Long-term consumption of a typical American diet promotes hepatic lipid deposition and soluble amyloid-beta in the brain, in comparison to a Mediterranean diet

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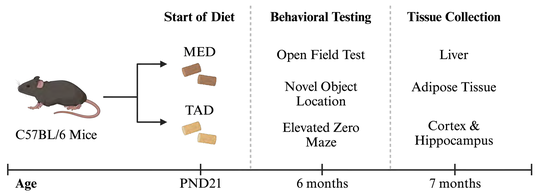
Approximately 1 in 9 Americans over the age of 65 has Alzheimer's disease (AD). As the size of this age group is expected to more than double by 2040, the AD prevalence is likewise predicted to increase rapidly. Two key risk factors for late-onset AD include poor diet and obesity. Therefore, long-term nutritional strategies could potentially reduce the development of hallmark AD biomarkers, such as amyloid beta (Aβ), later in adulthood. Researchers have found that diets extremely rich in saturated fats are associated with increased Aβ production in both the cortex and hippocampus of rodents. Conversely, plant-based Mediterranean diets (MED) that are plentiful in unsaturated fatty acids were shown to mitigate Aβ levels. The relationship between diet and AD biomarkers has been explored in prior animal research, yet most studies utilize extremely high fat diets (40-60% kcal fat) or supplement with individual MD nutritional components. To address these limitations, we designed comprehensive, macronutrient-matched Mediterranean and typical American diets (TAD) that mimic human diets in Mediterranean regions and the U.S., respectively. C57BL/6J mice were weaned onto the diets at postnatal day 21. Following 6 months of diet consumption, we found that the TAD increased soluble $A\beta_{1\text{-}42}$ in the brain. Additionally, mice on the TAD had excess hepatic lipid deposition, which is a hallmark of insulin resistance and metabolic dysregulation, a comorbidity linked to AD risk.

Introduction

- Alzheimer's disease (AD) impacts 10.8% of American adults above the age of 65 (Rajan et al., 2021).
- Key pathologies of AD include chronic inflammation and amyloid-beta plaques, primarily in the hippocampus and cortical regions.
- In the absence of a cure, modifiable risk factors, such as obesity, may be effective targets for reducing AD risk (Livingston et al., 2020; Whitmer et al., 2007).
- A typical American diet (TAD) high in saturated fats and processed sugars is associated with increased obesity risk (Cordain et al., 2005).
- Strict adherence to a largely plant-based Mediterranean diet (MED) rich in fiber and monosaturated fats has been found to reduce the risk of obesity, amyloid-beta accumulation, and cognitive decline (Agarwal et al., 2023; Berti et al., 2018).

Methods



	% kcal	MED	TAD
Carb	50	Brown rice & wheat starch	Corn starch
Fat	35	Olive oil, fish oil, & flaxseed oil	Safflower oil, beef fat, butter
Protein	15	Egg whites, soy, & fish protein	Casein (milk fat)

- Soluble amyloid-beta ($A\beta_{1\text{-}42}$) from the cortex and hippocampus was quantified using an ELISA.
- Paraffin embedded or cryosectioned liver samples were subjected to hematoxylin and eosin (H&E) or Oil Red O staining, respectively.

Results

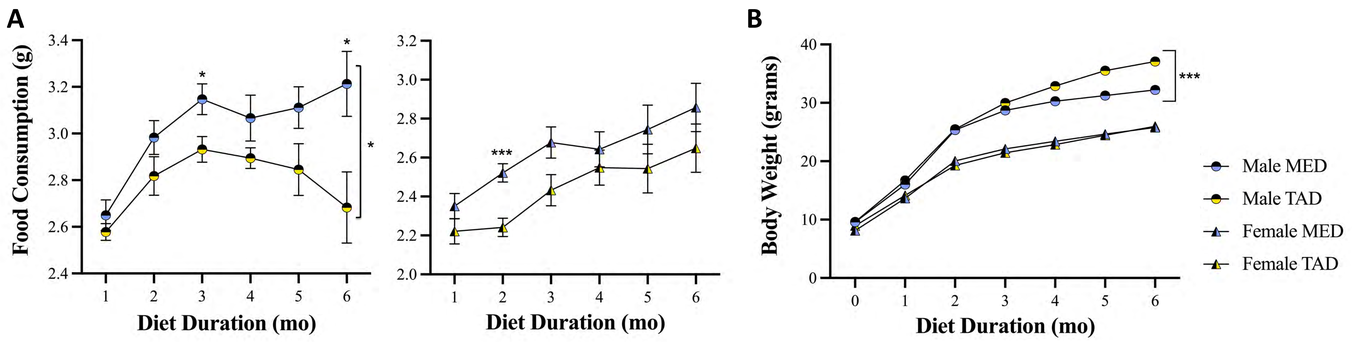


Figure 1. Food consumption and body weight. (A) A mixed design ANOVA revealed a significant main effect of diet (MED vs. TAD) on food intake throughout six months of diet administration in males, such that males on the MED consumed more food. There was no significant main effect of diet on food intake in female mice. **(B)** A mixed design ANOVA revealed a significant main effect of diet (MED vs. TAD) on body weight in male mice, such that males on the MED weighed less than those on the TAD following six months of diet administration. *$p \leq 0.05$, ***$p \leq 0.001$. Bars represent mean ± SEM.

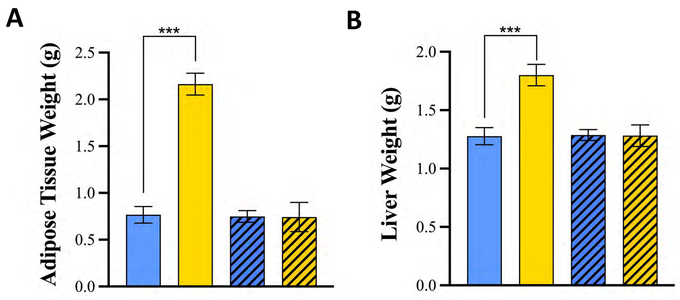


Figure 3. Organ mass. Male mice on the TAD had significantly increased **(A)** abdominal adipose tissue and **(B)** liver mass, compared to males on the MED. There was no significant difference between diet conditions in the female mice. ***$p \leq 0.001$. Bars represent mean ± SEM.

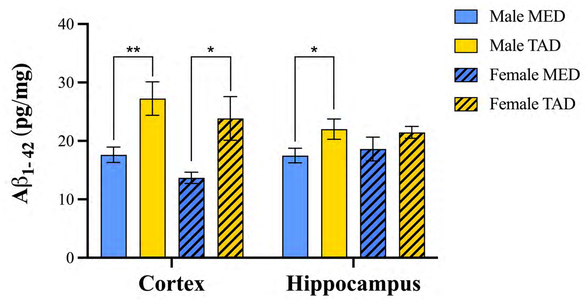


Figure 4. Soluble Aβ in the brain. Male and female mice on the TAD had significantly more cortical amyloid beta ($A\beta_{1\text{-}42}$) compared to mice on the MED. Male mice on the TAD had more hippocampal $A\beta_{1\text{-}42}$ than males on the MED, but this was not observed in females. *$p \leq 0.05$, **$p \leq 0.01$. Bars represent mean ± SEM.

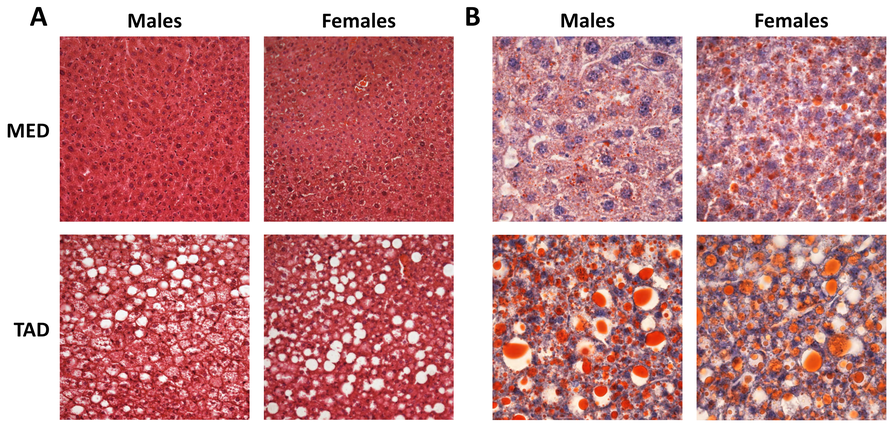


Figure 5. Excess hepatic lipid deposition following TAD consumption. Histological liver stains from male and female mice following six months of MED or TAD consumption. Representative stains using (**A**) H&E and (**B**) Oil Red O. Both male and female mice on the TAD had increased hepatic lipid deposition, compared to mice on the MED.

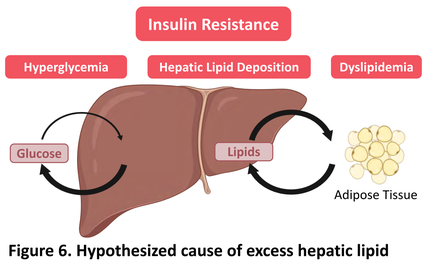


Figure 6. Hypothesized cause of excess hepatic lipid deposition following TAD consumption.

Conclusions

- Male mice on the MED had increased food consumption yet a reduced body weight, in comparison to the TAD. No difference was observed in the females.
- An increase in adipose tissue and liver weight was observed in male mice on the TAD, in comparison to the MED. No difference was observed in the females.
- Males and females on the TAD had increased soluble $A\beta_{1\text{-}42}$ in the cortex, compared to the MED. Only males on the TAD had increased soluble $A\beta_{1\text{-}42}$ in the hippocampus, compared to the MED.
- TAD consumption promoted excess hepatic lipid deposition in males and females, in comparison to the MED.

Future Directions

- Investigate the presence of insulin resistance and its connection to excess hepatic lipid deposition.
- Explore sexual dimorphisms in C57BL/6J mice and the combined effects of diet and estrogen loss on AD neuropathology and hepatic lipid deposition in female mice.

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