Impact of APOE Genotype on Cardiorespiratory Fitness in Aging and AD

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Overview

Introduction

Research Goal

1. Alzheimer's disease(AD) has a high prevelance in United States;
2. No disease-modifying or preventive treatment currently;
3. Exercise effecitve therapeutic for AD or cognitive decline?
4. Our goal: characterize the impact of cognitive impariment and genetic AD risk on maximal measures of cardiorespiratory fitness (VO_2).

Method: Participants and Inclusion

Participants

1. Participats were recruited from KU and UW as part of intervention and observation studies;
2. All measurements were collected at baseline;
3. Individuals from UW have normal cognition (no AD).

Inclusion Criteria

1. Individuals with a respiratory exchange ratio(RER) ≥ 1.1 were included;
2. Initial dataset has 510 participants;
3. 304 were included in the anaysis.

Method: Analysis

Analysis

1. Investigate dichotomous variables of interest (Gender, DX, and E4 carrier);
2. Discussion linear regression model (VO_2 as response), discuss model selections;
3. We aim to identify the most parsimonous model, while during model selection we try to find and interpret information about subgroups.

Results: Categorical Analysis

Gender / DX	ND	AD	Row Total
Male	84	46	130
Female	135	39	174
Column Total	219	85	304

Pearson χ^2	df	p	Fisher's exact test	
Pearson χ^2 test			estimate odds ratio:	0.529
6.215	1	0.013	H_a : odds ratio < 1	
Pearson χ^2 with Yate's continuity correction			p	0.009
5.588	1	0.018	95% CI	$(0, 0.833)$

TABLE 1 Gender vs Diagnosis

Results: Categorical Analysis

Gender / E4	Noncarrier	Carrier	Row Total
Male	82	48	130
Female	91	83	174
Column Total	173	131	304

Pearson χ^2	df	p	Fisher's exact test	
Pearson χ^2 test			estimate odds ratio:	1.556
3.525	1	0.060	H_a :odds ratio > 1	
Pearson χ^2 with Yate's continuity correction			p	0.039
3.100	1	0.078	95% CI	$(1.028, +\infty)$

TABLE 2 Gender vs E4

Results: Categorical Analysis

Gender / E4	Noncarrier	Carrier	Row Total
Male	82	48	130
Female	91	83	174
Column Total	173	131	304

Pearson χ^2	df	p	Fisher's exact test	
Pearson χ^2 test			estimate odds ratio:	1.556
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TABLE 2 Gender vs E4

Results: Categorical Analysis

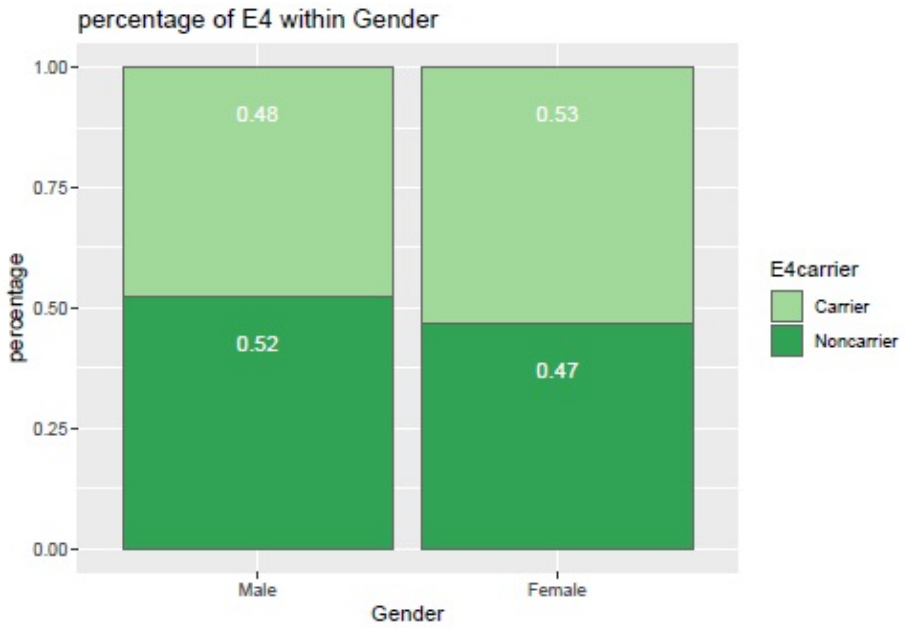

FIGURE 1 percentage of E4carrier from UW

Results: Categorical Analysis

Diagnosis / E4	Noncarrier	Carrier	Row Total
ND	140	79	219
AD	33	52	85
Column Total	173	131	304

Pearson χ^2	df	p	Fisher's exact test	
Pearson χ^2 test			estimate odds ratio:	2.783
15.736	1	< 0.001	H_a :odds ratio > 1	
Pearson χ^2 with Yate's continuity correction			p	< 0.001
14.729	1	< 0.001	95% CI	$(1.752, +\infty)$

TABLE 3 Diagnosis vs E4

Results: Categorical Analysis

Stratification

1. Among Gender, DX and E4 carrier, Breslow-Day test acommodating the hypothesis of common odds ratio between any of the two, stratifying on the third.
2. Cochran-Mantel-Haenszel test supports pairwise association between any of the two when stratifying on the third variable.

Results: Model Selection

Single Variables

1. Age($p < 0.001$), BMI($p < 0.001$), Gender($p < 0.001$), DX($p = 0.003$), Site($p < 0.001$) and E4carrier($p = 0.28$);
2. All significant except for E4 carrier.

Regression Models

$$\begin{aligned} \text{VO}_2 &= \beta_0 + \beta_1 \cdot \text{Age} + \beta_2 \cdot \text{BMI} + \beta_3 \cdot \text{Gender} + \beta_4 \cdot \text{DX} \\ &\quad + \beta_5 \cdot \text{Site} + \beta_6 \cdot \text{E4}(\text{ Reduced }) \\ \text{VO}_2 &= \beta_0 + \beta_1 \cdot \text{Age} + \beta_2 \cdot \text{BMI} + \beta_3 \cdot \text{Gender} + \beta_4 \cdot \text{DX} \\ &\quad + \beta_5 \cdot \text{Site} + \beta_6 \cdot \text{E4} + \beta_7 \cdot \text{Gender} \cdot \text{DX} \\ &\quad + \beta_8 \cdot \text{Gender} \cdot \text{E4} + \beta_9 \cdot \text{DX} \cdot \text{E4}(\text{ Complete }) \end{aligned}$$

Results: Model Selection

Selection Results

1. a lack-of-fit F test suggests for the reduced model($F_{3,295} = 1.786, p = 0.150$);
2. for the reduced model, a stepwise/forward/backward selection suggests a more parsimonious model:

$$\text{VO}_2 = \beta_0 + \beta_1 \cdot \text{Age} + \beta_2 \cdot \text{BMI} + \beta_3 \cdot \text{Gender} + \beta_4 \cdot \text{DX}$$

Results: Model Selection

What can complete model still tell us?

AD vs ND		Female vs Male		E4 vs NonE4	
	p		p		p
(male, nonE4)	0.004	(ND, nonE4)	< 0.001	(male, ND)	0.34
(male, E4)	< 0.001	(ND, E4)	< 0.001	(male, AD)	0.1
(female, nonE4)	0.36	(AD, nonE4)	< 0.001	(female, ND)	0.5
(female, E4)	0.04	(AD, E4)	< 0.001	(female, AD)	0.7

TABLE 4 VO2 performance on subgroups

Results: Model Selection

Model with only KS data

$$\begin{aligned}\text{VO}_2 &= \beta_0 + \beta_1 \cdot \text{Age} + \beta_2 \cdot \text{BMI} + \beta_3 \cdot \text{Gender} + \beta_4 \cdot \text{DX} \\ &\quad + \beta_5 \cdot \text{E4}(\text{ Reduced }) \\ \text{VO}_2 &= \beta_0 + \beta_1 \cdot \text{Age} + \beta_2 \cdot \text{BMI} + \beta_3 \cdot \text{Gender} + \beta_4 \cdot \text{DX} \\ &\quad + \beta_5 \cdot \text{E4} + \beta_6 \cdot \text{Gender} \cdot \text{DX} + \beta_7 \cdot \text{Gender} \cdot \text{E4} \\ &\quad + \beta_8 \cdot \text{DX} \cdot \text{E4}(\text{ Complete })\end{aligned}$$

Results: Model Selection for KS data

Selection Results for KS data

1. a lack-of-fit F test suggests for the reduced model($F_{3,227} = 1.443$, $p = 0.23$);
2. for the reduced model, a stepwise/forward/backward selection suggests the same parsimonious model:

$$\text{VO}_2 = \beta_0 + \beta_1 \cdot \text{Age} + \beta_2 \cdot \text{BMI} + \beta_3 \cdot \text{Gender} + \beta_4 \cdot \text{DX}$$

Results: Subgroup Aalysis for KS data

We perform the same subgroup analysis on KS data only:

AD vs ND		Female vs Male		E4 vs NonE4	
	p		p		p
(male, nonE4)	0.008	(ND, nonE4)	< 0.001	(male, ND)	0.42
(male, E4)	0.003	(ND, E4)	< 0.001	(male, AD)	0.1
(female, nonE4)	0.39	(AD, nonE4)	< 0.001	(female, ND)	0.66
(female, E4)	0.05	(AD, E4)	< 0.001	(female, AD)	0.66

TABLE 5 VO2 performance on subgroups in KS

Conclusion: Using KS data only gives us similar p values and same significant results. To boost power we decide that both datasets should be included in our analysis.

Results: Model Selection with APOE information

APOE	E2/E2	E2/E3	E2/E4	E3/E3	E3/E4	E4/E4
Count	5	28	8	140	106	17

TABLE 6 Count of APOE allele Combinations

Results: Model Selection with APOE information

Consider $E2$, $E3$, and $E4$

1. Assign scores to different alleles: $E4 = -1$, $E3 = 0$ and $E2 = 1$;
2. Propose the following regression model:

$$\begin{aligned} \text{VO}_2 = \beta_0 &+ \beta_1 \cdot \text{Age} + \beta_2 \cdot \text{BMI} + \beta_3 \cdot \text{Gender} + \beta_4 \cdot \text{DX} \\ &+ \beta_5 \cdot \text{Site} + \beta_6 \cdot I(\text{alleles} = -2) \\ &+ \beta_7 \cdot I(\text{alleles} = -1) + \beta_8 \cdot I(\text{alleles} = 1) \\ &+ \beta_9 \cdot I(\text{allele} = 2) \end{aligned}$$

Results: Model Selection with APOE information

Results

1. A Cochran-Armitage test shows a decreasing trend between AD and allele scores ($p < 0.001$);
2. The p values for allele groups are (β_6: 0.15, β_7: 0.76, β_8: 0.65 and β_9: 0.48), which says the allele combinations are not significant in predicting VO_2 scores;
3. A lack-of-fit test suggests for the same reduced main effect model($F_{4,294} = 0.75$, $p = 0.56$).

Discussion

What we have tried

1. Explored the current Alzheimer's disease data and discussed relationships between categorical variables under interest;
2. Tried to look for parsimonious but informational regression models to profile the significant predictor variables for VO_2 performance.

Conclusion

1. No significant effet from E4 allele carrier;
2. No interaction between Gender, Diagnosis, and E4 carrier;
3. No significant effect from APOE genotypes;
4. We suggest the reduced main effect model as the final model.

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The University of Kansas

Thank You!