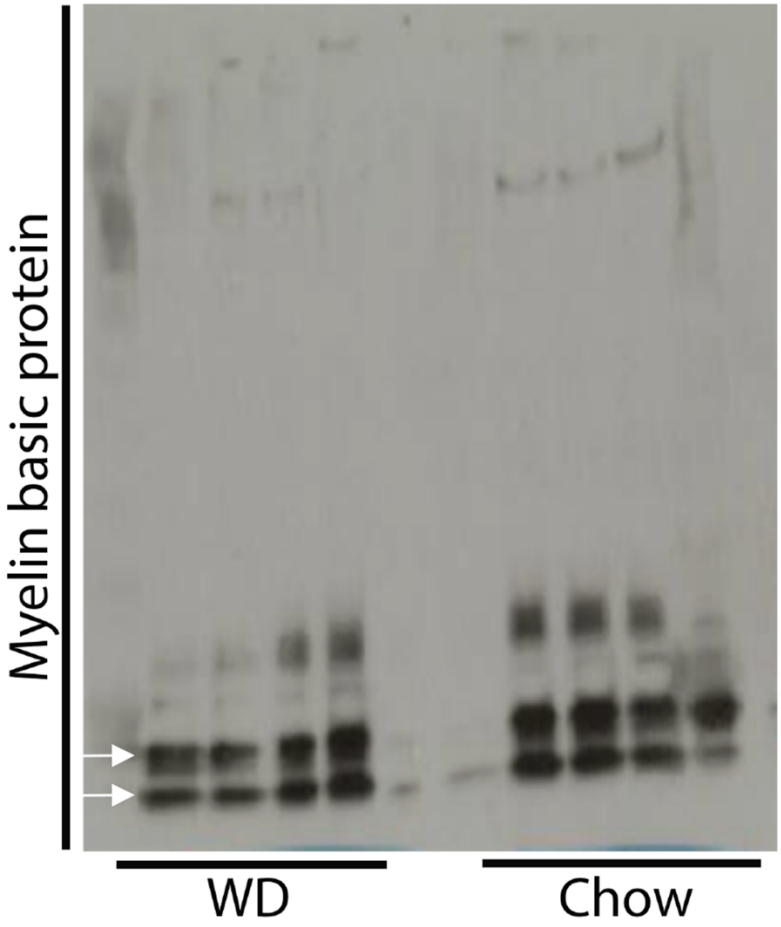
Chow (LabDiet 5K52)		WD (TestDiet 5W80)	
Ingredient	**Composition**	**Ingredient**	**Percentage composition**
Protein	19.3%	Protein	16.0%
Fat	6.2%	Fat	16.4%
Cholesterol	0.240 ppm	Cholesterol	1,739 ppm
Linoleic Acid	2.88%	Linoleic Acid	1.31%
Linolenic Acid	0.37%	Linolenic Acid	0.15%
Omega-3 Fatty Acids	0.46%	Omega-3 Fatty Acids	0.22%
Saturated Fatty Acids	1.24%	Saturated Fatty Acids	8.04%
Fiber	4.3%	Fiber	4.3%
Carbohydrates	61.7%	Carbohydrates	57.6%
Calories provided by:		**Calories provided by:**	
Protein	22.238%	Protein	14.5%
Fat	16.028%	Fat	33.4%
Carbohydrates	61.734%	Carbohydrates	52.1%

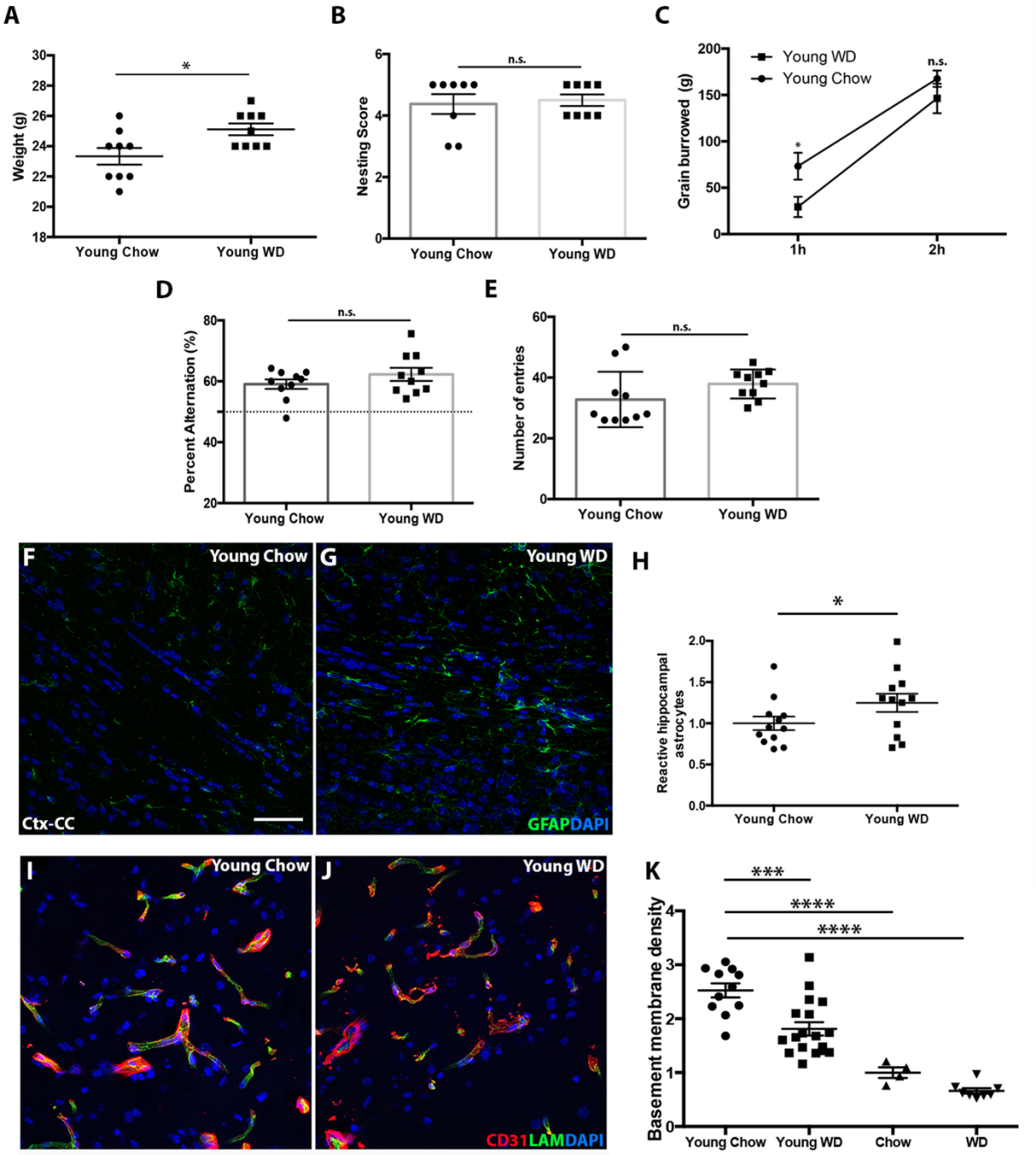
Chow (LabDiet 5K52) Ingredients: Ground wheat, ground corn, wheat middlings, ground oats, fish meal, dehulled soybean meal, soybean oil, corn gluten meal, dehydrated alfalfa meal, dicalcium phosphate, brewers dried yeast, calcium carbonate, menadione dimethylpyrimidinol bisulfite, salt, DL-methionine, choline chloride, magnesium oxide, thiamine mononitrate, pyridoxine hydrochloride, cholecalciferol, vitamin A acetate, calcium pantothenate, ferrous sulfate, biotin, manganous oxide, dl-alpha tocopherylacetate,folicacid,vitaminB_{12} supplement, riboflavin, nicotinic acid, zinc oxide, ferrous carbonate, copper sulfate, zinc sulfate, cobalt carbonate, calcium iodate.

WD (TestDiet 5W80) Ingredients: Corn starch, casein, dextrin, milk fat, high fructose corn syrup, sucrose, fiber, lard, vegetable shortening, powdered cellulose, inulin, vitamin mix/fiber, soybean oil, salt, corn oil, L-cystine, choline bitartrate, cholesterol, t-butylhydroquinone

Supplemental Figure 1. Control chow and WD composition and ingredient lists.

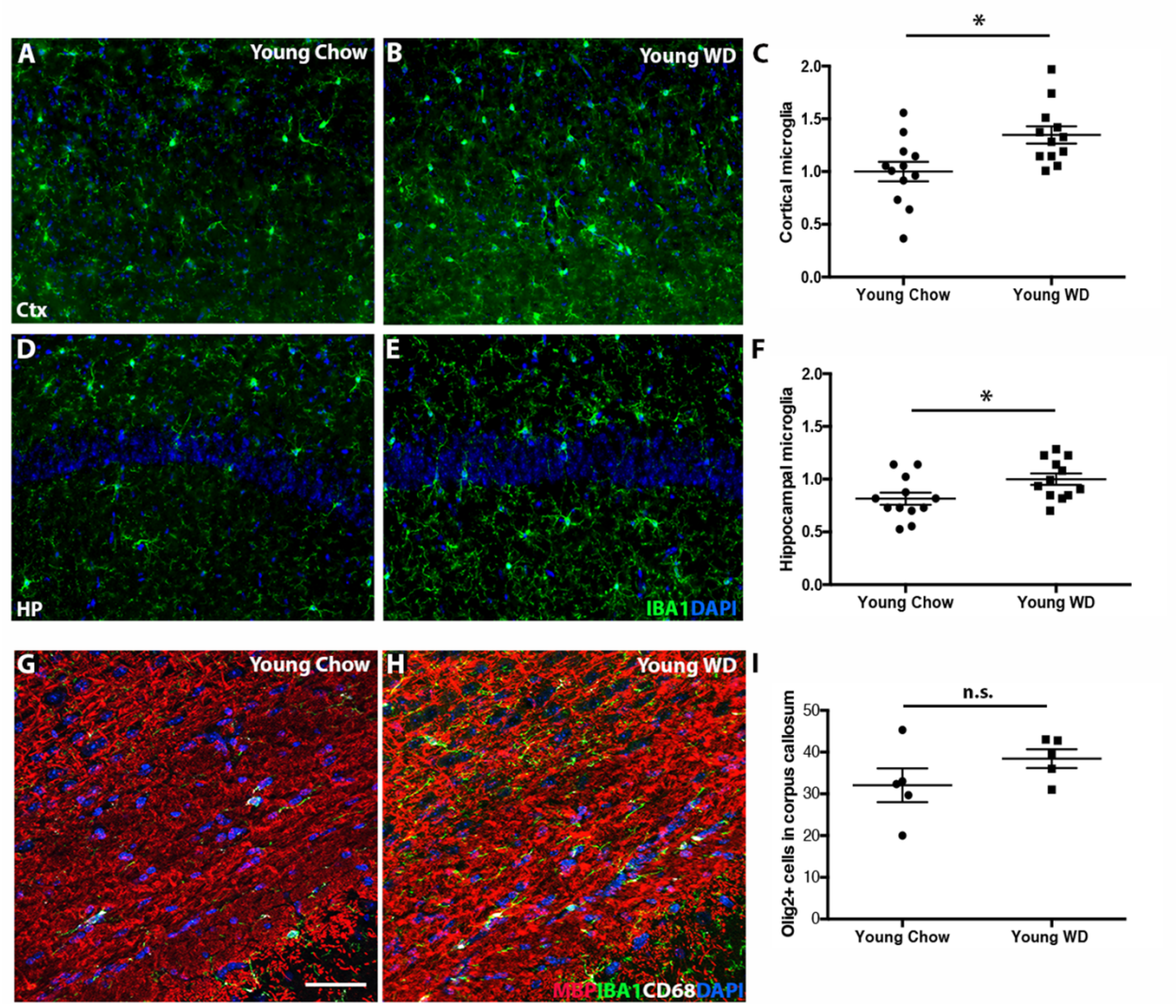


Supplemental Figure 2. Full western blot for myelin basic protein predicted band size 19kDa and 26kDa (Abcam cat#7349).

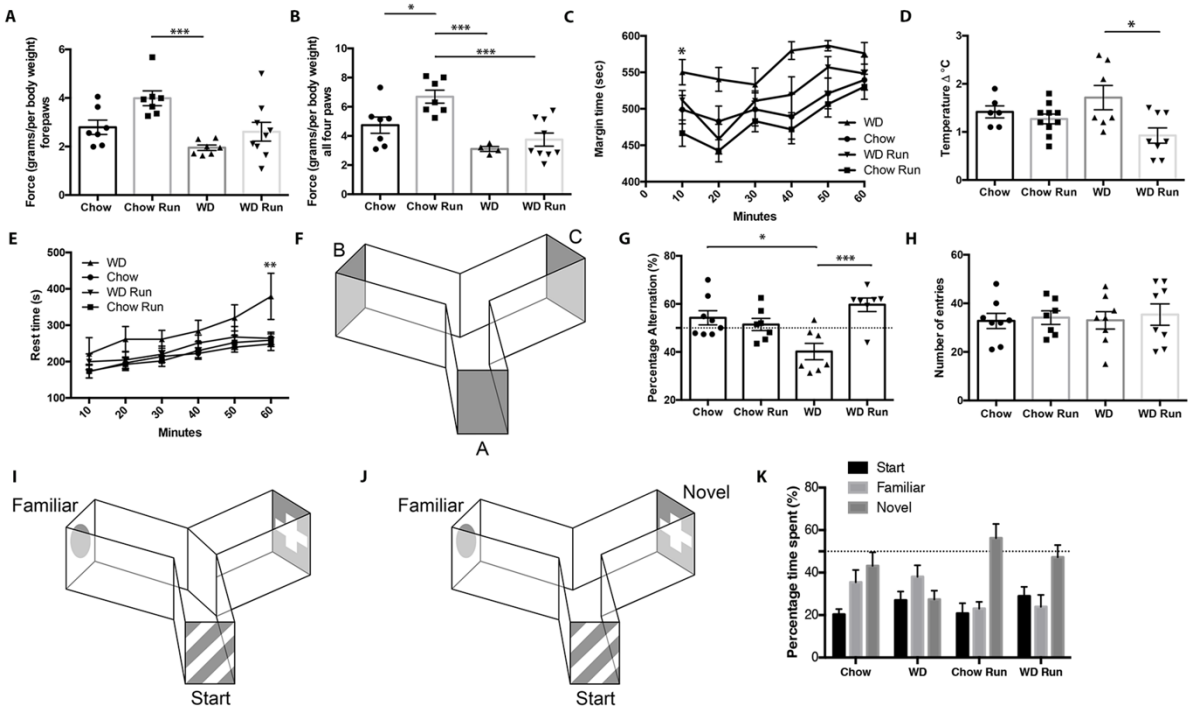


Supplemental Figure 3. Astrocyte reactivity and cerebrovascular decline occurs in young western diet-fed mice, but myelin loss and cognitive deficits do not. (**A**) Short-term WD feeding in young mice significantly increases weight compared to controls (n=9, *p<0.05). (**B**) Nest construction, a natural behavior in cognitively normal

mice, was not significantly different in young WD-fed compared to young chow-fed mice, (*95*) (n=8). (**C**) No significant differences were seen in burrowing, a commonly used assay to measure normal behavior in mice (*113*), in young WD-fed compared to young chow fed mice after two hours (n=8). (**D**) Spontaneous alternation shows no significant difference between young WD-fed and young control chow-fed mice (n=10). (**E**) There is also no significant difference between the number of arm entries comparing young WD-fed mice to young control chow-fed mice (n=10). (**F-K**) Young WD-fed mice show an increase in GFAP+ reactive astrocytes (F-H, green, n=12, *$p<0.05$), a decrease in CD31+ endothelial cells (I, J, red) and a decrease in basement membrane (I-K, green laminin, n≥5, ***$p<0.01$, ****$p<0.001$) in the HP of WD-fed young mice compared to young chow mice. Scale bar 100μm.



Supplemental Figure 4. (**A-F**) WD induces a significant increase in the number of microglia (green) in the cortex (A-C, n=12, *p<0.05) and HP (D-E, n=12, *p<0.05) of WD-fed young mice compared to young chow mice. (**G, H**) Representative images show phagocytosing microglia (white, green) but no loss in myelin (MBP, red) in the FPC/corpus callosum of WD-fed young mice compared to young chow mice. All scale bars are 40mm. (**I**) The number of OLIG2+ cells in the corpus callosum of young chow versus young WD mice is not significant. Scale bar for all images 40μm.



Supplemental Figure 5. Voluntary running prevents WD-induced frailty and cognitive impairment. (**A, B**) Running increases grip strength of forepaws and all four paws in both chow and WD-fed mice (E, n≥7, ***p<0.001) (F, n≥4, *p<0.05, ***p<0.001). (**C**) Running prevents WD-fed mice from spending more time around the margin of the open field arena, a common sign of anxiety (n≥8, *p=0.0273). (**D**) WD causes an increased body temperature change, a phenotype of anxiety. Running prevents this increase. (**E**) Running prevents inactivity caused by WD (n≥8, **p<0.01 specific to 60 minute time point). (**F**) Representative depiction of the Y maze used for spontaneous alternation (see also Fig. 1). (**G**) Running prevents cognitive deficits seen in WD-fed sedentary mice (n≥7, *p<0.05, ***p<0.001). (**H**) Mice in all groups explored the Y maze with the same number of entries (**I, J**) Representative depictions of the Y maze used for novel spatial (refer to Figure 1) (**K**) Both chow and WD running mice show a prevention in short term cognitive impairment. Running mice explore the novel arm more than the

start and familiar arms unlike sedentary mice (n≥7) (****p<0.0001, Chow run novel vs. start and familiar arms) (*p<0.05, WD run novel vs. start arm **p<0.01 WD run novel vs. familiar arm).