

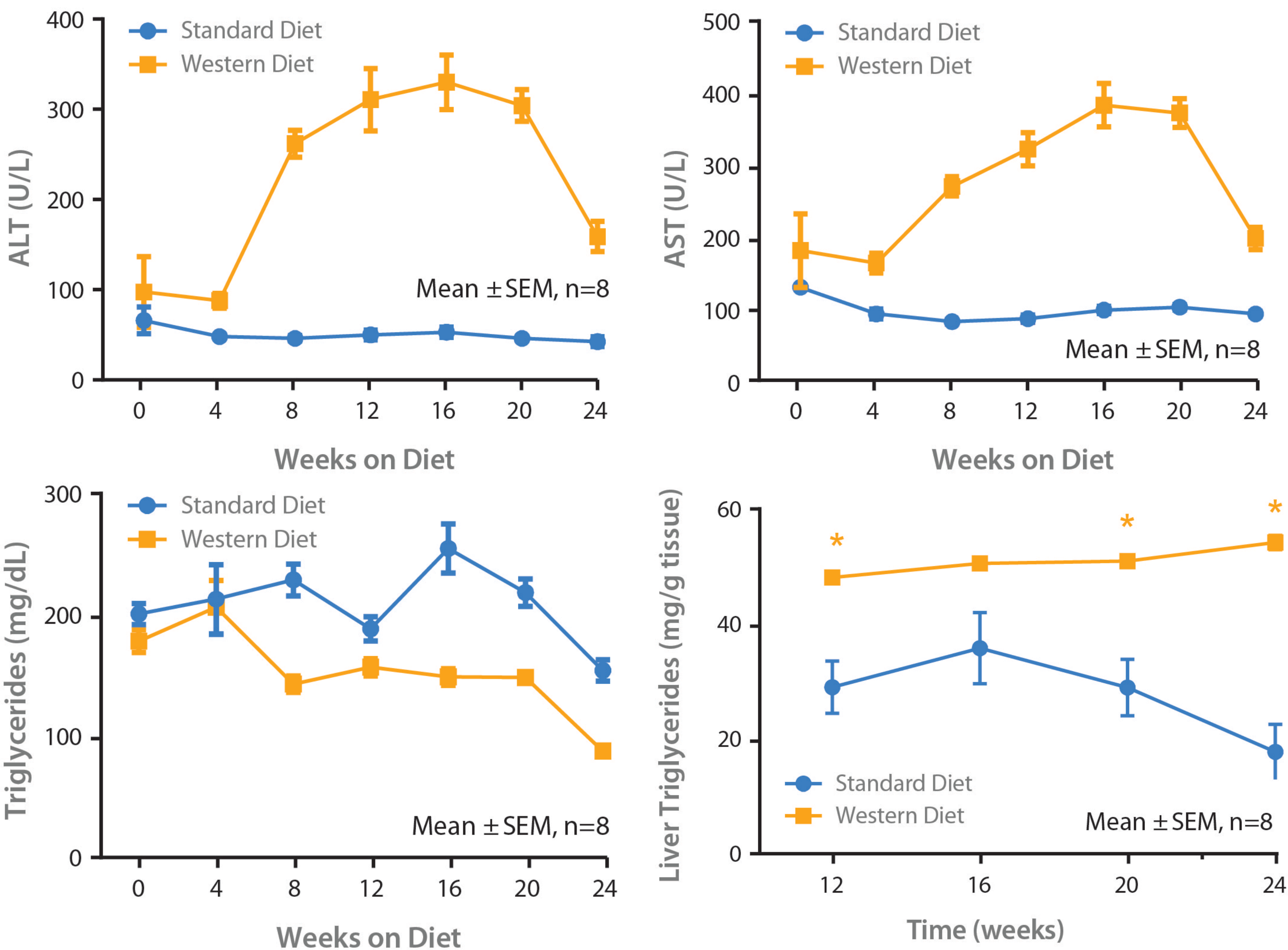
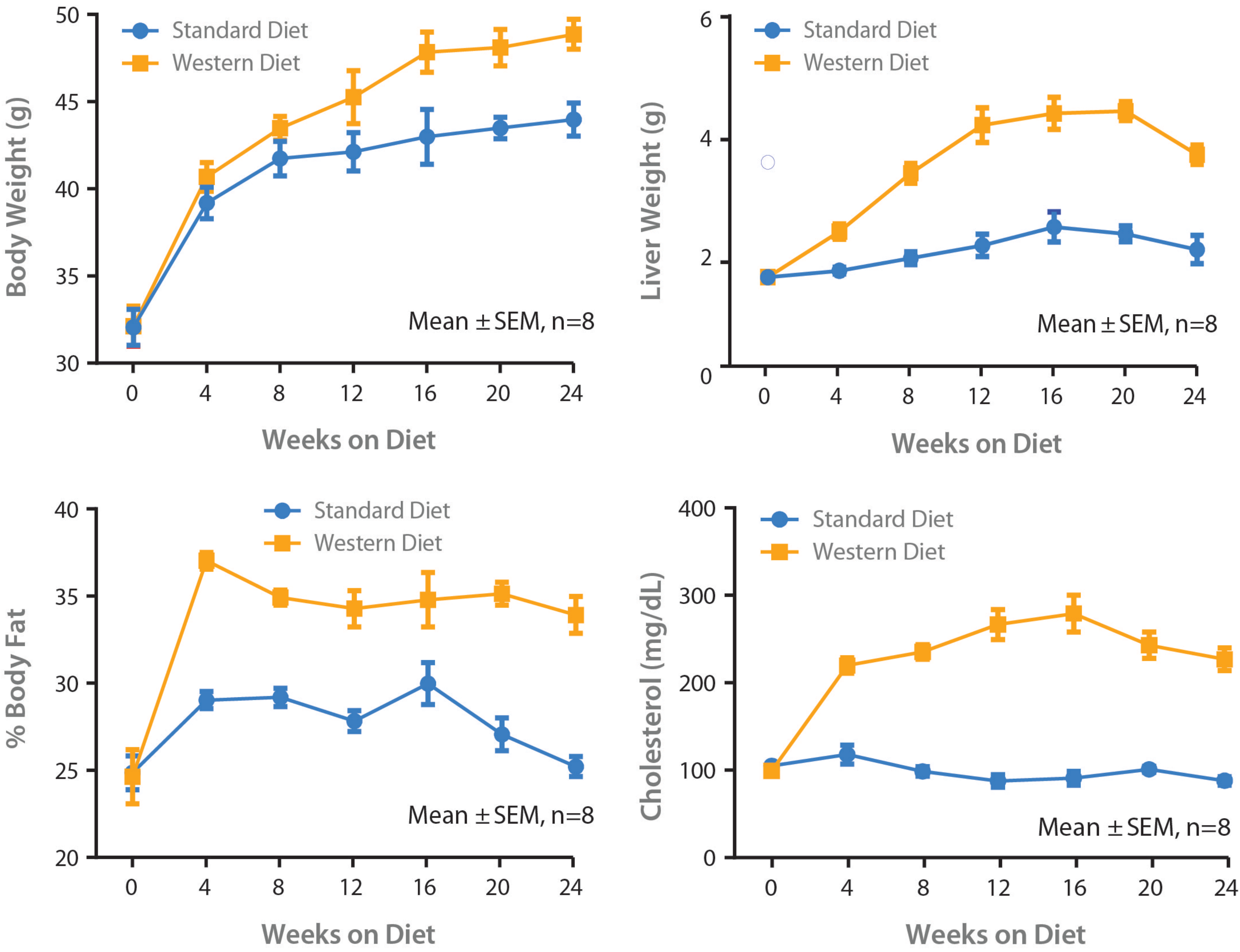
The FATZO Mouse Fed a Western Diet + 5% Fructose Develops NAFLD and NASH

Charles Jackson, Sandeep Sinha, Amar Thyagarajan, and Richard Peterson
Crown Bioscience, Indianapolis, IN 46268

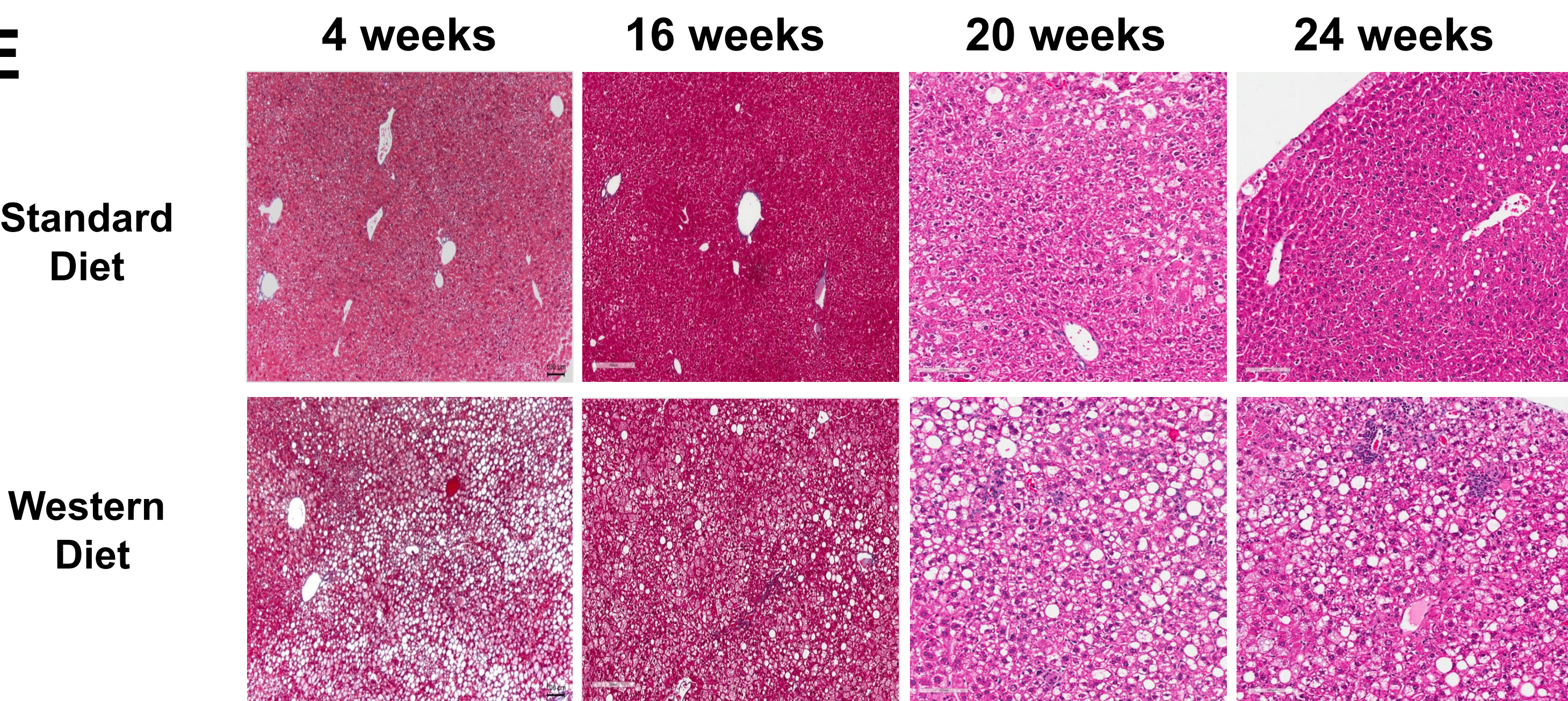
ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is a marker of pathological ectopic fat accumulation combined with a low-grade chronic inflammatory state. The progression of NAFLD from mild steatosis up to severe steatohepatitis (NASH) and even liver cirrhosis and hepatocellular carcinoma, varies widely between individual patients. Insulin resistance and obesity, both key features of the metabolic syndrome, are strongly associated with NAFLD progression. There are no approved pharmacotherapies for the treatment of NAFLD or NASH. The FATZO mouse is a model of type 2 diabetes, with an intact leptin pathway, and spontaneously develops obesity, hyperglycemia, glucose intolerance, and insulin resistance. The purpose of this investigation was to characterize the FATZO mouse fed a Western diet supplemented with fructose in the drinking water as a potential model for NALFD and NASH. Eight week old, FATZO mice (n=96) were randomized based on body weight and glucose into 2 groups of 48 animals each. One group was placed on a Western diet + 5% fructose in their drinking water, the other group remained on regular Purina 5008 diet. Each month 8 animals from each group were terminated and blood was collected via cardiac puncture for the plasma analysis of insulin, ALT, cholesterol, and triglycerides. At termination, livers were collected, weighed, and then split with one part fixed in 10% buffered formalin for histology. The FATZO mouse, when fed a Western diet + fructose demonstrated significant increases in body weight, liver weight, plasma ALT, AST, and cholesterol, liver triglyceride levels, and insulin resistance when compared to animals fed 5008 diet. In addition, animals that were fed the Western diet + fructose for 6 months demonstrated liver steatosis, lobular inflammation, ballooning, and fibrosis compared to animals fed 5008 diet. In conclusion, the FATZO mouse developed NAFLD that progressed to NASH when fed a high fat diet supplemented with fructose. This study suggests that the FATZO mouse can be induced to develop NAFLD and eventually NASH, and can be used as a translational model for the development of anti-NAFLD/NASH pharmacotherapies.

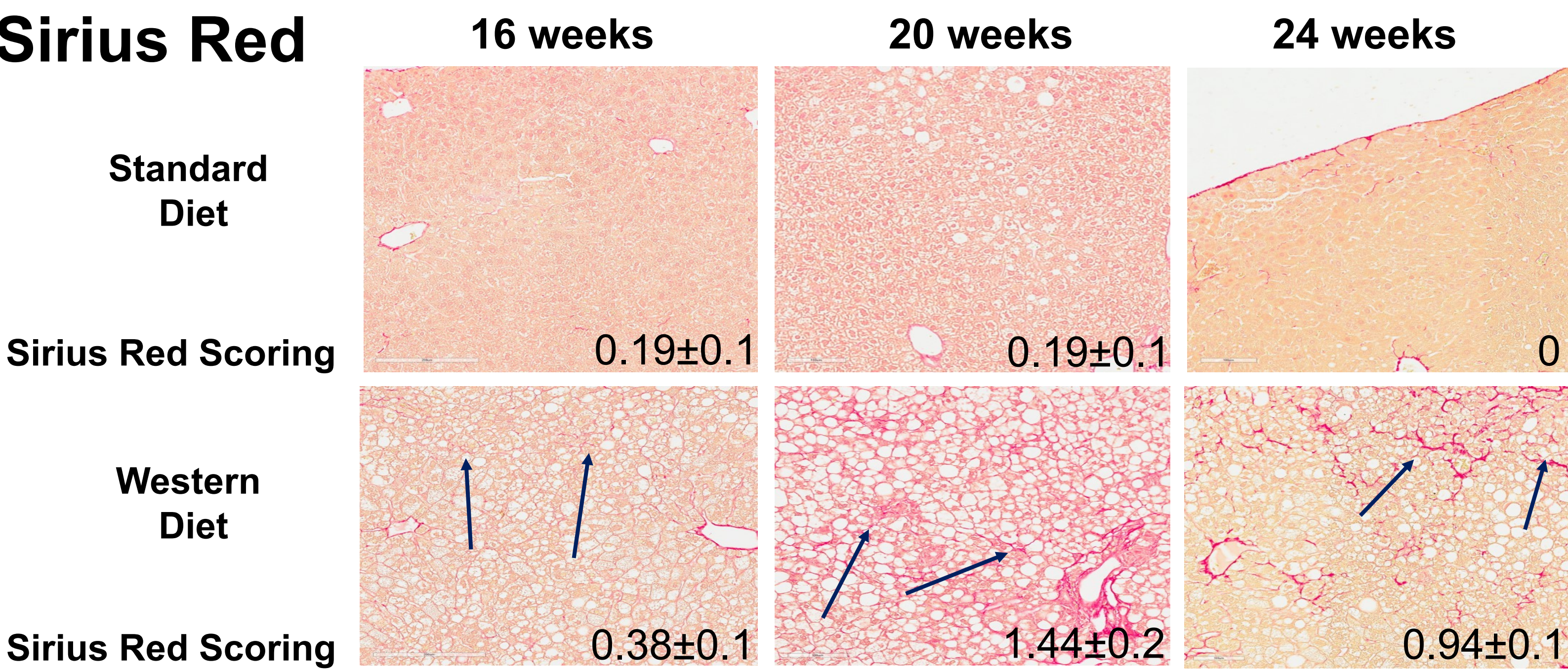
RESULTS



H&E



Sirius Red



SUMMARY

The FATZO mouse develops NAFLD after 2 months on a Western diet + 5% fructose and this phenotype is maintained for up to 5 months. At 4 months, NASH histological scoring demonstrates steatosis, inflammation, ballooning, and early signs of fibrosis.