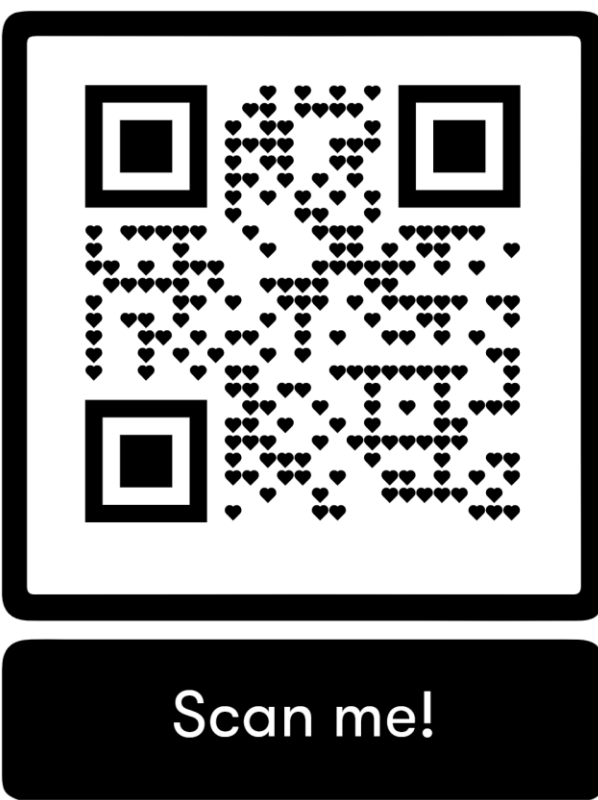


Combined Effects of Hypercholesterolemia and PM_{2.5} Exposure on Endothelial Dysfunction and Cognitive Performance

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INTRODUCTION

Hypercholesterolemia (cholesterol levels > 200 mg/dL) is a recognized risk factor for cardiovascular and neurodegenerative diseases. Recently, exposure to the air pollutant fine particulate matter (PM_{2.5}) was also highlighted as an environmental contributor to dementia. PM_{2.5} exhibits potent oxidative and inflammatory properties that can compromise the integrity of the peripheral vascular endothelium and the blood-brain barrier, potentially leading to memory deficits. In this context, we investigated whether PM_{2.5} could exacerbate the cognitive impairments associated with hypercholesterolemia by promoting vascular endothelial dysfunction and increased permeability.

METHODS

Male CF-1 mice were initially divided into Ctrl and HCD groups. The HCD group received a high-cholesterol diet (2.5% of cholesterol), and Ctrl received a standard diet for four weeks. At the end of the second week, they were subdivided into Ctrl, Polluted, HCD, and HCD+Polluted. The Polluted and HCD+Polluted groups received intranasal instillation of PM_{2.5} (30 µg/10 µL), whilst the Ctrl and DHC received saline solution (NaCl 0.9%) once a day, 5 d/week, for two weeks (Ethics committee 38492). At the end of the fourth week, animals underwent Y-Maze testing, followed by anesthesia and euthanasia.

RESULTS

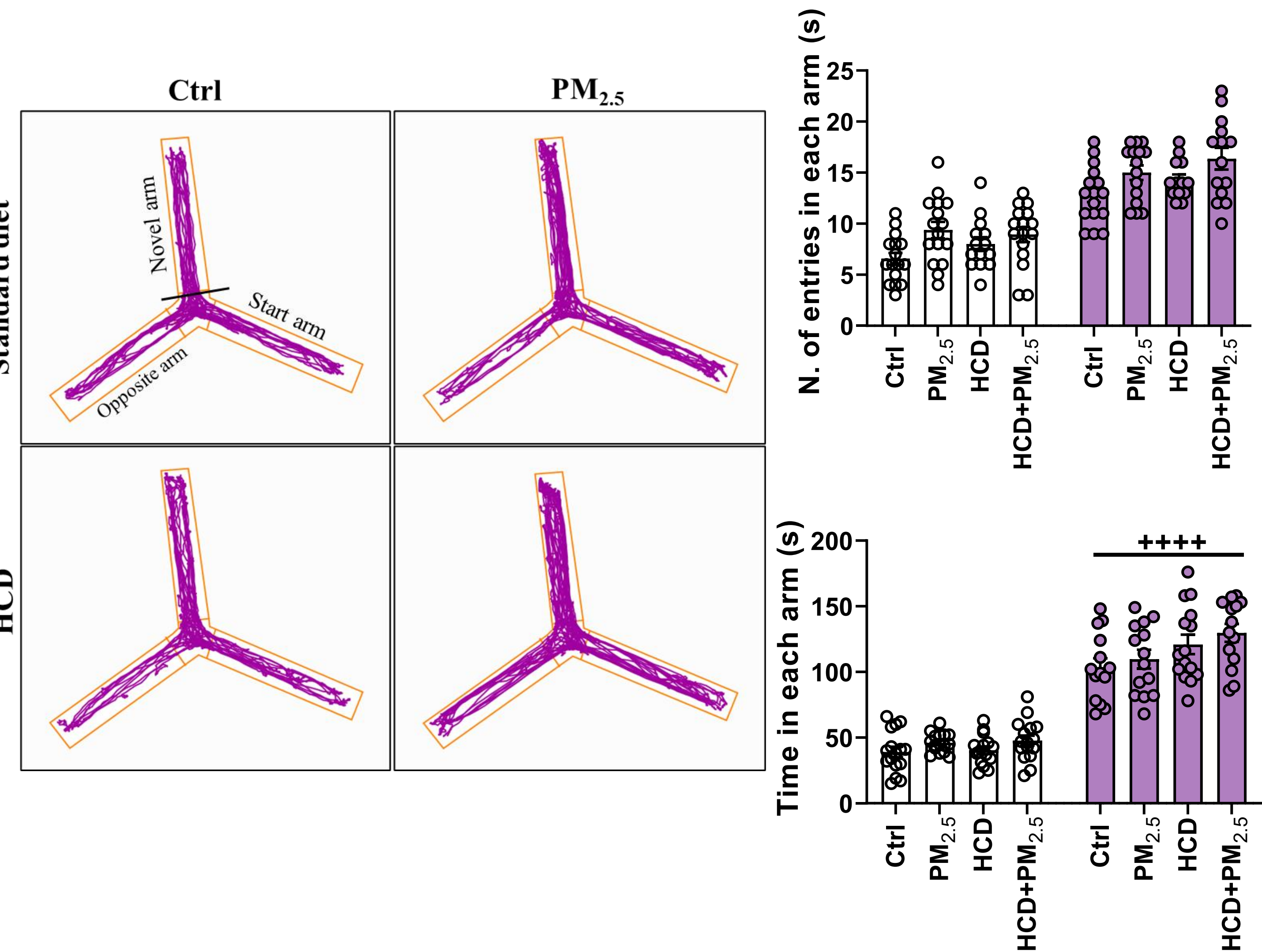


Figure 1: PM_{2.5} increases exploration whilst jeopardizing spatial memory in hypercholesterolemic animals in the Y-Maze. A. Representative images from the mouse trajectory during the second phase of the Y-Maze. B. Number of entries in each arm. Opposite arm. HCD: P = 0.170; Pollution: P = 0.001**. Novel Arm. HCD: P = 0.07; Pollution: P = 0.008**. C. Time spent in each arm. Opposite arm. HCD: P = 0.660; Pollution: P = 0.031*. Novel Arm. HCD: P = 0.010*; Pollution: P = 0.294. C. Data were expressed as mean ± SEM and compared using Two-way ANOVA, followed by Tukey's test.

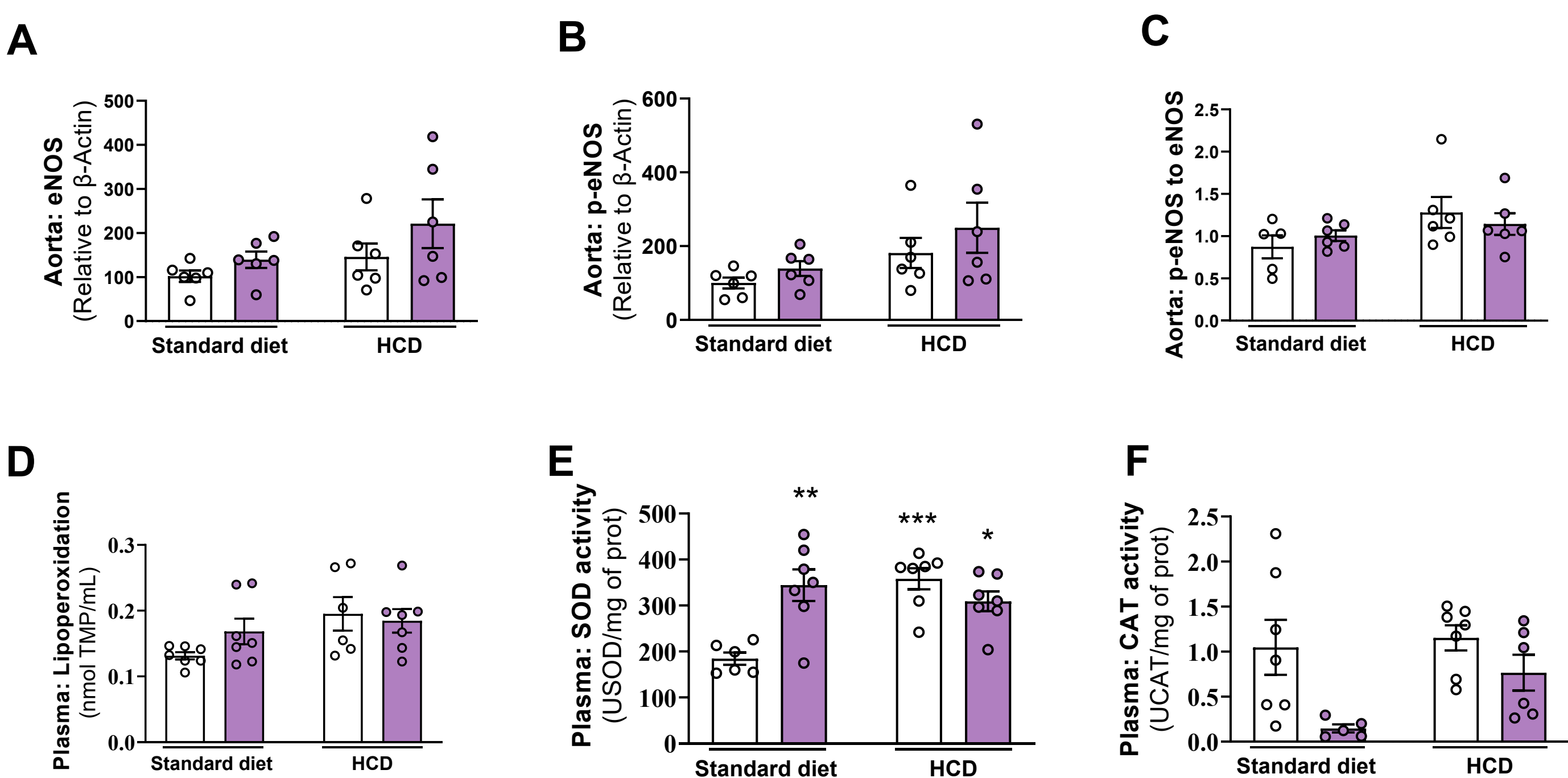


Figure 2: High-cholesterol diet and PM_{2.5} exposure present independent and interactive effects on plasmatic oxidative stress and peripheral endothelial dysfunction. A. Total eNOS. HCD: P = 0.075; Pollution: P = 0.108. B. p-eNOS. HCD: P = 0.031*; Pollution: P = 0.211. C. p-eNOS to total eNOS ratio. HCD: P = 0.059; Pollution: P = 0.996. D. Lipoperoxidation. HCD: P = 0.036*; Pollution: P = 0.471. E. SOD activity. HCD: P = 0.010; Pollution: P = 0.036; Interaction: P = 0.0004. Tukey's test: * P < 0.05, ** P < 0.01, *** P < 0.001 vs Ctrl. F. CAT activity. HCD: P = 0.105; Pollution: P = 0.007**.

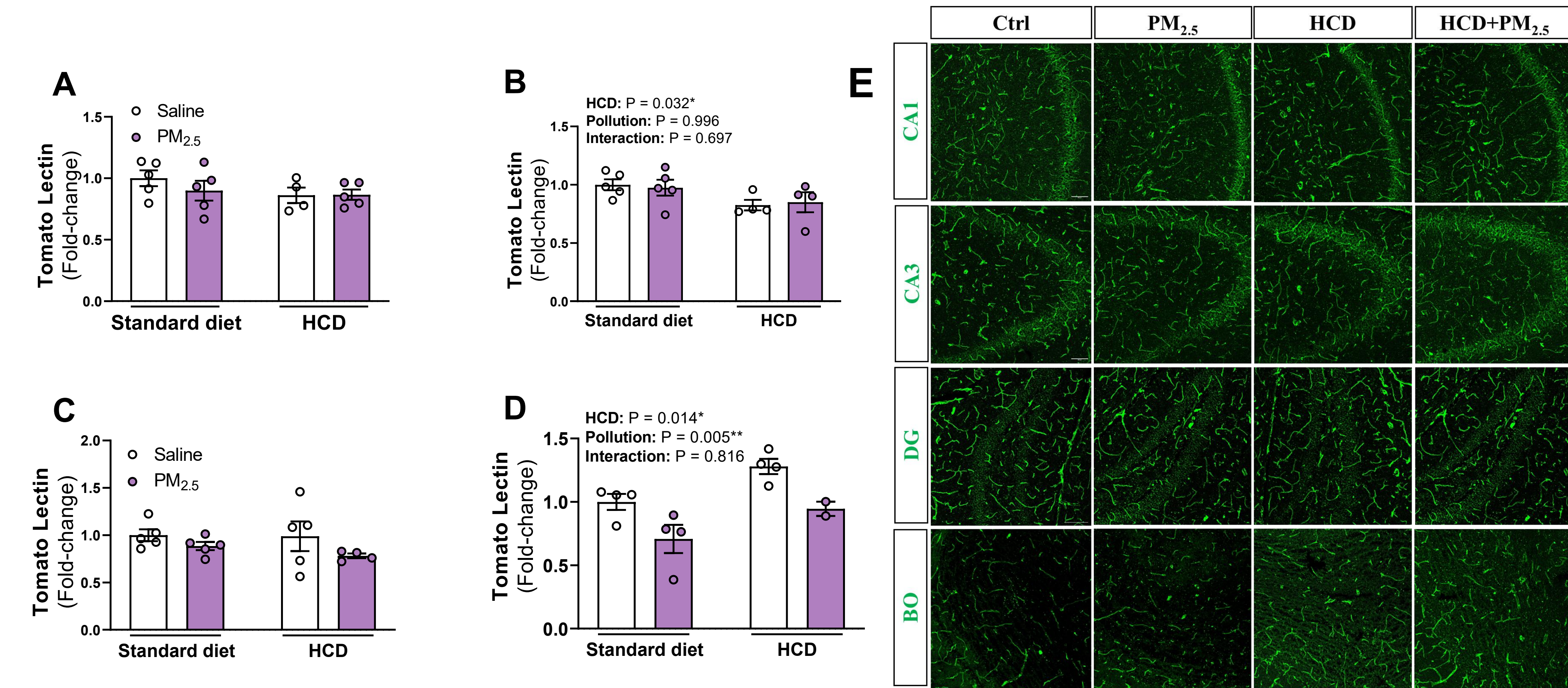


Figure 3: High-cholesterol diet and PM_{2.5} exposure present independent effects on the hippocampus and olfactory bulb vasculature. A. CA1. HCD: P = 0.206; Pollution: P = 0.469. B. CA3. HCD: P = 0.032*; Pollution: P = 0.996. C. DG. HCD: P = 0.550; Pollution: P = 0.105. D. OB. HCD: P = 0.014*; Pollution: P = 0.005**. E. Representative Images from graphics A-D.

CONCLUSION

HCD and PM_{2.5} exert distinct yet complementary effects on oxidative stress and endothelial dysfunction. Their combined impact poses a significant threat to both peripheral and central vasculature, potentially impacting cognitive performance.