models to indicate the level of variation in these measures described. Last, to assess model assumptions, we conducted residual analyses, including assessments for normality for residuals using histograms and quantile-quantile plots, and for homogeneity of variance evaluated residual by predicted value plots. We considered the following complete and reduced models for VO₂ max and OUES outcomes, below.

Full model for VO₂ max:

$$\begin{aligned} \text{VO2max} = & \beta_0 + \beta_1 \cdot \text{Age} + \beta_2 \cdot \text{Sex} + \beta_3 \cdot \text{DX} + \beta_4 \cdot \text{E4} + \beta_5 \cdot \text{Age} * \text{Sex} \\ & + \beta_6 \cdot \text{Age} * \text{DX} + \beta_7 \cdot \text{Age} * \text{E4} + \beta_8 \cdot \text{Sex} * \text{DX} \\ & + \beta_9 \cdot \text{Sex} * \text{E4} + \beta_{10} \cdot \text{DX} * \text{E4} + \beta_{11} \cdot \text{Age} * \text{Sex} * \text{DX} \\ & + \beta_{12} \text{Age} * \text{Sex} * \text{E4} + \beta_{13} \text{Age} * \text{DX} * \text{E4} \\ & + \beta_{14} \text{Sex} * \text{DX} * \text{E4} + \beta_{15} \text{Age} * \text{Sex} * \text{DX} * \text{E4} \end{aligned}$$

Reduced model for VO₂ max (after backward selection; $R_{adj} = 0.4210$):

$$\begin{aligned} \text{VO2max} = & \beta_0 + \beta_1 \cdot \text{Age} + \beta_2 \cdot \text{DX} + \beta_3 \cdot \text{E4} + \beta_4 \cdot \text{Age} * \text{Sex} \\ & + \beta_5 \cdot \text{Sex} * \text{DX} + \beta_6 \cdot \text{Age} * \text{Sex} * \text{DX} + \beta_7 \cdot \text{Age} * \text{Sex} * \text{E4} \end{aligned}$$

Full model for OUES:

$$\begin{aligned} \text{OUES} = & \beta_0 + \beta_1 \cdot \text{Age} + \beta_2 \cdot \text{Sex} + \beta_3 \cdot \text{DX} + \beta_4 \cdot \text{E4} + \beta_5 \cdot \text{Age} * \text{Sex} \\ & + \beta_6 \cdot \text{Age} * \text{DX} + \beta_7 \cdot \text{Age} * \text{E4} + \beta_8 \cdot \text{Sex} * \text{DX} \\ & + \beta_9 \cdot \text{Sex} * \text{E4} + \beta_{10} \cdot \text{DX} * \text{E4} + \beta_{11} \cdot \text{Age} * \text{Sex} * \text{DX} \\ & + \beta_{12} \text{Age} * \text{Sex} * \text{E4} + \beta_{13} \text{Age} * \text{DX} * \text{E4} + \beta_{14} \text{Sex} * \text{DX} * \text{E4} \\ & + \beta_{15} \text{Age} * \text{Sex} * \text{DX} * \text{E4} \end{aligned}$$

Reduced model for OUES (after backward selection; $R_{adj} = 0.524$):

$$\begin{aligned} \text{OUES} = & \beta_0 + \beta_1 \cdot \text{Age} + \beta_2 \cdot \text{Sex} + \beta_3 \cdot \text{E4} + \beta_4 \cdot \text{Age} * \text{Sex} \\ & + \beta_5 \cdot \text{Age} * \text{E4} + \beta_6 \cdot \text{DX} * \text{E4} \end{aligned}$$

3 | RESULTS

3.1 | Cohort characteristics

As expected, the two cohorts differed in age ($P < .001$). Because the UW cohort was 9.7 years younger on average and were not diagnosed with cognitive impairment, the observed higher VO₂ max and OUES values were expected ($P < .01$). The UW cohort also had a slightly higher proportion of females ($P = .04$).

Across both cohorts (Table 1), females were younger ($P = .015$) and had lower CRF ($P < .001$). Females also had a higher rate of APOE4 carriage and slightly lower RER at VO₂ max, though these did not reach significance ($P > .06$). Individuals diagnosed with cognitive impairment

TABLE 2 Regression model results for CRF outcomes

Subgroups		Linear relationship (P value)	Slope (P value, estimate)	Intercept (P value, estimate)
Male subjects				
VO ₂ max	(ND, E4) vs (ND, Non E4)	.044	.044	−1.481
	(AD, E4) vs (AD, Non E4)	.044	.044	−1.481
OUES	(ND, E4) vs (ND, Non E4)	.026	0.009 16.855	.012 −1133.793
	(AD, E4) vs (AD, Non E4)	<.001	0.009 16.855	.002 −1430.924
Female subjects				
VO ₂ max	(ND, E4) vs (ND, Non E4)	.124	0.101 0.144	.044 −1.481
	(AD, E4) vs (AD, Non E4)	.124	0.295 −0.291	.044 −1.481
OUES	(ND, E4) vs (ND, Non E4)	.026	0.009 16.855	.012 −1133.793
	(AD, E4) vs (AD, Non E4)	<.001	0.009 16.855	.002 −1430.924

Notes: Regression model values are given for cardiorespiratory fitness outcomes using threshold $P = .015$ for backward elimination.

Abbreviations: CRF, cardiorespiratory fitness; OUES, oxygen uptake efficiency slope.

were older, more likely to carry the E4 allele, and have lower VO₂max ($P < .05$) and marginally lower OUES ($P = .07$). E4 carriers were slightly older ($P = .05$), but did not differ on RER, VO₂ max, or OUES ($P > .2$).

3.2 | Regression analyses

The full regression model indicated that female sex, APOE4 carriage, and diagnosis all contributed to lower CRF. Because large effects of the categorical variable sex on both VO₂ max and OUES are well established, we elected to further explore the collective contribution of our other variables (age, cognitive status, and APOE4) on CRF on males and females separately. Table 2 contains regression model results for CRF outcomes for these analyses.

3.3 | Male subjects

Males who were APOE4 carriers showed lower VO₂ max ($P = .044$; Figure 1A) both for comparisons within AD and within ND individuals. Diagnosis of AD was also associated with reliably lower VO₂ max ($P = .002$) for both within E4 carriers and noncarriers (Table 2). Across all males, we observed the expected negative relationships between age and VO₂ max. This decline with advancing age did not differ by carrier status.

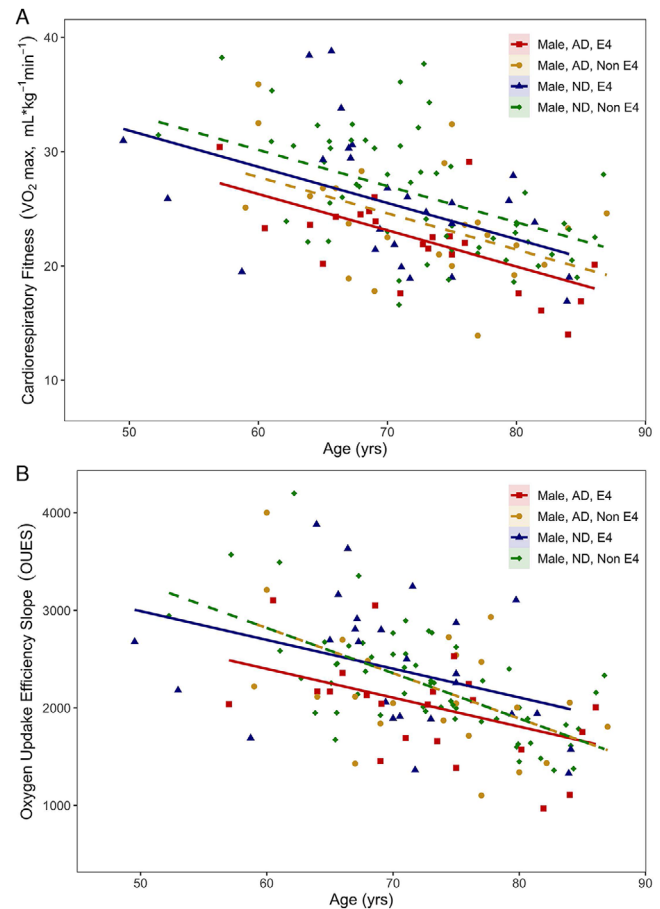


FIGURE 1 A, VO₂max and (B) oxygen uptake efficiency slope values for all male participants plotted by age and shown with the corrected regression line of best fit

Similarly, age was negatively associated with OUES across all males. OUES is also different between APOE4 genetic risk groups in both ND and AD participants. Regardless of diagnosis younger APOE4 carriers showed lower OUES ($P < .03$; Figure 1B) at an earlier age, with OUES values converging with advancing age (ie, noncarrier OUES dropping more rapidly).

3.4 | Female subjects

Unlike male subjects, female APOE4 carriers did not exhibit differences in VO₂ max compared to noncarriers (Figure 2A). At young ages differences in VO₂ max were observed in AD females and marginally converged as VO₂ max values declined with advancing age (Table 2). The decline in VO₂ max with advancing age did not differ by APOE4 carrier status.

Consistent with the findings in males, OUES was significantly different based on APOE4 carrier status in both ND ($P = .026$) and AD ($P < .001$) participants. Lower OUES was observed at younger ages in APOE4 carriers (Figure 2B).

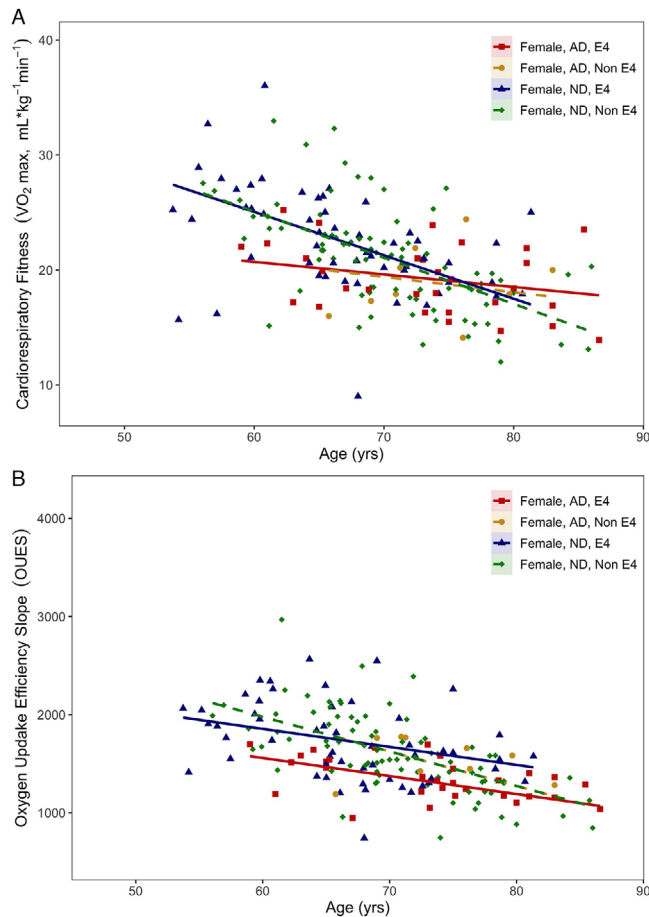


FIGURE 2 A, $VO_{2\max}$ and (B) oxygen uptake efficiency slope values for all female participants plotted by age and shown with the corrected regression line of best fit

4 | DISCUSSION

We present here the first study to characterize how varying age, cognitive status, *APOE* genotype, and sex affect CRF. Given the heterogeneity of cohorts enrolled into ongoing clinical trials, it is important to understand these relationships. Our analysis revealed several interesting findings specifically regarding *APOE4*, the primary late onset AD risk gene. Regardless of diagnosis, positive *APOE4* carrier status was associated with lower maximal fitness ($VO_{2\max}$) in male subjects, but not in female subjects. However, *APOE4* was associated with lower submaximal fitness (OUES) at younger ages, regardless of sex.

$VO_{2\max}$ is the gold standard for measuring CRF and is a marker of the body's maximal ability to transport and use oxygen. Thus, $VO_{2\max}$ reflects a combination of both cardiovascular function and energy demand and use. We show here that both ND and AD male *APOE4* carriers had marginally lower $VO_{2\max}$ overall than *APOE4* noncarriers. Interestingly, the rate of $VO_{2\max}$ decline with increasing age did not differ based upon *APOE4* carrier status. No difference in $VO_{2\max}$ scores between risk groups was observed in female subjects of either diagnosis. This suggests that AD genetic risk status negatively affects an individual's baseline CRF value most strongly in males. In addition,

APOE4 individuals (in both sexes) do not change differently over time. This provides important information for longitudinal trials assessing CRF.

In contrast, OUES is a function of both oxygen consumption and ventilation. Because OUES is affected by perfusion to both lungs and skeletal muscle it is said to reflect system efficiency.²⁶ Here, we show that at younger ages, *APOE4* carriers have lower OUES values compared to *APOE4* noncarriers, regardless of diagnosis group or sex. It is possible that these findings are affected by survival bias, as older *APOE4* subjects do not have lower OUES. However, to our knowledge, no studies directly assess *APOE4* genotype and OUES and additional work is needed to investigate this relationship.

Strengths of this study include our relatively large sample size, thorough diagnostic characterization, multiple cohorts, and robust characterization of CRF, using gold-standard methods and accepted cut-points for valid $VO_{2\max}$ values. Our values are in line with previously published norms,²⁸ with consideration of our clinical population. However, there are important study limitations that must be considered. First, we combined data collected at two sites to obtain a larger and more diverse sample set, but GXT protocols differed at the sites. Bruce and Balke GXT protocols have shown similar fitness values when compared directly,²⁹ but there is limited data comparing the modified Bruce and Balke protocols. In addition, even with our combined sites, additional weaknesses are the small number of female *APOE4* noncarriers who met criteria for inclusion in the study, and the relatively low numbers of younger subjects due to the nature of the parent studies. Finally, we cannot rule out potential reverse causation due to functional impairments in AD. Our strict inclusion criteria of $RER \leq 1.10$ likely minimizes protocol-related and effort-related differences, but may limit generalizability, thus we have included the demographic information for the full set of individuals considered for the study for comparison purposes (Table S1 in supporting information). Finally, there was limited quantification of other factors that could affect CRF, such as cardiovascular or metabolic comorbidities. Further studies should examine mechanisms for the effect of *APOE4* differences on fitness.

In conclusion, we present here a relatively large, multi-cohort study that characterizes the collective relationship of age, sex, cognitive status, and *APOE4* carrier status on CRF. These findings suggest that *APOE* genotype and sex should be considered for ongoing clinical trials examining CRF in aging and AD.

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CONFLICTS OF INTEREST

The authors have no competing interests to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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