**Supplementary File 6**. Results of statistical analyses. f, female; m, male.

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| **Figure** | **Sample size (n)** | **Statistical test** | **Values** |
| Fig. 1B | 10 (f)mice/group | Two-way ANOVA for AUC with Sidak posthoc test | diet: F (2, 54) = 81.3, *p < 0.0001*treatment: F (1, 54) = 39.89, *p < 0.0001*interaction: F (2, 54) = 149.5, p < 0.0001LAD veh vs. LAD DMF:*p < 0.0001*NCD veh vs. NCD DMF:*p < 0.0001*HFbD veh vs. HFbD DMF:*p < 0.0001* |
| Fig. 1D, AUC | 10 (f)mice/group | Scheirer-Ray-Hare test followed by targeted Mann-Whitney U test; Bonferroni-Holm corrected | diet: *χ²* (2) = 6.39, *p = 0.0268*treatment: *χ²* (1) = 6.44, *p = 0.041*interaction: χ² (2) = 7.24, *p = 0.0112*HFbD DMF vs. HFbD veh: *p = 0.0148*NCD DMF vs. LAD DMF: *p = 0.0084*HFbD DMF vs. LAD DMF: *p = 0.0095* |
| Fig. 1D, Neuroscore | 10 (f)mice/group | Scheirer-Ray-Hare test followed by targeted Mann-Whitney U test; Bonferroni-Holm corrected | diet: *χ²* (2) = 7.55, *p = 0.0229*treatment: *χ²* (1) = 4.74, *p = 0.0295*interaction: χ² (2) = 8.97, *p = 0.0113*HFbD DMF vs. HFbD veh: *p = 0.0092*NCD DMF vs. LAD DMF: *p = 0.005*HFbD DMF vs. LAD DMF: *p = 0.0048*  |
| Fig. 1D, Onset | 10 (f)mice/group | Scheirer-Ray-Hare test followed by targeted Mann-Whitney U test; Bonferroni-Holm corrected | diet: *χ²* (2) = 4.11, *p = 0.1281*treatment: *χ²* (1) = 13.12, *p < 0.0003*interaction: χ² (2) = 6.66, *p = 0.0358*HFbD DMF vs. HFbD veh: *p = 0.0012*NCD DMF vs. LAD DMF: *p = 0.006*HFbD DMF vs. LAD DMF: *p = 0.006*   |
| Fig. 2A | 9-10 (f) mice/group | One-way ANOVA | *F* (2, 26) = 22.73, *p = 0.0839* |
| Fig. 2C | 9-10 (f) mice/group | Mann-Whitney U test, FDR adjusted | *p* values for individual lipids are listed in Supplementary Table 2 |
| Fig. 2D | 9-10 (f) mice/group | Kruskal-Wallis test with Dunn’s posthoc test | LAD vs. NCD: *p* = 0.0086LAD vs. HFbD: *p* = 0.0001 |
| Fig. 2E | 8-10 (f) mice/group | Mann-Whitney U test | *p* values for individual lipids are listed in Supplementary Table 3 |
| Figure 2 – figure supplement 1A, Acetic Acid | 9-10 (f) mice/group | Two – way ANOVA | diet: *F* (2, 52) = 2.59,*p* = *0.0842*treatment: *F* (1,52) = 0.7765, *p* = *0.3823*interaction: *F* (2,52) = 1.21, *p* = *0.3074* |
| Figure 2 – figure supplement 1B, Propionic Acid | 9-10 (f) mice/group | Two – way ANOVA | diet: *F* (2, 52) = 0.05,*p* = *0.9512*treatment: *F* (1,52) = 0.6346, *p* = *0.4293*interaction: *F* (2,52) = 0.40, *p* = *0.6708* |
| Fig. 3B, Glycitein | 8-10 (f) mice/group | Scheirer-Ray-Hare test followed by targeted Mann-Whitney U test; Bonferroni-Holm corrected | diet: *χ²* (2) = 42.94, *p < 0.0001**treatment: χ²* (1) = 0.07, *p = 0.7913*interaction: χ² (2) = 0.32, *p = 0.8521*NCD DMF vs. LAD DMF: *p < 0.001*HFbD DMF vs. NCD DMF: *p < 0.001*NCD veh vs. LAD veh: *p < 0.001*HFbD veh vs. LAD veh: *p = 0.0082*HFbD veh vs. NCD veh: *p < 0.001* |
| Fig. 3B, Equol | 8-10 (f) mice/group | Scheirer-Ray-Hare test followed by targeted Mann-Whitney U test; Bonferroni-Holm corrected | diet: *χ²* (2) = 40.77, *p < 0.0001**treatment: χ²* (1) = 0.01, *p = 0.9203*interaction: χ² (2) = 1.54, *p = 0.4630*NCD DMF vs. LAD DMF: *p < 0.001*HFbD DMF vs. NCD DMF: *p < 0.001*NCD veh vs. LAD veh: *p < 0.001*HFbD veh vs. LAD veh: *p = 0.0105*HFbD veh vs. NCD veh: *p < 0.001* |
| Fig. 3C, N-Acetyltyrosine | 8-10 (f) mice/group | Scheirer-Ray-Hare test followed by targeted Mann-Whitney U test; Bonferroni-Holm corrected | diet: *χ²* (2) = 15.69, *p = 0.0004*treatment: *χ²* (1) = 0.07, *p = 0.7913*interaction: χ² (2) = 0.98, *p = 0.6126*HFbD veh vs. LAD veh: *p = 0.0246*  |
| Fig. 3C,sphingosine 1-phosphate | 8-10 (f) mice/group | Scheirer-Ray-Hare test followed by targeted Mann-Whitney U test; Bonferroni-Holm corrected | diet: *χ²* (2) = 14.85, *p = 0.0006*treatment: *χ²* (1) = 0.80, *p = 0.3711*interaction: χ² (2) = 2.74, *p = 0.2541*NCD DMF vs. LAD DMF: *p = 0.031* HFbD DMF vs. LAD DMF: *p = 0.0126* |
| Fig. 3D, Glutamyl-glutamine | 8-10 (f) mice/group | Scheirer-Ray-Hare test followed by targeted Mann-Whitney U test; Bonferroni-Holm corrected | diet: *χ²* (2) = 4.13, *p = 0.1268*treatment: *χ²* (1) = 22.45, *p < 0.0001*interaction: χ² (2) = 3.08, *p = 0.2144*LAD DMF vs. LAD veh: *p = 0.002*HFbD DMF vs. HFbD veh: *p < .001* |
| Fig. 3D, Uracil | 8-10 (f) mice/group | Scheirer-Ray-Hare test followed by targeted Mann-Whitney U test; Bonferroni-Holm corrected | diet: *χ²* (2) = 5.20, *p = 0.0743*treatment: *χ²* (1) = 22.45, *p < 0.0001*interaction: χ² (2) = 1.47, *p = 0.4795*LAD DMF vs. LAD veh: *p = p < .001*NCD DMF vs. NCD veh: *p = 0.0104*HFbD DMF vs. HFbD veh: *p = 0.0232* |
| Fig. 4B, Alpha diversity | 9-10 (f) mice/group | Scheirer-Ray-Hare test followed by targeted Mann-Whitney U test; Bonferroni-Holm corrected | diet: *χ²* (2) = 36.63, *p < 0.0001*treatment: *χ²* (1) = 0.03, *p = 0,8625*interaction: χ² (2) = 0.46, *p = 0,4976*HFbD DMF vs. LAD DMF: *p < 0.001*HFbD DMF vs. NCD DMF: *p < 0.001*HFbD veh vs. LAD veh: *p < 0.001*HFbD veh vs. NCD veh: *p < 0.001* |
| Fig. 4C, Prevotellamassila | 9-10 (f) mice/group | Scheirer-Ray-Hare test followed by targeted Mann-Whitney U test; Bonferroni-Holm corrected | diet: *χ²* (2) = 26.87, *p < 0.0001*treatment: *χ²* (1) = 0.74, *p = 0,3897*interaction: χ² (2) = 0.25, *p = 0,8825*HFbD DMF vs. LAD DMF: *p = 0.0048*HFbD DMF vs. NCD DMF: *p = 0.0048*HFbD veh vs. LAD veh: *p = 0.0025*HFbD veh vs. NCD veh: *p = 0.0012* |
| Fig. 4C,*Parabacteriodes* | 9-10 (f) mice/group | Scheirer-Ray-Hare test followed by targeted Mann-Whitney U test; Bonferroni-Holm corrected,  | diet: *χ²* (2) = 47.08, *p < 0.0001*treatment: *χ²* (1) = 0.01, *p = 0.9203*interaction: χ² (2) = 0.75, *p = 0.6873*NCD DMF vs. LAD DMF: *p < 0.001*HFbD DMF vs. LAD DMF: *p < 0.001*HFbD DMF vs. NCD DMF: *p < 0.001*NCD veh vs. LAD veh: *p < 0.001*HFbD veh vs. LAD veh: *p < 0.001*HFbD veh vs. NCD veh: *p < 0.001* |
| Fig. 4C,*Acetatifactor* | 9-10 (f) mice/group | Scheirer-Ray-Hare test followed by targeted Mann-Whitney U test; Bonferroni-Holm corrected | diet: *χ²* (2) = 10.20, *p = 0.0061**treatment: χ²* (1) = 1.48, *p = 0.2238*interaction: χ² (2) = 6.64, *p = 0.0362*NCD DMF vs. LAD DMF: *p = 0.024*NCD veh vs. LAD veh: *p = 0.0135*HFbD veh vs. LAD veh: *p = 0.0441*HFbD DMF vs. HFbD veh: *p = 0.0441* |
| Fig. 5B  | 8-10 (3-4f, 5-6m)mice/group;excluded, 4 mice found dead (2 DMF and 2 Vehicle)  | Scheirer-Ray-Hare test followed by targeted Mann-Whitney U test; Bonferroni-Holm corrected | genotype: *χ²* (1) = 0.90, *p = 0.3428*treatment: *χ²* (1) = 8.97, p = 0.0027interaction: χ² (1) = 4.83, *p* = 0.028*Hca2****+/+*** DMF vs. *Hca2****+/+*** veh: *p* = 0.0052*Hca2****-/-*** DMF vs. *Hca2****+/+*** DMF: *p* = 0.0165*Hca2+/+* veh vs. *Hca2-/-* veh*: p* = 0.4044 |
| Fig. 6C, monocytes intermediate | 5-6 (1-4f, 3-5m)mice/group; excluded, 1 mouse terminated due to eczema (LAD/DMF) | Two-way ANOVA,with Bonferroni posthoc test | diet: *F* (1,19) = 7.76,*p* = *0.0118*treatment: *F* (1,19) = *0.99*,*p* = *0.3325*interaction: *F* (1,19) = 0.34, *p* = *0.5675*HFbD veh vs. LAD veh: *p = 0.0493* |
| Fig. 6 – figure supplement 1B, monocytes high | 5-6(1-4f, 3-5m)mice/group; excluded, 1 mouse terminated due to eczema (LAD/DMF) | Two – way ANOVAwith Bonferroni posthoc test | diet: *F* (1, 19) = 4.70,*p* = *0.0431*treatment: *F* (1,19) = 1.07,*p* = *0.3142*interaction: *F* (1,19) = 0.68, *p* = *0.4181*HFbD DMF vs. LAD DMF: *p = 0.1047*HFbD veh vs. LAD veh: *p = 0.6874* |
| Fig. 6 – figure supplement 2A, microglia | 4-6(1-4f, 3-5m) mice/group | Two-way ANOVA, with Bonferroni posthoc test | diet: F (1, 17) = 8.331, *p = 0.0103*treatment: F (1, 17) = 0.7878, *p = 0.3872*interaction: F (1, 17) = 0.8181, *p = 0.3784*HFbD DMF vs. LAD DMF: *p = 0.0374* |
| Fig. 7B  | 4 (1-3f, 1-3m)mice/group,50 cells/mouse | One-way ANOVAwith Bonferroni posthoc test | *F* (3,12) = 35.00,*p* < 0.0001 *Hca2Fl/Fl*vs. *Hca2****nKO:*** *p = 0.0089**Hca2+/+*vs. *Hca2****-/-:*** *p = <0.0001**Hca2+/+*vs. *Hca2****nKO****p = 0.0014, p =*  |
| Fig. 7D | 4 (4m) mice per group | Unpaired Student t-test | Hca2Fl/Fl vs Hca2nKO: T (6) = 14.59, *p < 0.0001* |
| Fig. 8B, AUC  | 10-13 (5-7f, 4-8m)mice/group | Scheirer-Ray-Hare test followed by targeted Mann-Whitney U test; Bonferroni-Holm corrected | treatment: *χ²* (1) = 10.35, *p = 0.0013**genotype: χ²* (1) = 0.39, *p = 0.5323*interaction: χ² (1) = 2.30, *p = 0.1294* *Hca2Fl/Fl*DMF vs. *Hca2Fl/Fl*veh: *p = 0.0038* |
| Fig. 9C, *Btg2* | 5 (7f, 8m)mice/group | Two-way ANOVAwith Bonferroni posthoc test | diet: *F* (2,24) = 0.83,*p = 0.4500*treatment: *F* (1,24) = *7.37**p* = *0.0121*interaction: *F* (2,24) = 0.87, *p* = *0.4306* |
| Fig. 9C, *Il1b* | 5 (7f, 8m)mice/group | Two-way ANOVAwith Bonferroni posthoc test | diet: *F* (2,24) = 0.35,*p = 0.0356*treatment: *F* (1,24) = 0.21*p* = *0.6509*interaction: *F* (2,24) = 0.42, *p* = *0.6636* |
| Fig. 10A | 6-8 wells/group | Unpaired Student t-test | HFbD MMF vs. HFbD veh: *T* (14) = 3.99, *p = 0.0013* |
| Fig. 10B | 5-6 wells/group | One-way ANOVAwith Bonferroni posthoc test | *LAD*F (2, 15) = 3,795, *p = 0.0464*CTRL vs. MMF: *p = 0.0447**HFbD**F* (2, 14) = 5.66, *p = 0.0158*CTRL vs. PMA: *p = 0.0298*PMA vs. MMF: *p = 0.0236* |