

Conjugated GLP-1 Estradiol as a Novel Treatment for Alzheimer's Disease Endophenotypes



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INTRODUCTION

Alzheimer's disease (AD) is the most common dementia, and its prevalence increases sharply with age.¹

Modifiable factors such as obesity, diabetes, hypertension, and low physical activity are major risk factors for AD.^{2,3}

Females are disproportionately affected by AD, suggesting important sex-related differences in disease risk and progression.^{4,5}

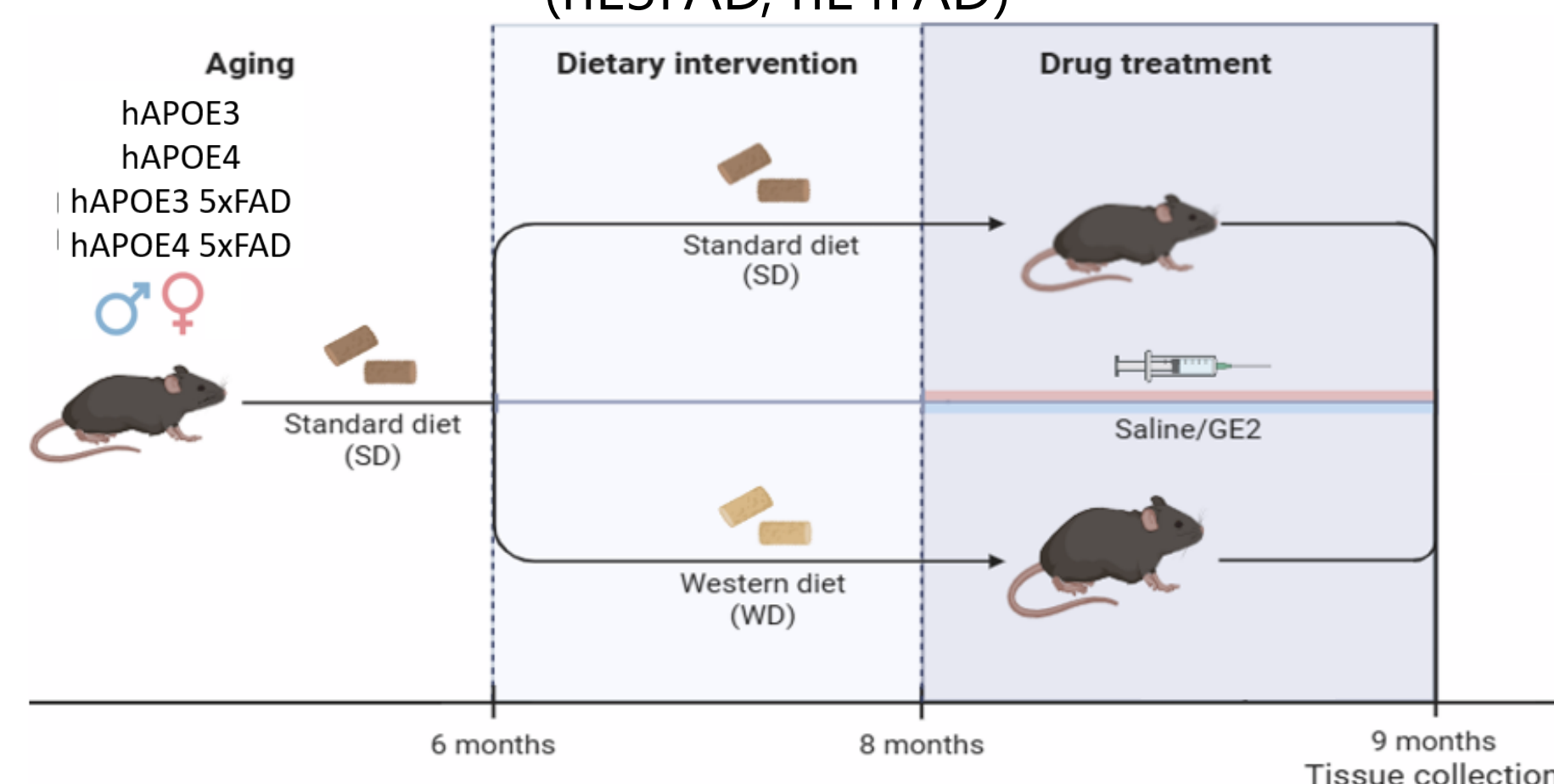
Glucagon like-peptide 1 (GLP-1) receptor agonists⁶ and estradiol⁷ may have protective effects against metabolic dysfunction and neurodegeneration.

A GLP-1 estradiol conjugate (GE2) can deliver estradiol into cells through GLP-1 receptor binding, linking receptor-mediated uptake to enhanced neuroprotective signaling.⁸

Does GE2 modulate metabolic and inflammatory biomarkers in a genotype, sex, or diet specific manner?

METHODS

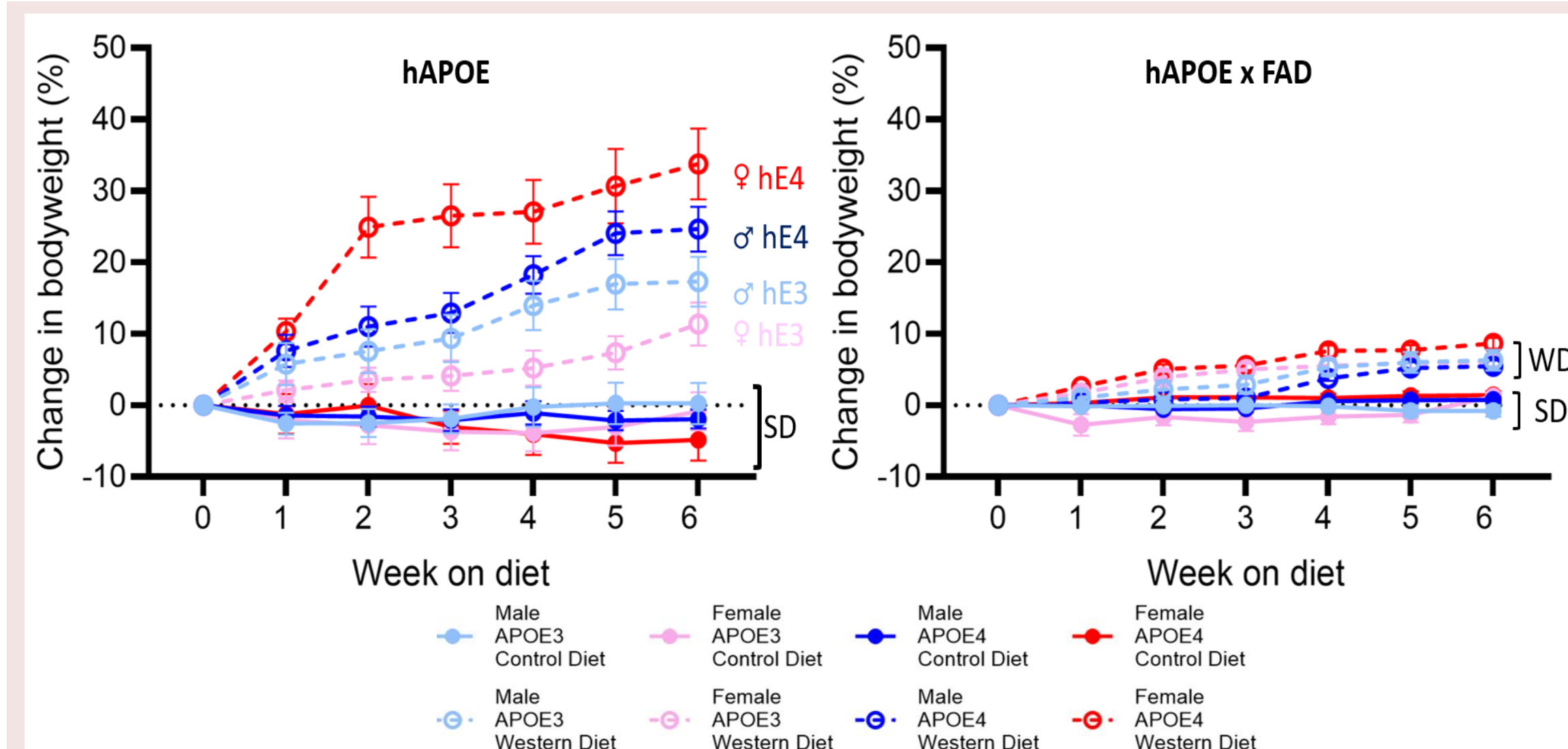
Transgenic mice with humanized APOE $\epsilon 3$ or $\epsilon 4$ alleles alone (hE3, hE4) or with 5xFamilial AD (FAD) risk genes (hE3FAD, hE4FAD)



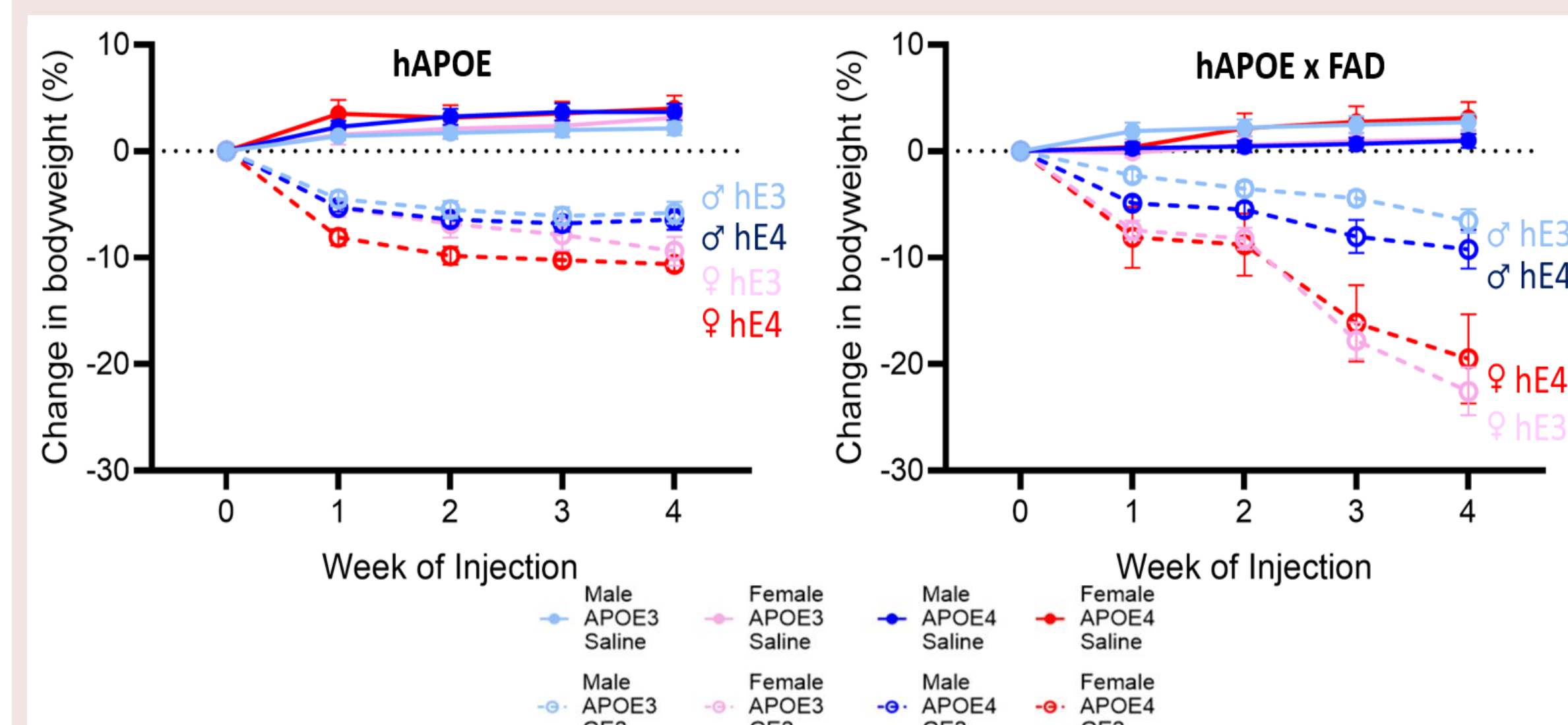
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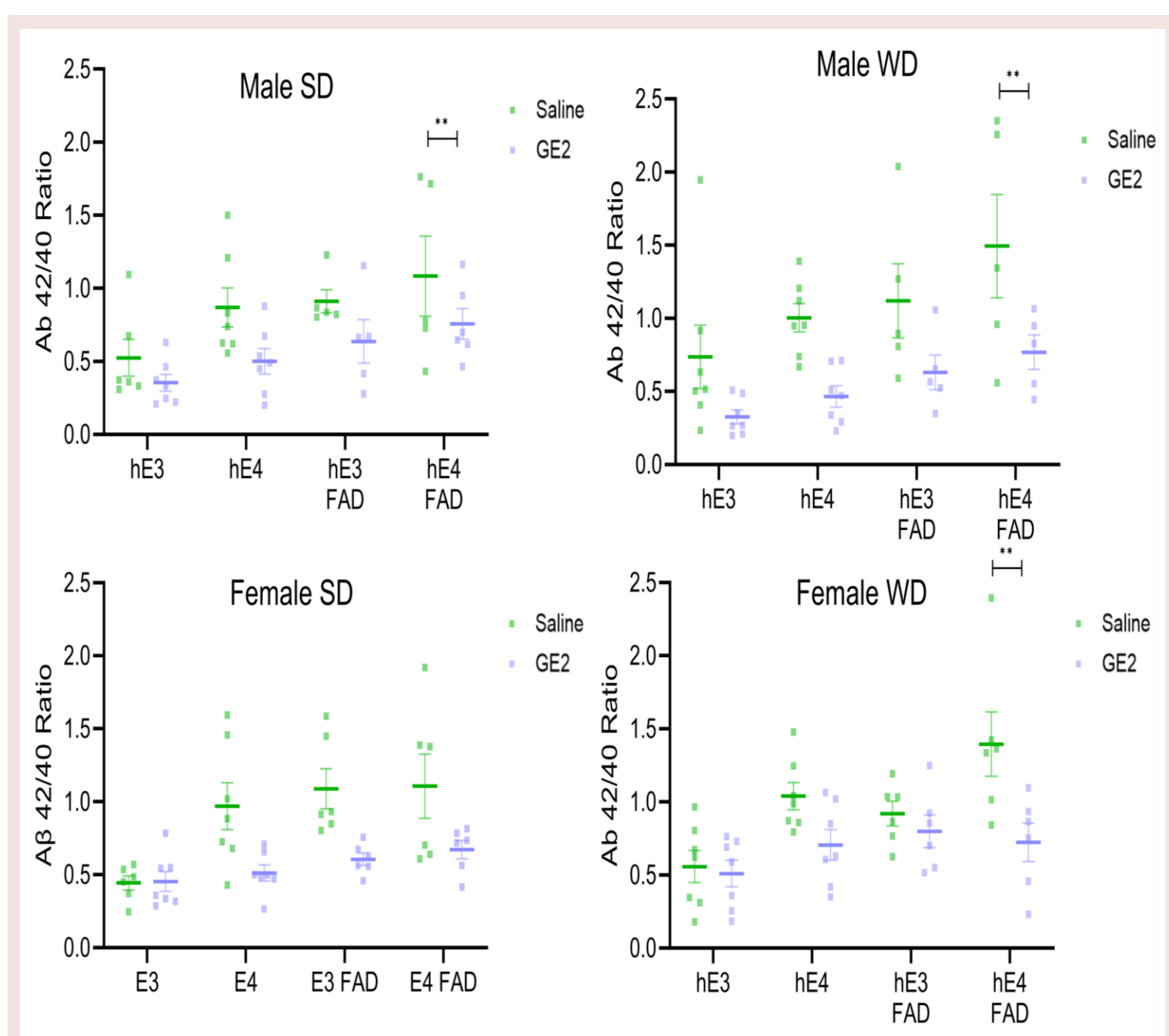
hE4 female mice gained the most weight while FAD animals gained less



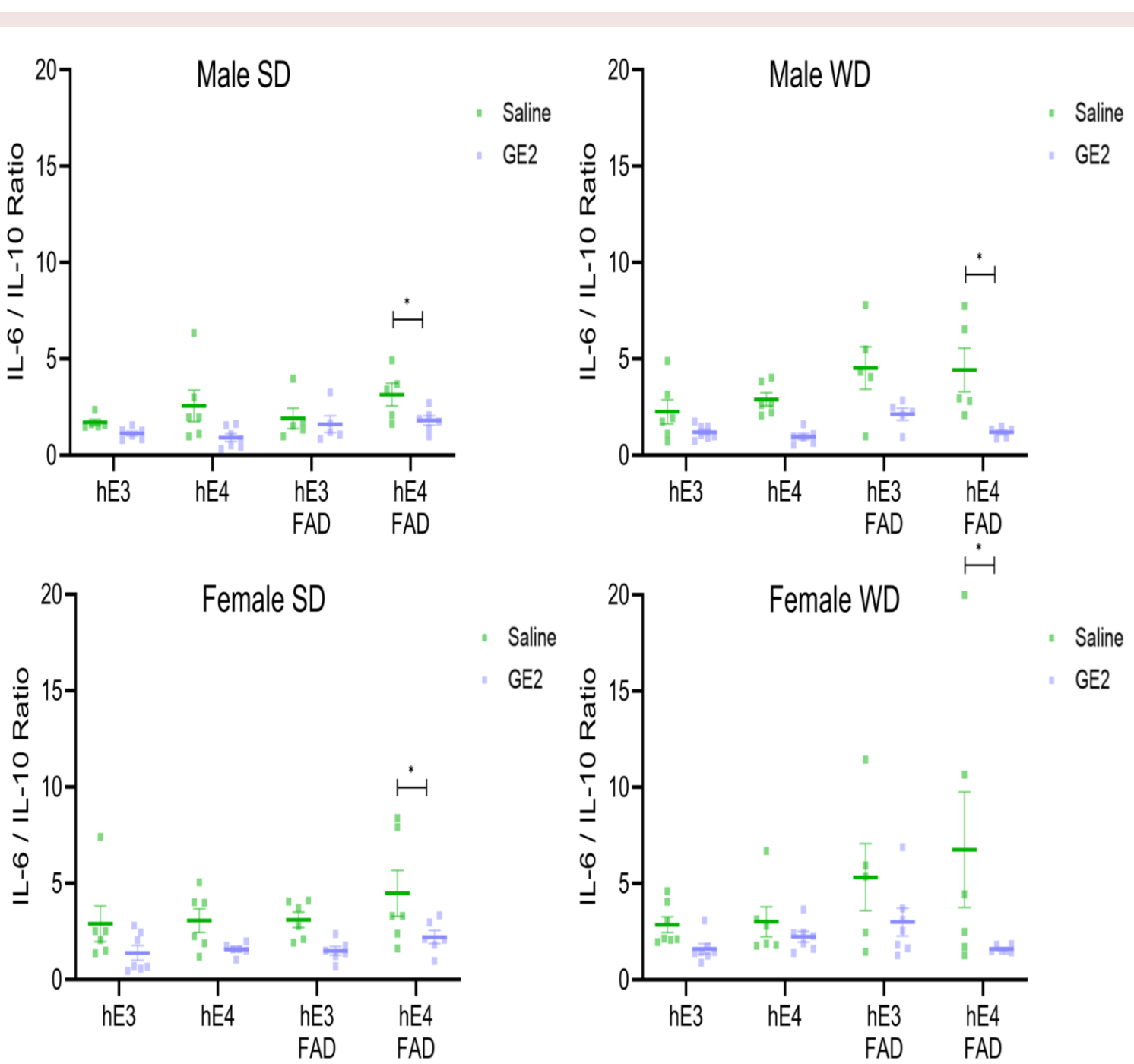
All mice lost weight with daily GE2 injections, but female FAD mice lost the most weight



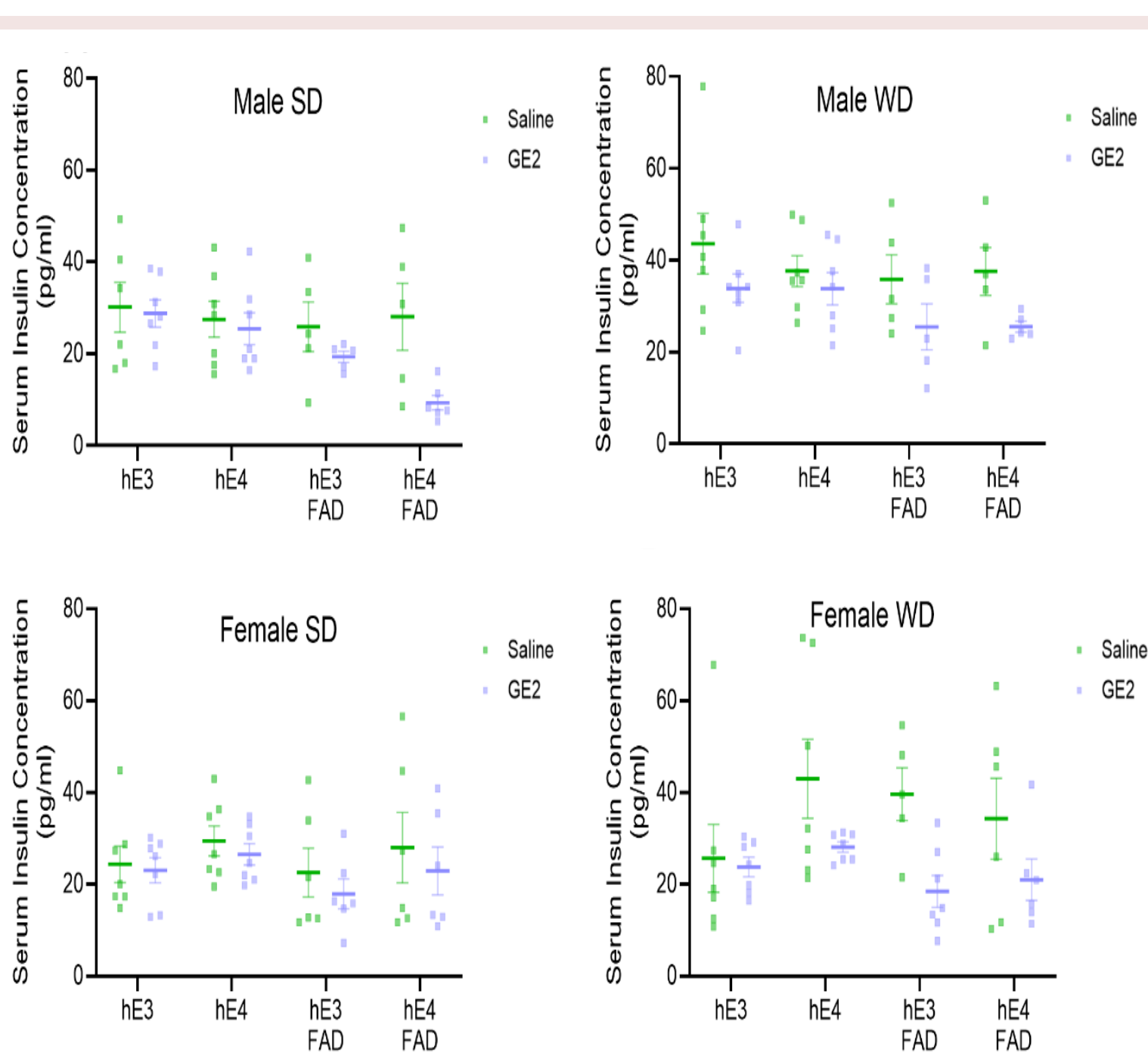
hE4FAD had the highest A β 42/40 ratio. GE2 reduced the ratio in most groups



Females had higher IL-6/IL-10 ratios. GE2 reduced the ratio most in hE4FAD groups



WD increased while GE2 reduced serum insulin levels in all groups



DISCUSSION

GE2 induces significant weight loss across all genotypes, with the most pronounced reduction in female 5xFAD mice.

hE4FAD mice exhibit an elevated A β 42/40 ratio. GE2 treatment successfully attenuates this ratio, particularly in WD fed mice. Notably hE4 mice also had elevated A β pathology compared to hE3.

GE2 modulates the inflammatory landscape by reducing the IL-6/IL-10 ratio, demonstrating its potential to alleviate neuroinflammation in a sex and genotype dependent manner.

This suggests that GE2 administration effectively shifts the metabolic and inflammatory landscape in a genotype dependent manner, with therapeutic efficacy heavily contingent upon metabolic status.

ACKNOWLEDGEMENTS

