Methods

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
NCBI Short Read Archive: raw sequencing data from all samples, including sample metadata	Kap et al., 2018	PRJAN693190
Software and algorithms		
R code required to reproduce all analyses	This paper	https://github.com/sasugden/marmosets

Resource Availability

Lead contact

All inquiries and requests for further information should be directed to and will be fulfilled by the Lead Contact, Jens Walter, jenswalter@ucc.ie.

Materials availability

This study did not generate any new specimens or materials.

Data and code availability

The raw sequencing data obtained by Kap et al. has been deposited under the NCBI BioProject accession PRJAN693190. The R code required to reproduce all analyses is available from https://github.com/sasugden/marmosets.

Experimental Model and Subject Details

This study is based exclusively on publicly available data generated by Kap et al. (2018). All experiments were conducted on eight adult dizygotic bone marrow-chimeric common marmoset (*Callithrix jacchus*) twin pairs of equal gender that were housed at the

Biomedical Primate Research Centre (Rijswijk, the Netherlands). Full details on animal models, husbandry, and care are available in the original manuscript.

Method Details

In Kap et al.'s experiment, one sibling from each of the marmoset twin pairs was reverted to the WBS diet, while the other sibling was kept on the YBS diet for the duration of the experiment. EAE was induced via injection of rhMOG into the dorsal skin eight weeks after the dietary change. Marmosets were euthanized within three days of developing an EAE score of 2.5 (paresis of one or more limbs) or at the predetermined end day of the study (120 days after immunization) if they did not reach that EAE score. Microbiome samples were collected at four separate time points, which we identified using the same titles at Kap et al.(2018): day -56 refers to the baseline (time point before diet change, 56 days before EAE induction), day -7 refers to animals seven weeks after the diet change (or one week before EAE induction), and day 21 and day 49 refer to three and seven weeks after disease induction, respectively.

Quantification and Statistical Analysis

16S rRNA gene sequence processing

Although Kap et al. used the PANDAseq QIIME pipeline for read processing, we chose to use a previously established pipeline in our lab (Deehan et al., 2020; Nguyen et al., 2020; Patry et al., 2019) that uses a combination of publicly available tools. This decision was made in recognition of the fact that there is no single best bioinformatics pipeline. Our goal

was to mirror the natural variation in results associated with different bioinformatics approaches as a way of getting a different perspective of the data.

In our pipeline, raw paired-end reads provided by Kap et al.(2018) were trimmed to 250 bases using the FASTX-toolkit (hannonlab.cshl.edu/fastx_toolkit/index.html). Reads were quality-filtered and paired using the merge-illumina-pairs application from Illumina utils (Eren et al., 2013). Sequences that did not meet the quality criteria (p-value of 0.03 or three or fewer mismatches in the overlapped region, enforced Q30 check, perfect matching to primers, and no ambiguous nucleotides) were discarded. If data for a later time point was missing (as in the case of marmosets that met endpoint criteria before day 49), data obtained from the samples collected at necropsy was carried forward.

After trimming and quality filtering, we obtained a total of 4,315,807 paired sequences (average 55,331±12,922; minimum=16,413; maximum=83,126). Files were subsampled to 16,000 sequences based on the sample with the lowest number of reads. Usearch v.10 (Edgar, 2013) was used to compile and dereplicate sequences, discard singletons, remove chimeras, cluster OTUs at 98% identity, identify representative sequences for OTUs, and generate a final OTU table. Non-chimeric sequences were binned by sample/subject and submitted to the Ribosomal Database Project Classifier (Wang et al., 2007) for taxonomic assignment from phyla to genera. OTUs were assigned a species identity by submitting representative sequences to the Silva ACT database (Quast et al., 2013), and taxonomic assignments confirmed using NCBI blastn (Altschul et al., 1990),

EZ biocloud (Yoon et al., 2017), and Ribosomal Database Project Seqmatch (Michigan State University, 2016).

OTU tables were imported into R 3.6.3 (R Core Team, 2018) for statistical analyses. Raw sequence counts were transformed to relative abundance in percent, and, with the exception of the yogurt species *Lactobacillus delbrueckii*, taxa with a mean relative abundance of ≤0.10% in the entire dataset were removed. All downstream analyses were performed in the R statistical environment.

Mixed-effect models and diversity analyses

We used a combination of mixed-effect models and ordination analyses to test for significant differences in alpha- and beta-diversity between treatment groups and among time points. Alpha diversity measures, including species richness, Simpson's diversity, and Pielou's evenness, were calculated using the package *phyloseq* (McMurdie and Holmes, 2013), and a Bray-Curtis distance matrix was generated using the package *vegan* (Oksanen et al., 2019). We calculated inter-individual Bray-Curtis distances at each time point as the average distance from each sample to every other sample taken at that same time point and intra-individual Bray-Curtis distances as the average distance among all samples from the same individual.

We then used linear mixed-effect models implemented in the package lme4 (Bates et al., 2015) to determine whether diet or the development of pathology affected microbiome diversity. For each diversity measure, we designed models predicting diversity as a

function of diet (WBS or YBS), pathology (diseased or healthy), and time point (to account for the fact that pathology was only observed at the fourth time point). We originally tested models that included interactions between diet and pathology and between diet and time, but few of these interactions were significant and, due to the small sample size, including these terms often led to overfit or singular models, so we therefore proceeded with our three-predictor model structure. All models also included a random intercept term for subject nested within twin pair to account for the repeated-measures nature of the study and natural similarities among marmoset twins, as follows:

$$\text{Diversity} = \text{Diet}_{(\text{WBS or YBS})} + \text{Time}_{(\text{day } -56,-21,7,49)} + \text{Pathology}_{(\text{yes or no})} + (1|\text{TwinPair/Subject})$$

All response variables were mean-centered and standardized prior to model construction to facilitate comparisons across models. We fit models using maximum likelihood to enable among-model comparisons, and we identified the best predictors of diversity by evaluating all subsets of each model construction using the corrected Akaike's information criterion (AICc) and averaging predictor coefficients for all models with a ΔAICc < 2. A variable was considered significant if the 95% confidence interval of its coefficient did not overlap zero.

We tested for differences in overall community composition using a Bray-Curtis distance-based permutational multivariate analysis of variance (PERMANOVA) and the permutational test for multivariate dispersion (PERMDISP), and we visualized compositional differences using non-metric dimensional scaling (NMDS). These analyses were executed using the metaMDS, adonis and betadisper functions from the R package

vegan (Oksanen et al., 2019). To thoroughly investigate variation throughout the experiment, we compared communities between diets at each time point, within diets relative to the previous time point, and between healthy and symptomatic monkeys on each diet. We used the R^2 value from each PERMANOVA comparison as a measure of the percentage of variation in community composition that was explained by each analysis, with larger R^2 values indicating that a variable was a better indicator of group differences.

To identify how individual taxa were related to diet or pathology, we repeated our mixed-effect model procedure (as described above) using $\log_{10}$-transformed taxon abundances as the response variables, as follows:

$$\log_{10}(\text{relative abundance}) = \text{Diet}_{(\text{WBS or YBS})} + \text{Time}_{(\text{day } -56,-21,7,49)} + \text{Pathology}_{(\text{yes or no})} + (1|\text{TwinPair/Subject})$$

We also attempted to pinpoint specific taxonomic changes caused by diet and/or disease induction on the gut microbiome by calculating the $\log_{10}$-transformed changes in relative abundance between consecutive time points for each marmoset and running the same models using the absolute value of this "delta abundance" as a response variable, as follows:

$$\log_{10}(|\text{delta abundance}|) = \text{Diet}_{(\text{WBS or YBS})} + \text{Time}_{(\text{day } -56,-21,7,49)} + \text{Pathology}_{(\text{yes or no})} + (1|\text{TwinPair/Subject})$$

Where $\text{delta abundance} = (\text{relative abundance})_{t+1} - (\text{relative abundance})_t$ and *t* indicates the experimental time point. In this way, we tested for both (1) consistent microbial associations with diet and/or pathology throughout the entire experiment and (2) diet and/or pathology-related shifts in taxon abundances between experimental time points. In the manuscript, we only display results for taxa present at ≥0.05% relative abundance and for which the absolute values of predictor coefficients were ≥0.5.

All modeling procedures were supported by pairwise comparisons among marmoset groups separated by diet, time point, and the presence of pathology: we compared WBS- and YBS-fed monkeys at each time point, as well as diseased and healthy monkeys within each diet group at the fourth time point. We also tested between-time point comparisons within each diet group to isolate specific changes caused by the intervention between time points (day -56 to -7 for the effect of diet, day -7 to day 21 for the effect of disease induction, and day -7 to 49 for the effect of pathology). These pairwise comparisons were implemented for alpha-diversity data and both absolute and delta relative abundances. Alpha diversity data was tested using an ANOVA followed by Tukey's *post hoc* test, with pairwise comparisons restricted to only the comparisons of interest (described above). Species abundances were tested using Student's t-tests, with p-values corrected for multiple comparisons using the false discovery rate (FDR) correction. Statistical significance was defined at $p < 0.05$ after the FDR correction.

Additional ecological effects

To determine how diet, pathology and other ecological variables (sibling pair, cage, time) affected overall community composition, or β-diversity, we used both unsupervised and supervised clustering approaches. In the supervised approach, we performed Bray-Curtis distance-based redundancy analysis (dbRDA) based on diet, pathology, time point, cage, sibling pair, and subject identity and used an ANOVA to identify which terms contributed significantly to community structure. Statistical significance was defined at $p<0.05$ for all β-diversity analysis. We additionally determined which predictors had the strongest

explanatory power by examining the adjusted-R^2 values of separate dbRDA models in which each variable was the sole predictor, as well as using a forward selection procedure implemented with the ordi2step function in *vegan* (Oksanen et al., 2019). We evaluated R^2 values from the dbRDA using the same criteria as before.

We also evaluated the importance of including sibling pair and individual identity as a nested random effect in our mixed-effect models (above) by comparing the conditional and marginal R^2 values for each model. These values were calculated using the r.squaredGLMM function in the package MuMIn; we used the marginal R^2 as an indicator of the variance explained by the fixed effects, and the difference between the conditional and marginal R^2 as an indicator of the variance explained by random effects. Larger R^2 values indicated that a given component of the model, either the fixed effects (diet, pathology, and time) or random effects (sibling pair and individual identity), was a better predictor of taxon abundances.

Marmoset nutritional demands

To ensure that any diet-related health benefits of the YBS supplement were the result of any differences in overall nutrient provisioning, we additionally assessed whether both the YBS and WBS diets met all the nutritional requirements for moderately active marmosets. Notably, the YBS provided more total protein and calories than the WBS. Of the total weekly number of calories provided by each supplement, 18% came from protein in the YBS compared to only 15% in the WBS. With respect to energy requirements, the basal metabolic rate (BMR) and field metabolic rate (FMR) for non-pregnant marmosets (which

weigh approximately 250 g) with a moderately active lifestyle have been estimated to be around 25 kcal/d (102 Kj/d) and 43 kcal (79 Kj), respectively (National Research Council, 2003). The WBS provided approximately 200 kcal (838 Kj) per week, while the YBS provided around 216 kcal (905 Kj) per week. Therefore, even though both supplements met more than 100% of the BMR of the marmosets, the WBS and YBS met only 67% and 72% of the marmoset FMR, respectively. To meet the marmoset FMR, Kap et al. (2018) supplied the difference in energy requirements as food sources other than the supplement (e.g., nuts, fruits, and gums). It therefore appears that all major nutritional requirements were met by both diets.

References

Afrache, H., Gouret, P., Ainouche, S., Pontarotti, P., Olive, D., 2012. The butyrophilin (BTN) gene family: from milk fat to the regulation of the immune response. Immunogenetics *64*, 781–794. 10.1007/s00251-012-0619-z

Al-Ghezi, Z.Z., Busbee, P.B., Alghetaa, H., Nagarkatti, P.S., Nagarkatti, M., 2019. Combination of cannabinoids, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), mitigates experimental autoimmune encephalomyelitis (EAE) by altering the gut microbiome. Brain. Behav. Immun. *82*, 25–35. 10.1016/j.bbi.2019.07.028

AlAmmar, W.A., Albeesh, F.H., Ibrahim, L.M., Algindan, Y.Y., Yamani, L.Z., Khattab, R.Y., 2019. Effect of omega-3 fatty acids and fish oil supplementation on multiple sclerosis: a systematic review. Nutr. Neurosci. 10.1080/1028415X.2019.1659560

Altschul, S.F., Gish, W., Miller, W., Myers, E.W., Lipman, D.J., 1990. Basic local alignment search tool. J. Mol. Biol. *215*, 403–410. 10.1016/S0022-2836(05)80360-2

Alvarez, J.I., Cayrol, R., Prat, A., 2011. Disruption of central nervous system barriers in multiple sclerosis. Biochim. Biophys. Acta *1812*, 252–264. 10.1016/j.bbadis.2010.06.017

Arboleya, S., Watkins, C., Stanton, C., Ross, R.P., 2016. Gut *Bifidobacteria* populations in human health and aging. Front. Microbiol. *7*, 1204. 10.3389/fmicb.2016.01204

Bander, Z. Al, Nitert, M.D., Mousa, A., Naderpoor, N., 2020. The gut microbiota and inflammation: An overview. Int. J. Environ. Res. Public Health *17*, 7618. 10.3390/ijerph17207618

Barnard, D., Knapka, J., Renquist, D., 1988. The apparent reversal of a wasting syndrome by nutritional intervention in *Saguinus mystax*. Lab. Anim. Sci. *38*, 282–288.

Barnes, C.J., Rasmussen, L., Asplund, M., Knudsen, S.W., Clausen, M.-L., Agner, T., Hansen, A.J., 2020. Comparing DADA2 and OTU clustering approaches in studying the bacterial communities of atopic dermatitis. J. Med. Microbiol. *69*, 1293–1302. 10.1099/jmm.0.001256

Bates, D., Mächler, M., Bolker, B.M., Walker, S.C., 2015. Fitting linear mixed-effects models using lme4. J. Stat. Softw. *67*, 1–48. 10.18637/jss.v067.i01

Beltrán, E., Gerdes, L.A., Hansen, J., Flierl-Hecht, A., Krebs, S., Blum, H., Ertl-Wagner, B., Barkhof, F., Kümpfel, T., Hohlfeld, R., Dornmair, K., 2019. Early adaptive immune activation detected in monozygotic twins with prodromal multiple sclerosis. J. Clin. Invest. *129*, 4758–4768. 10.1172/JCI128475

Berer, K., Gerdes, L.A., Cekanaviciute, E., Jia, X., Xiao, L., Xia, Z., Liu, C., Klotz, L., Stauffer, U., Baranzini, S.E., et al., 2017. Gut microbiota from multiple sclerosis patients enables spontaneous autoimmune encephalomyelitis in mice. Proc. Natl.

Acad. Sci. U. S. A. *114*, 10719–10724. 10.1073/pnas.1711233114

Berer, K., Martínez, I., Walker, A., Kunkel, B., Schmitt-Kopplin, P., Walter, J., Krishnamoorthy, G., 2018. Dietary non-fermentable fiber prevents autoimmune neurological disease by changing gut metabolic and immune status. Sci. Rep. *8*, 10431. 10.1038/s41598-018-28839-3

Berer, K., Mues, M., Koutrolos, M., Rasbi, Z. Al, Boziki, M., Johner, C., Wekerle, H., Krishnamoorthy, G., 2011. Commensal microbiota and myelin autoantigen cooperate to trigger autoimmune demyelination. Nature *479*, 538–541. 10.1038/nature10554

Berghoff, S.A., Gerndt, N., Winchenbach, J., Stumpf, S.K., Hosang, L., Odoardi, F., Ruhwedel, T., Böhler, C., Barrette, B., Stassart, R., et al., 2017. Dietary cholesterol promotes repair of demyelinated lesions in the adult brain. Nat. Commun. *8*, 14241. 10.1038/ncomms14241

Bindels, L.B., Segura Munoz, R.R., Gomes-Neto, J.C., Mutemberezi, V., Martínez, I., Salazar, N., Cody, E.A., Quintero-Villegas, M.I., Kittana, H., de los Reyes-Gavilán, C.G., et al., 2017. Resistant starch can improve insulin sensitivity independently of the gut microbiota. Microbiome *5*, 12. 10.1186/s40168-017-0230-5

Bitarafan, S., Harirchian, M.-H., Nafissi, S., Sahraian, M.-A., Togha, M., Siassi, F., Saedisomeolia, A., Alipour, E., Mohammadpour, N., Chamary, M., et al., 2014. Dietary intake of nutrients and its correlation with fatigue in multiple sclerosis patients. Iran. J. Neurol. *13*, 28–32.

Bivona, G., Gambino, C.M., Iacolino, G., Ciaccio, M., 2019. Vitamin D and the nervous system. Neurol. Res. *41*, 827–835. 10.1080/01616412.2019.1622872

Blanchard, B., Heurtaux, T., Garcia, C., Moll, N.M., Caillava, C., Grandbarbe, L.,

Klosptein, A., Kerninon, C., Frah, M., Coowar, D., et al., 2013. Tocopherol derivative tfa-12 promotes myelin repair in experimental models of multiple sclerosis. J. Neurosci. *33*, 11633–11642. 10.1523/JNEUROSCI.0774-13.2013

Bokulich, N.A., Kaehler, B.D., Rideout, J.R., Dillon, M., Bolyen, E., Knight, R., Huttley, G.A., Caporaso, J.G., 2018. Optimizing taxonomic classification of marker-gene amplicon sequences with QIIME 2's q2-feature-classifier plugin. Microbiome *6,* 90. 10.1186/s40168-018-0470-z

Bromley, L., Horvath, P.J., Bennett, S.E., Weinstock-Guttman, B., Ray, A.D., 2019. Impact of nutritional intake on function in people with mild-to-moderate multiple sclerosis. Int. J. MS Care *21*, 1–9. 10.7224/1537-2073.2017-039

Butcher, P.J., 1986. Milk consumption and multiple sclerosis--an etiological hypothesis. Med. Hypotheses *19*, 169–178.

Caballero-Villarraso, J., Jiménez-Jiménez, M.J., Escribano, B.M., Agüera, E., Santamaría, A., Túnez, I., 2019. Role of vitamin D in multiple sclerosis and other neurodegenerative processes: bibliometric analysis and systematic review. CNS Neurol. Disord. - Drug Targets 18. 10.2174/1871527318666190703102330

Cantorna, M.T., Humpal-Winter, J., DeLuca, H.F., 1999. Dietary calcium is a major factor in 1,25-dihydroxycholecalciferol suppression of experimental autoimmune encephalomyelitis in mice. J. Nutr. *129*, 1966–1971. 10.1093/jn/129.11.1966

Castelo-Branco, G., Stridh, P., Guerreiro-Cacais, A.O., Adzemovic, M.Z., Falcão, A.M., Marta, M., Berglund, R., Gillett, A., Hamza, K.H., Lassmann, H., et al., 2014. Acute treatment with valproic acid and l-thyroxine ameliorates clinical signs of experimental autoimmune encephalomyelitis and prevents brain pathology in DA rats. Neurobiol.

Dis. *71*, 220–233. 10.1016/j.nbd.2014.08.019

Cekanaviciute, E., Yoo, B.B., Runia, T.F., Debelius, J.W., Singh, S., Nelson, C.A., Kanner, R., Bencosme, Y., Lee, Y.K., Hauser, S.L., et al., 2017. Gut bacteria from multiple sclerosis patients modulate human T cells and exacerbate symptoms in mouse models. Proc. Natl. Acad. Sci. U. S. A. *114*, 10713–10718. 10.1073/pnas.1711235114

Chen, H., Ma, X.X., Liu, Y., Ma, L., Chen, Z., Lin, X., Si, L., Ma, X.X., Chen, X., 2019. Gut microbiota interventions with *Clostridium butyricum* and norfloxacin modulate immune response in experimental autoimmune encephalomyelitis mice. Front. Immunol. *10*, 1662. 10.3389/fimmu.2019.01662

Chen, J., Chia, N., Kalari, K.R., Yao, J.Z., Novotna, M., Soldan, M.M.P., Luckey, D.H., Marietta, E. V., Jeraldo, P.R., Chen, X., et al., 2016. Multiple sclerosis patients have a distinct gut microbiota compared to healthy controls. Sci. Rep. *6*, 28484. 10.1038/srep28484

Chen, T., Noto, D., Hoshino, Y., Mizuno, M., Miyake, S., 2019. Butyrate suppresses demyelination and enhances remyelination. J. Neuroinflammation *16*, 165. 10.1186/s12974-019-1552-y

Chu, F., Shi, M., Lang, Y., Shen, D., Jin, T., Zhu, J., Cui, L., 2018. Gut microbiota in multiple sclerosis and experimental autoimmune encephalomyelitis: current applications and future perspectives. Mediat. Inflamm *2018*, 8168717. 10.1155/2018/8168717

Claesson, M.J., Cusack, S., O'Sullivan, O., Greene-Diniz, R., De Weerd, H., Flannery, E., Marchesi, J.R., Falush, D., Dinan, T., Fitzgerald, G., et al., 2011. Composition,

variability, and temporal stability of the intestinal microbiota of the elderly. Proc. Natl. Acad. Sci. U. S. A. *108*, 4586–4591. 10.1073/pnas.1000097107

Cree, B.A.C., Spencer, C.M., Varrin-Doyer, M., Baranzini, S.E., Zamvil, S.S., 2016. Gut microbiome analysis in neuromyelitis optica reveals overabundance of Clostridium perfringens. Ann. Neurol. *80*, 443–447. 10.1002/ana.24718

Cryan, J.F., O'riordan, K.J., Cowan, C.S.M., Sandhu, K. V., Bastiaanssen, T.F.S., Boehme, M., Codagnone, M.G., Cussotto, S., Fulling, C., Golubeva, A. V., et al., 2019. The microbiota-gut-brain axis. Physiol. Rev. *99*, 1877–2013. 10.1152/physrev.00018.2018

Daddaoua, A., Puerta, V., Zarzuelo, A., Suárez, M.D., Sánchez de Medina, F., Martínez-Augustin, O., 2005. Bovine glycomacropeptide is anti-inflammatory in rats with hapten-induced colitis. J. Nutr. *135*, 1164–1170. 10.1093/jn/135.5.1164

Dalla Costa, G., Romeo, M., Esposito, F., Sangalli, F., Colombo, B., Radaelli, M., Moiola, L., Comi, G., Martinelli, V., 2019. Caesarean section and infant formula feeding are associated with an earlier age of onset of multiple sclerosis. Mult. Scler. Relat. Disord. *33*, 75–77. 10.1016/j.msard.2019.05.010

Dargahi, N., Matsoukas, J., Apostolopoulos, V., 2020. *Streptococcus thermophilus* ST285 alters pro-inflammatory to anti-inflammatory cytokine secretion against multiple sclerosis peptide in mice. Brain. Sci. *10*, 126. 10.3390/brainsci10020126

David, L.A., Maurice, C.F., Carmody, R.N., Gootenberg, D.B., Button, J.E., Wolfe, B.E., Ling, A. V., Devlin, A.S., Varma, Y., Fischbach, M.A., et al., 2014. Diet rapidly and reproducibly alters the human gut microbiome. Nature *505*, 559–563. 10.1038/nature12820

Deehan, E.C., Yang, C., Perez-Muñoz, M.E., Nguyen, N.K., Cheng, C.C., Triador, L., Zhang, Z., Bakal, J.A., Walter, J., 2020. Precision microbiome modulation with discrete dietary fiber structures directs short-chain fatty acid production. Cell Host Microbe *27*, 389–404.e6. 10.1016/j.chom.2020.01.006

Dobbing, J., 1964. The influence of early nutrition on the development and myelination of the brain. Proc. R. Soc. London. Ser. B. Biol. Sci. *159*, 503–509. 10.1098/rspb.1964.0016

Edgar, R.C., 2013. UPARSE: highly accurate OTU sequences from microbial amplicon reads. Nat. Methods *10*, 996–998. 10.1038/nmeth.2604

Eren, A.M., Vineis, J.H., Morrison, H.G., Sogin, M.L., 2013. A filtering method to generate high quality short reads using illumina paired-end technology. PLoS One *8*, e66643. 10.1371/journal.pone.0066643

Esposito, S., Sparaco, M., Maniscalco, G.T., Signoriello, E., Lanzillo, R., Russo, C., Carmisciano, L., Cepparulo, S., Lavorgna, L., Gallo, A., et al., 2021. Lifestyle and Mediterranean diet adherence in a cohort of Southern Italian patients with multiple sclerosis. Mult. Scler. Relat. Disord. *47*, 102636. 10.1016/j.msard.2020.102636

Fairlie-Clarke, K.J., Shuker, D.M., Graham, A.L., 2009. Why do adaptive immune responses cross-react? Evol. Appl. *2*, 122. 10.1111/J.1752-4571.2008.00052.X

Fan, Y., Zhang, J., 2019. Dietary modulation of intestinal microbiota: future opportunities in experimental autoimmune encephalomyelitis and multiple sclerosis. Front. Microbiol. *10,* 740. 10.3389/fmicb.2019.00740

Fischbach, M.A., 2018. Microbiome: focus on causation and mechanism. Cell *174*, 785–790. 10.1016/j.cell.2018.07.038

342 Forsythe, P., Kunze, W.A., 2013. Voices from within: gut microbes and the CNS. Cell.
343 Mol. Life Sci *70*, 55–69. 10.1007/s00018-012-1028-z
344 Freedman, S.N., Shahi, S.K., Mangalam, A.K., 2018. The “gut feeling”: breaking down the
345 role of gut microbiome in multiple sclerosis. Neurotherapeutics *15*, 109–125.
346 10.1007/s13311-017-0588-x
347 Ogunrinola, G.A., Oyewale, J.O., Oshamika, O.O., Olasehinde, G.I., 2020. The human
348 microbiome and its impacts on health. Int. J. Microbiol. *2020*, 8045646.
349 10.1155/2020/8045646
350 Gandy, K.A.O., Zhang, J., Nagarkatti, P., Nagarkatti, M., 2019. The role of gut microbiota
351 in shaping the relapse-remitting and chronic-progressive forms of multiple sclerosis
352 in mouse models. Sci. Rep. *9*, 6923. 10.1038/s41598-019-43356-7
353 Gerdes, L.A., Janoschka, C., Eveslage, M., Mannig, B., Wirth, T., Schulte-Mecklenbeck,
354 A., Lauks, S., Glau, L., Gross, C.C., Tolosa, E., et al., 2020. Immune signatures of
355 prodromal multiple sclerosis in monozygotic twins. Proc. Natl. Acad. Sci. U. S. A. *117*,
356 21546–21556. 10.1073/pnas.2003339117
357 Goldberg, P., Fleming, M.C., Picard, E.H., 1986. Multiple sclerosis: decreased relapse
358 rate through dietary supplementation with calcium, magnesium and vitamin D. Med.
359 Hypotheses *21*, 193–200. 10.1016/0306-9877(86)90010-1
360 Goodrich, J.K., Davenport, E.R., Beaumont, M., Jackson, M.A., Knight, R., Ober, C.,
361 Spector, T.D., Bell, J.T., Clark, A.G., Ley, R.E., 2016. Genetic determinants of the gut
362 microbiome in UK twins. Cell Host Microbe *19*, 731–743.
363 10.1016/j.chom.2016.04.017
364 Goodrich, J.K., Waters, J.L., Poole, A.C., Sutter, J.L., Koren, O., Blekhman, R., Beaumont,

M., Van Treuren, W., Knight, R., Bell, J.T., et al., 2014. Human genetics shape the gut microbiome. Cell *159*, 789–799. 10.1016/j.cell.2014.09.053

Goudarzvand, M., Javan, M., Mirnajafi-Zadeh, J., Mozafari, S., Tiraihi, T., 2010. Vitamins E and D3 attenuate demyelination and potentiate remyelination processes of hippocampal formation of rats following local injection of ethidium bromide. Cell. Mol. Neurobiol. *30*, 289–299. 10.1007/s10571-009-9451-x

Grice, E.A., Segre, J.A., 2012. The human microbiome: our second genome. Annu. Rev. Genomics Hum. Genet. *13*, 151–170. 10.1146/annurev-genom-090711-163814

Guggenmos, J., Schubart, A.S., Ogg, S., Andersson, M., Olsson, T., Mather, I.H., Linington, C., 2004. Antibody cross-reactivity between myelin oligodendrocyte glycoprotein and the milk protein butyrophilin in multiple sclerosis. J. Immunol. *172*, 661–668. 10.4049/jimmunol.172.1.661

Hadley, K., Ryan, A., Forsyth, S., Gautier, S., Salem, N., 2016. The essentiality of arachidonic acid in infant development. Nutrients *8*, 216. 10.3390/nu8040216

Haghikia, A., Jörg, S., Duscha, A., Berg, J., Manzel, A., Waschbisch, A., Hammer, A., Lee, D.-H., May, C., Wilck, N., et al., 2015. Dietary fatty acids directly impact central nervous system autoimmunity via the small intestine. Immunity *43*, 817–829. 10.1016/j.immuni.2015.09.007

He, B., Hoang, T.K., Tian, X., Taylor, C.M., Blanchard, E., Luo, M., Bhattacharjee, M.B., Freeborn, J., Park, S., Couturier, J., et al., 2019. *Lactobacillus reuteri* reduces the severity of experimental autoimmune encephalomyelitis in mice by modulating gut microbiota. Front. Immunol. 10, 385. 10.3389/fimmu.2019.00385

Hill, M.O., 1973. Diversity and evenness: a unifying notation and its consequences.

Ecology *54*, 427–432. 10.2307/1934352

Hirschberg, S., Gisevius, B., Duscha, A., Haghikia, A., 2019. Implications of diet and the gut microbiome in neuroinflammatory and neurodegenerative diseases. Int. J. Mol. Sci. *20*, 3109. 10.3390/ijms20123109

Ismailova, K., Poudel, P., Parlesak, A., Frederiksen, P., Heitmann, B.L., 2019. Vitamin D in early life and later risk of multiple sclerosis—a systematic review, meta-analysis. PLoS One *14,* e0221645. 10.1371/journal.pone.0221645

Jagannath, V.A., Filippini, G., Di Pietrantonj, C., Asokan, G. V, Robak, E.W., Whamond, L., Robinson, S.A., 2018. Vitamin D for the management of multiple sclerosis. Cochrane Database Syst. Rev. *9*, CD008422. 10.1002/14651858.CD008422.pub3

Janakiraman, M., Krishnamoorthy, G., 2018. Emerging role of diet and microbiota interactions in neuroinflammation. Front. Immunol. *9,* 2067. 10.3389/fimmu.2018.02067

Jangi, S., Gandhi, R., Cox, L.M., Li, N., Von Glehn, F., Yan, R., Patel, B., Mazzola, M.A., Liu, S., Glanz, B.L., et al., 2016. Alterations of the human gut microbiome in multiple sclerosis. Nat. Commun. *7*, 12015. 10.1038/ncomms12015

Jun, S.M., Ochoa-Repáraz, J., Zlotkowska, D., Hoyt, T., Pascual, D.W., 2012. Bystander-mediated stimulation of proteolipid protein-specific regulatory T (Treg) cells confers protection against experimental autoimmune encephalomyelitis (EAE) via TGF-β. J. Neuroimmunol. *245*, 39–47. 10.1016/j.jneuroim.2012.02.003

Kap, Y.S., Bus-Spoor, C., van Driel, N., Dubbelaar, M.L., Grit, C., Kooistra, S.M., Fagrouch, Z.C., Verschoor, E.J., Bauer, J., Eggen, B.J.L., et al., 2018. Targeted diet modification reduces multiple sclerosis–like disease in adult marmoset monkeys from

an outbred colony. J. Immunol. *201*, 3229–3243. 10.4049/jimmunol.1800822

Karav, S., Le Parc, A., Leite Nobrega de Moura Bell, J.M., Frese, S.A., Kirmiz, N., Block, D.E., Barile, D., Mills, D.A., 2016. Oligosaccharides released from milk glycoproteins are selective growth substrates for infant-associated Bifidobacteria. Appl. Environ. Microbiol. *82*, 3622–3630. 10.1128/AEM.00547-16

Katz Sand, I., 2018. The role of diet in multiple sclerosis: mechanistic connections and current evidence. Curr. Nutr. Rep *7,* 150–160. 10.1007/s13668-018-0236-z

Kaya, M., Ahishali, B., 2011. The role of magnesium in edema and blood brain barrier disruption. In Magnesium in the Central Nervous System, R. Vink, M. Nechifor, eds. (University of Adelaide Press).

Kim, M., Kim, C.H., 2017. Regulation of humoral immunity by gut microbial products. Gut Microbes *8*, 392–399. 10.1080/19490976.2017.1299311

Kinross, J.M., Darzi, A.W., Nicholson, J.K., 2011. Gut microbiome-host interactions in health and disease. Genome Med. *3,* 14. 10.1186/gm228

Kobayashi, T., Suzuki, T., Kaji, R., Serata, M., Nagata, T., Ando, M., Iizuka, R., Tsujibe, S., Murakami, J., Kiyoshima-Shibata, J., et al., 2012. Probiotic upregulation of peripheral IL-17 responses does not exacerbate neurological symptoms in experimental autoimmune encephalomyelitis mouse models. Immunopharmacol. Immunotoxicol. *34*, 423–433. 10.3109/08923973.2010.617755

Lee, Y.K., Menezes, J.S., Umesaki, Y., Mazmanian, S.K., 2011. Proinflammatory T-cell responses to gut microbiota promote experimental autoimmune encephalomyelitis. Proc. Natl. Acad. Sci. U. S. A. *108 Suppl 1*, 4615–4622. 10.1073/pnas.1000082107

Lei, Y.M.K., Nair, L., Alegre, M.-L., 2015. The interplay between the intestinal microbiota

and the immune system. Clin. Res. Hepatol. Gastroenterol. *39*, 9–19. 10.1016/j.clinre.2014.10.008

Lemire, J.M., Clay Archer, D., 1991. 1,25-dihydroxyvitamin D3 prevents the *in vivo* induction of murine experimental autoimmune encephalomyelitis. J. Clin. Invest. *87*, 1103–1107. 10.1172/JCI115072

Leong, C., Haszard, J.J., Lawley, B., Otal, A., Taylor, R.W., Szymlek-Gay, E.A., Fleming, E.A., Daniels, L., Fangupo, L.J., Tannock, G.W., Heath, A.L.M., 2018. Mediation analysis as a means of identifying dietary components that differentially affect the fecal microbiota of infants weaned by modified baby-led and traditional approaches. Appl. Environ. Microbiol. *84*, e00914-18. 10.1128/AEM.00914-18

Linden, J.R., Ma, Y., Zhao, B., Harris, J.M., Rumah, K.R., Schaeren-Wiemers, N., Vartanian, T., 2015. *Clostridium perfringens* epsilon toxin causes selective death of mature oligodendrocytes and central nervous system demyelination. mBio *6*, e02513. 10.1128/mBio.02513-14

Liu, Q., Li, H., Yang, J., Niu, X., Zhao, C., Zhao, L., Wang, Z., 2017. Valproic acid attenuates inflammation of optic nerve and apoptosis of retinal ganglion cells in a rat model of optic neuritis. Biomed. Pharmacother. *96*, 1363–1370. 10.1016/j.biopha.2017.11.066

Liu, S., Rezende, R.M., Moreira, T.G., Tankou, S.K., Cox, L.M., Wu, M., Song, A., Dhang, F.H., Wei, Z., Costamagna, G., Weiner, H.L., 2019. Oral administration of miR-30d from feces of MS patients suppresses MS-like symptoms in mice by expanding *Akkermansia muciniphila*. Cell Host Microbe *26,* 779–794.e8. 10.1016/j.chom.2019.10.008

Lozupone, C.A., Stombaugh, J.I., Gordon, J.I., Jansson, J.K., Knight, R., 2012. Diversity, stability and resilience of the human gut microbiota. Nature *489*, 220–30. 10.1038/nature11550

Lynch, K.E., Parke, E.C., O'Malley, M.A., 2019. How causal are microbiomes? A comparison with the *Helicobacter pylori* explanation of ulcers. Biol. Philos. *34,* 62. 10.1007/s10539-019-9702-2

Maghzi, A.-H., Etemadifar, M., Heshmat-Ghahdarijani, K., Nonahal, S., Minagar, A., Moradi, V., 2012. Cesarean delivery may increase the risk of multiple sclerosis. Mult. Scler. *18*, 468–71. 10.1177/1352458511424904

Mana, P., Goodyear, M., Bernard, C., Tomioka, R., Freire-Garabal, M., Liñares, D., 2004. Tolerance induction by molecular mimicry: prevention and suppression of experimental autoimmune encephalomyelitis with the milk protein butyrophilin. Int. Immunol. *16*, 489–499. 10.1093/intimm/dxh049

Mangalam, A., Shahi, S.K., Luckey, D., Karau, M., Marietta, E., Luo, N., Choung, R.S., Ju, J., Sompallae, R., Gibson-Corley, K., et al., 2017. Human gut-derived commensal bacteria suppress CNS inflammatory and demyelinating disease. Cell Rep. *20*, 1269–1277. 10.1016/j.celrep.2017.07.031

Martínez, I., Maldonado-Gomez, M.X., Gomes-Neto, J.C., Kittana, H., Ding, H., Schmaltz, R., Joglekar, P., Cardona, R.J., Marsteller, N.L., Kembel, S.W., et al., 2018. Experimental evaluation of the importance of colonization history in early-life gut microbiota assembly. eLife *7*, e36521. 10.7554/eLife.36521

Martínez, I., Perdicaro, D.J., Brown, A.W., Hammons, S., Carden, T.J., Carr, T.P., Eskridge, K.M., Walter, J., 2013. Diet-induced alterations of host cholesterol

metabolism are likely to affect the gut microbiota composition in hamsters. Appl. Environ. Microbiol. *79,* 516–524. 10.1128/AEM.03046-12

McCoy, K.D., Geuking, M.B., Ronchi, F., 2017. Gut microbiome standardization in control and experimental mice. Curr. Protoc. Immunol. *117,* 23.1.1–23.1.13. 10.1002/cpim.25

McLaughlin, L., Clarke, L., Khalilidehkordi, E., Butzkueven, H., Taylor, B., Broadley, S.A., 2018. Vitamin D for the treatment of multiple sclerosis: a meta-analysis. J. Neurol. *265,* 2893–2905. 10.1007/s00415-018-9074-6

McMurdie, P.J., Holmes, S., 2013. Phyloseq: an R package for reproducible interactive analysis and graphics of microbiome census data. PLoS One *8,* e61217. 10.1371/journal.pone.0061217

Mirza, A., Forbes, J.D., Zhu, F., Bernstein, C.N., Van Domselaar, G., Graham, M., Waubant, E., Tremlett, H., 2020. The multiple sclerosis gut microbiota: a systematic review. Mult. Scler. Relat. Disord. *37,* 101427 10.1016/j.msard.2019.101427

Miyake, S., Kim, S., Suda, W., Oshima, K., Nakamura, M., Matsuoka, T., Chihara, N., Tomita, A., Sato, W., Kim, S.-W., et al., 2015. Dysbiosis in the gut microbiota of patients with multiple sclerosis, with a striking depletion of species belonging to Clostridia XIVa and IV clusters. PLoS One *10,* e0137429. 10.1371/journal.pone.0137429

Mizuno, M., Noto, D., Kaga, N., Chiba, A., Miyake, S., 2017. The dual role of short fatty acid chains in the pathogenesis of autoimmune disease models. PLoS One *12,* e0173032. 10.1371/journal.pone.0173032

Nakagawa, S., Schielzeth, H., 2013. A general and simple method for obtaining R^2 from

generalized linear mixed-effects models. Methods Ecol. Evol. *4,* 133–142. 10.1111/j.2041-210x.2012.00261.x

National Research Council, 2003. Nutrient Requirements of Nonhuman Primates. National Academies Press, Washington, D.C. 10.17226/9826

Neis, E.P.J.G., Dejong, C.H.C., Rensen, S.S., 2015. The role of microbial amino acid metabolism in host metabolism. Nutrients *7,* 2930–46. 10.3390/nu7042930

Nemazannikova, N., Mikkelsen, K., Stojanovska, L., Blatch, G.L., Apostolopoulos, V., 2018. Is there a link between vitamin B and multiple sclerosis? Med. Chem. *14,* 170–180. 10.2174/1573406413666170906123857

Nguyen, N.K., Deehan, E.C., Zhang, Z., Jin, M., Baskota, N., Perez-Muñoz, M.E., Cole, J., Tuncil, Y.E., Seethaler, B., Wang, T., et al., 2020. Gut microbiota modulation with long-chain corn bran arabinoxylan in adults with overweight and obesity is linked to an individualized temporal increase in fecal propionate. Microbiome *8*, 118. 10.1186/s40168-020-00887-w

Nongonierma, A.B., FitzGerald, R.J., 2015. Milk proteins as a source of tryptophan-containing bioactive peptides. Food Funct. *6,* 2115–2127. 10.1039/C5FO00407A

Norgaard, M., Nielsen, R.B., Jacobsen, J.B., Gradus, J.L., Stenager, E., Koch-Henriksen, N., Lash, T.L., Sorensen, H.T., 2011. Use of penicillin and other antibiotics and risk of multiple sclerosis: a population-based case-control study. Am. J. Epidemiol. *174,* 945–8. 10.1093/aje/kwr201

Nourbakhsh, B., Bhargava, P., Tremlett, H., Hart, J., Graves, J., Waubant, E., 2018. Altered tryptophan metabolism is associated with pediatric multiple sclerosis risk and course. Ann. Clin. Transl. Neurol. *5,* 1211–1221. 10.1002/acn3.637

Nouri, M., Bredberg, A., Weström, B., Lavasani, S., 2014. Intestinal barrier dysfunction develops at the onset of experimental autoimmune encephalomyelitis, and can be induced by adoptive transfer of auto-reactive T cells. PLoS One *9,* e106335. 10.1371/journal.pone.0106335

Nwosu, C.C., Aldredge, D.L., Lee, H., Lerno, L.A., Zivkovic, A.M., German, J.B., Lebrilla, C.B., 2012. Comparison of the human and bovine milk N-glycome via high-performance microfluidic chip liquid chromatography and tandem mass spectrometry. J. Proteome Res. *11,* 2912–2924. 10.1021/pr300008u

O'Rourke, D.R., Bokulich, N.A., Jusino, M.A., MacManes, M.D., Foster, J.T., 2020. A total crapshoot? Evaluating bioinformatic decisions in animal diet metabarcoding analyses. Ecol. Evol. *10,* 9721–9739. 10.1002/ece3.6594

Ochoa-Reparaz, J., Magori, K., Kasper, L.H., 2017. The chicken or the egg dilemma: intestinal dysbiosis in multiple sclerosis. Ann. Transl. Med. *5*, 145. 10.21037/atm.2017.01.18

Ochoa-Repáraz, J., Mielcarz, D.W., Ditrio, L.E., Burroughs, A.R., Begum-Haque, S., Dasgupta, S., Kasper, D.L., Kasper, L.H., 2010. Central nervous system demyelinating disease protection by the human commensal *Bacteroides fragilis* depends on polysaccharide A expression. J. Immunol. *185,* 4101–4108. 10.4049/jimmunol.1001443

Ochoa-Reparaz, J., Mielcarz, D.W., Ditrio, L.E., Burroughs, A.R., Foureau, D.M., Haque-Begum, S., Kasper, L.H., 2009. Role of gut commensal microflora in the development of experimental autoimmune encephalomyelitis. J. Immunol. *183,* 6041–6050. 10.4049/jimmunol.0900747

549 Ochoa-Repáraz, J., Mielcarz, D.W., Wang, Y., Begum-Haque, S., Dasgupta, S., Kasper,
550 D.L., Kasper, L.H., 2010. A polysaccharide from the human commensal Bacteroides
551 fragilis protects against CNS demyelinating disease. Mucosal Immunol. *3,* 487–95.
552 10.1038/mi.2010.29
553 Ochoa-Repáraz, J., Riccardi, C., Rynda, A., Jun, S., Callis, G., Pascual, D.W., 2007.
554 Regulatory T cell vaccination without autoantigen protects against experimental
555 autoimmune encephalomyelitis. J. Immunol. *178,* 1791–1799.
556 10.4049/jimmunol.178.3.1791
557 Oksanen, J., Blanchet, F.G., Friendly, M., Kindt, R., Legendre, P., Mcglinn, D., Minchin,
558 P.R., O'Hara, R.B., Simpson, G.L., Solymos, P., et al., 2019. "vegan": Community
559 Ecology Package Version 2.5-6.
560 Oshida, K., Shimizu, T., Takase, M., Tamura, Y., Shimizu, T., Yamashiro, Y., 2003. Effects
561 of dietary sphingomyelin on central nervous system myelination in developing rats.
562 Pediatr. Res. *53,* 589–593. 10.1203/01.PDR.0000054654.73826.AC
563 Otaegui, D., Mostafavi, S., Bernard, C.C.A., Lopez de Munain, A., Mousavi, P.,
564 Oksenberg, J.R., Baranzini, S.E., 2007. Increased transcriptional activity of milk-
565 related genes following the active phase of experimental autoimmune
566 encephalomyelitis and multiple sclerosis. J. Immunol. *179,* 4074–82.
567 10.4049/jimmunol.179.6.4074
568 Otani, H., Watanabe, T., Tashiro, Y., 2001. Effects of bovine beta-casein (1-28) and its
569 chemically synthesized partial fragments on proliferative responses and
570 immunoglobulin production in mouse spleen cell cultures. Biosci. Biotechnol.
571 Biochem. *65,* 2489–95. 10.1271/bbb.65.2489

572 Patry, R.T., Stahl, M., Perez-Munoz, M.E., Nothaft, H., Wenzel, C.Q., Sacher, J.C.,
573 Coros, C., Walter, J., Vallance, B.A., Szymanski, C.M., 2019. Bacterial AB 5 toxins
574 inhibit the growth of gut bacteria by targeting ganglioside-like glycoconjugates. Nat.
575 Commun. *10,* 1390. 10.1038/s41467-019-09362-z
576 Pielou, E.C., 1966. The measurement of diversity in different types of biological
577 collections. J. Theor. Biol. *13,* 131–144. 10.1016/0022-5193(66)90013-0
578 Pommerich, U.M., Brincks, J., Christensen, M.E., 2018. Is there an effect of dietary intake
579 on MS-related fatigue? – a systematic literature review. Mult. Scler. Relat. Disord. *25,*
580 282–291. 10.1016/j.msard.2018.08.017
581 Pröbstel, A.K., Baranzini, S.E., 2018. The role of the gut microbiome in multiple sclerosis
582 risk and progression: towards characterization of the "MS microbiome."
583 Neurotherapeutics *15*, 126-134. 10.1007/s13311-017-0587-y
584 Quast, C., Pruesse, E., Yilmaz, P., Gerken, J., Schweer, T., Yarza, P., Peplies, J.,
585 Glöckner, F.O., 2013. The SILVA ribosomal RNA gene database project: Improved
586 data processing and web-based tools. Nucleic Acids Res. *41*, D59-D596.
587 10.1093/nar/gks1219
588 R Core Team, 2018. R: a language and environment for statistical computing.
589 Rajan, S.K., Lindqvist, M., Brummer, R.J., Schoultz, I., Repsilber, D., 2019. Phylogenetic
590 microbiota profiling in fecal samples depends on combination of sequencing depth
591 and choice of NGS analysis method. PLoS One *14,* e0222171.
592 10.1371/journal.pone.0222171
593 Ramsaransing, G.S.M., Mellema, S.A., De Keyser, J., 2009. Dietary patterns in clinical
594 subtypes of multiple sclerosis: an exploratory study. Nutr. J. *8,* 36. 10.1186/1475-

2891-8-36

Rhodes, D.A., Reith, W., Trowsdale, J., 2016. Regulation of immunity by butyrophilins. Annu. Rev. Immunol. *34,* 151–172. 10.1146/annurev-immunol-041015-055435

Rothhammer, V., Borucki, D.M., Tjon, E.C., Takenaka, M.C., Chao, C.-C., Ardura-Fabregat, A., de Lima, K.A., Gutiérrez-Vázquez, C., Hewson, P., Staszewski, O., et al., 2018. Microglial control of astrocytes in response to microbial metabolites. Nature *557,* 724–728. 10.1038/s41586-018-0119-x

Rothhammer, V., Mascanfroni, I.D., Bunse, L., Takenaka, M.C., Kenison, J.E., Mayo, L., Chao, C.-C., Patel, B., Yan, R., Blain, M., et al., 2016. Type I interferons and microbial metabolites of tryptophan modulate astrocyte activity and central nervous system inflammation via the aryl hydrocarbon receptor. Nat. Med. *22,* 586–597. 10.1038/nm.4106

Rothschild D, Weissbrod O, Barkan E, Kurilshikov A, Korem T, Zeevi D, Costea PI, Godneva A, Kalka IN, Bar N, et al. Environment dominates over host genetics in shaping human gut microbiota. Nature *555*, 210–215. 10.1038/nature25973

Rumah, K.R., Linden, J., Fischetti, V.A., Vartanian, T., 2013. Isolation of *Clostridium perfringens* type B in an individual at first clinical presentation of multiple sclerosis provides clues for environmental triggers of the disease. PLoS One *8,* e76359. 10.1371/journal.pone.0076359

Saher, G., Brügger, B., Lappe-Siefke, C., Möbius, W., Tozawa, R., Wehr, M.C., Wieland, F., Ishibashi, S., Nave, K.-A., 2005. High cholesterol level is essential for myelin membrane growth. Nat. Neurosci. *8,* 468–475. 10.1038/nn1426

Sakamoto, M., Iino, T., Hamada, M., Ohkuma, M., 2018. *Parolsenella catena* gen. nov.,

sp. nov., isolated from human faeces. Int. J. Syst. Evol. Microbiol. *68,* 1165–1172. 10.1099/ijsem.0.002645

Salehipour, Z., Haghmorad, D., Sankian, M., Rastin, M., Nosratabadi, R., Soltan Dallal, M.M., Tabasi, N., Khazaee, M., Nasiraii, L.R., Mahmoudi, M., 2017. *Bifidobacterium animalis* in combination with human origin of *Lactobacillus plantarum* ameliorate neuroinflammation in experimental model of multiple sclerosis by altering CD4+ T cell subset balance. Biomed. Pharmacother. *95,* 1535–1548. 10.1016/j.biopha.2017.08.117

Saresella, M., Mendozzi, L., Rossi, V., Mazzali, F., Piancone, F., LaRosa, F., Marventano, I., Caputo, D., Felis, G.E., Clerici, M., 2017. Immunological and clinical effect of diet modulation of the gut microbiome in multiple sclerosis patients: a pilot study. Front. Immunol. *8,* 1391. 10.3389/fimmu.2017.01391

Schirmer, M., Smeekens, S.P., Vlamakis, H., Jaeger, M., Oosting, M., Franzosa, E.A., Jansen, T., Jacobs, L., Bonder, M.J., Kurilshikov, A., et al., 2016. Linking the human gut microbiome to inflammatory cytokine production capacity. Cell *167,* 1125–1136.e8. 10.1016/j.cell.2016.10.020

Schluter, J., Peled, J.U., Taylor, B.P., Markey, K.A., Smith, M., Taur, Y., Niehus, R., Staffas, A., Dai, A., Fontana, E., et al., 2020. The gut microbiota is associated with immune cell dynamics in humans. Nature *588,* 303–307. 10.1038/s41586-020-2971-8

Schmidt, V., Enav, H., Spector, T.D., Youngblut, N.D., Ley, R.E., 2020. Strain-level analysis of *Bifidobacterium* spp. from gut microbiomes of adults with differing lactase persistence genotypes. mSystems *5*, e00911-20. 10.1128/msystems.00911-20

641 Shahi, S.K., Freedman, S.N., Mangalam, A.K., 2017. Gut microbiome in multiple sclerosis:
642 the players involved and the roles they play. Gut Microbes *8,* 607–615.
643 10.1080/19490976.2017.1349041
644 Shahi, S.K., Freedman, S.N., Murra, A.C., Zarei, K., Sompallae, R., Gibson-Corley, K.N.,
645 Karandikar, N.J., Murray, J.A., Mangalam, A.K., 2019. *Prevotella histicola*, a human
646 gut commensal, is as potent as COPAXONE® in an animal model of multiple
647 sclerosis. Front. Immunol. *10,* 462. 10.3389/fimmu.2019.00462
648 Sizar, O., Givler, A., 2019. Vitamin D Deficiency, StatPearls.
649 Skripuletz, T., Manzel, A., Gropengießer, K., Schäfer, N., Gudi, V., Singh, V., Salinas
650 Tejedor, L., Jörg, S., Hammer, A., Voss, E., et al., 2015. Pivotal role of choline
651 metabolites in remyelination. Brain *138,* 398–413. 10.1093/brain/awu358
652 Sonner, J.K., Keil, M., Falk-Paulsen, M., Mishra, N., Rehman, A., Kramer, M.,
653 Deumelandt, K., Röwe, J., Sanghvi, K., Wolf, L., et al., 2019. Dietary tryptophan links
654 encephalogenicity of autoreactive T cells with gut microbial ecology. Nat. Commun.
655 *10,* 4877. 10.1038/s41467-019-12776-4
656 Spitsberg, V.L., 2005. Invited review: bovine milk fat globule membrane as a potential
657 nutraceutical. J. Dairy Sci. *88,* 2289–2294. 10.3168/jds.S0022-0302(05)72906-4
658 Stanisavljević, S., Dinić, M., Jevtić, B., Đedović, N., Momčilović, M., Đokić, J., Golić, N.,
659 Mostarica Stojković, M., Miljković, Đ., 2018. Gut microbiota confers resistance of
660 albino oxford rats to the induction of experimental autoimmune encephalomyelitis.
661 Front. Immunol. *9,* 942. 10.3389/fimmu.2018.00942
662 Stefferl, A., Schubart, A., Storch, M., Amini, A., Mather, I., Lassmann, H., Linington, C.,
663 2000. Butyrophilin, a milk protein, modulates the encephalitogenic T cell response to

myelin oligodendrocyte glycoprotein in experimental autoimmune encephalomyelitis. J. Immunol. *165,* 2859–2865. 10.4049/jimmunol.165.5.2859

Takiishi, T., Fenero, C.I.M., Câmara, N.O.S., 2017. Intestinal barrier and gut microbiota: shaping our immune responses throughout life. Tissue Barriers *5,* e1373208. 10.1080/21688370.2017.1373208

Tankou, S.K., Regev, K., Healy, B.C., Cox, L.M., Tjon, E., Kivisakk, P., Vanande, I.P., Cook, S., Gandhi, R., Glanz, B., et al., 2018. Investigation of probiotics in multiple sclerosis. Mult. Scler. Jour. *24*, 58–63. 10.1177/1352458517737390

Thorburn, A.N., Macia, L., Mackay, C.R., 2014. Diet, metabolites, and "Western-lifestyle" inflammatory diseases. Immunity *40*, P833-P842. 10.1016/j.immuni.2014.05.014

Toghi, M., Bitarafan, S., Kasmaei, H.D., Ghafouri-Fard, S., 2019. Bifidobacteria: a probable missing puzzle piece in the pathogenesis of multiple sclerosis. Mult. Scler. Relat. Disord. *36*, 101378. 10.1016/j.msard.2019.101378

Tremlett, H., Fadrosh, D.W., Faruqi, A.A., Hart, J., Roalstad, S., Graves, J., Lynch, S., Waubant, E., US Network of Pediatric MS Centers, 2016. Gut microbiota composition and relapse risk in pediatric MS: a pilot study. J. Neurol. Sci. *363,* 153–157. 10.1016/j.jns.2016.02.042

Tuomisto, H., 2010. A diversity of beta diversities: straightening up a concept gone awry. Part 1. Defining beta diversity as a function of alpha and gamma diversity. Ecography (Cop.). *33,* 2–22. 10.1111/j.1600-0587.2009.05880.x

Turnbaugh, P.J., Hamady, M., Yatsunenko, T., Cantarel, B.L., Ley, R.E., Sogin, M.L., Jones, W.J., Roe, B.A., Jason, P., Egholm, M., et al., 2009. A core gut microbiome in obese and lean twins. Nature *457,* 480–484. 10.1038/nature07540

687 Turroni, F., Peano, C., Pass, D.A., Foroni, E., Severgnini, M., Claesson, M.J., Kerr, C.,
688 Hourihane, J., Murray, D., Fuligni, F., et al., 2012. Diversity of bifidobacteria within
689 the infant gut microbiota. PLoS One *7,* e36957. 10.1371/journal.pone.0036957
690 Uauy, R., 2007. Academic-industry partnerships in addressing nutrition--[infection-
691 immunity-inflammation] interactions. Br. J. Nutr. *98 Suppl 1,* S17–23.
692 10.1017/S0007114507832892
693 Ubeda, C., Lipuma, L., Gobourne, A., Viale, A., Leiner, I., Equinda, M., Khanin, R., Pamer,
694 E.G., 2012. Familial transmission rather than defective innate immunity shapes the
695 distinct intestinal microbiota of TLR-deficient mice. J. Exp. Med. *209,* 1445–1456.
696 10.1084/jem.20120504
697 Uwitonze, A.M., Razzaque, M.S., 2018. Role of magnesium in Vitamin D activation and
698 function. J. Am. Osteopath. Assoc. *118,* 181. 10.7556/jaoa.2018.037
699 Vallet, J.L., Rempel, L.A., Miles, J.R., Webel, S.K., 2014. Effect of essential fatty acid and
700 zinc supplementation during pregnancy on birth intervals, neonatal piglet brain
701 myelination, stillbirth, and preweaning mortality. J. Anim. Sci. *92,* 2422–2432.
702 10.2527/jas.2013-7130
703 van Meeteren, M.E., Teunissen, C.E., Dijkstra, C.D., van Tol, E.A.F., 2005. Antioxidants
704 and polyunsaturated fatty acids in multiple sclerosis. Eur. J. Clin. Nutr. *59,* 1347–
705 1361. 10.1038/sj.ejcn.1602255
706 van Rensburg, S.J., Kotze, M.J., Hon, D., Haug, P., Kuyler, J., Hendricks, M., Botha, J.,
707 Potocnik, F.C. V., Matsha, T., Erasmus, R.T., 2006. Iron and the folate-vitamin B12-
708 methylation pathway in multiple sclerosis. Metab. Brain Dis. *21,* 117–133.
709 10.1007/s11011-006-9019-0

710 Vandeputte, D., Falony, G., Vieira-Silva, S., Tito, R.Y., Joossens, M., Raes, J., 2016. Stool
711 consistency is strongly associated with gut microbiota richness and composition,
712 enterotypes and bacterial growth rates. Gut 65, 57–62. 10.1136/gutjnl-2015-309618
713 Voreades, N., Kozil, A., Weir, T.L., 2014. Diet and the development of the human intestinal
714 microbiome. Front. Microbiol. 5, 494. 10.3389/fmicb.2014.00494
715 Vujkovic-Cvijin, I., Sklar, J., Jiang, L., Natarajan, L., Knight, R., Belkaid, Y., 2020. Host
716 variables confound gut microbiota studies of human disease. Nature 587, 448–454.
717 10.1038/s41586-020-2881-9
718 Walter, J., 2015. Murine gut microbiota-diet trumps genes. Cell Host Microbe 17, 3–5.
719 10.1016/j.chom.2014.12.004
720 Walter, J., Armet, A.M., Finlay, B.B., Shanahan, F., 2020. Establishing or Exaggerating
721 Causality for the Gut Microbiome: Lessons from Human Microbiota-Associated
722 Rodents. Cell. 10.1016/j.cell.2019.12.025
723 Walter, J., Ley, R., 2011. The human gut microbiome: ecology and recent evolutionary
724 changes. Annu. Rev. Microbiol. 65, 411–29. 10.1146/annurev-micro-090110-102830
725 Wang, Q., Garrity, G.M., Tiedje, J.M., Cole, J.R., 2007. Naive Bayesian classifier for
726 rapid assignment of rRNA sequences into the new bacterial taxonomy. Appl.
727 Environ. Microbiol. 73, 5261–5267. 10.1128/AEM.00062-07
728 Wekerle, H., 2017. Brain autoimmunity and intestinal microbiota: 100 trillion game
729 changers. Trends Immunol. *38*, 483–497. 10.1016/j.it.2017.03.008
730 Wekerle, H., 2015. Nature plus nurture: The triggering of multiple sclerosis. Swiss Med.
731 Wkly. *145*, w14189. 10.4414/smw.2015.14189
732 Wesemann, D.R., Portuguese, A.J., Meyers, R.M., Gallagher, M.P., Cluff-Jones, K.,

733 Magee, J.M., Panchakshari, R.A., Rodig, S.J., Kepler, T.B., Alt, F.W., 2013. Microbial
734 colonization influences early B-lineage development in the gut lamina propria. Nature
735 *501,* 112–115. 10.1038/nature12496
736 Winer, S., Astsaturov, I., Cheung, R.K., Schrade, K., Gunaratnam, L., Wood, D.D.,
737 Moscarello, M.A., O'Connor, P., McKerlie, C., Becker, D.J., Dosch, H.M., 2001. T
738 cells of multiple sclerosis patients target a common environmental peptide that
739 causes encephalitis in mice. J. Immunol. *166,* 4751–4756.
740 10.4049/jimmunol.166.7.4751
741 Wu, G.D., Chen, J., Hoffmann, C., Bittinger, K., Chen, Y.Y., Keilbaugh, S.A., Bewtra, M.,
742 Knights, D., Walters, W.A., Knight, R., et al., 2011. Linking long-term dietary patterns
743 with gut microbial enterotypes. Science *334,* 105–108. 10.1126/science.1208344
744 Xue, H., Ren, H., Zhang, L., Sun, X., Wang, W., Zhang, S., Zhao, J., Ming, L., 2016. Alpha-
745 tocopherol ameliorates experimental autoimmune encephalomyelitis through the
746 regulation of Th1 cells. Iran. J. Basic Med. Sci. *19,* 561–566.
747 Xue, Z., Kable, M.E., Marco, M.L., 2018. Impact of DNA sequencing and analysis methods
748 on 16s rRNA gene bacterial community analysis of dairy products. mSphere *3,*
749 e00410-18. 10.1128/msphere.00410-18
750 Yokote, H., Miyake, S., Croxford, J.L., Oki, S., Mizusawa, H., Yamamura, T., 2008. NKT
751 cell-dependent amelioration of a mouse model of multiple sclerosis by altering gut
752 flora. Am. J. Pathol. *173,* 1714–1723. 10.2353/ajpath.2008.080622
753 Yoon, S.-H., Ha, S.-M., Kwon, S., Lim, J., Kim, Y., Seo, H., Chun, J., 2017. Introducing
754 EzBioCloud: a taxonomically united database of 16S rRNA gene sequences and
755 whole-genome assemblies. Int. J. Syst. Evol. Microbiol. *67,* 1613–1617.

10.1099/ijsem.0.001755

Zapatera, B., Prados, A., Gómez-Martínez, S., Marcos, A., 2015. Immunonutrition: methodology and applications. Nutr. Hosp. *31 Suppl 3,* 145–154. 10.3305/nh.2015.31.sup3.8762

Zelante, T., Iannitti, R.G., Cunha, C., De Luca, A., Giovannini, G., Pieraccini, G., Zecchi, R., D'Angelo, C., Massi-Benedetti, C., Fallarino, F., et al., 2013. Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. Immunity *39,* 372–385. 10.1016/j.immuni.2013.08.003

Zeng, Q., Gong, J., Liu, X., Chen, C., Sun, X., Li, H., Zhou, Y., Cui, C., Wang, Y., Yang, Y., et al., 2019. Gut dysbiosis and lack of short chain fatty acids in a Chinese cohort of patients with multiple sclerosis. Neurochem. Int. *129,* 104468. 10.1016/j.neuint.2019.104468

Zhang, Z., Zhang, Z.-Y., Wu, Y., Schluesener, H.J., 2012. Valproic acid ameliorates inflammation in experimental autoimmune encephalomyelitis rats. Neuroscience *221,* 140–150. 10.1016/j.neuroscience.2012.07.013