

# [Role of the microbiome in alzheimer's disease](https://assignbuster.com/role-of-the-microbiome-in-alzheimers-disease/)

Specific Aim

Alzheimer’s disease (AD) is a devastating disease that manifests as Beta-amyloid plaques and tau aggregation that accumulate in the brain (1).  Currently, no treatment is available for patients, pushing the field to develop an alternative therapy (1).  The complexity of the disease is based on the interplay of both genetics and lifestyle, as both appear to play a role in the neuropathology (2).  The diet has an influential role on many diseases, AD being one of them (3).  A diet high in salt is associated with an increased risk of AD (3), and a high-salt diet is associated with reduced cognitive function through impaired hippocampal function in mice (4).   The role of salt was directly tested for its ability to impact β-amyloid, and in cells expressing the amyloid precursor protein, treatment with sodium chloride increased the amount of β-amyloid by negatively regulating the clearance mechanisms (5).  Contrary to other studies, in an APPswe/PSEN1 mouse model of AD, high-salt diet actually decreased the amount of β-amyloid plaques (6).  While there are discrepancies in the AD field, it does appear that the high-salt diet does have an association with neuropathy in AD patients.

The diet is a lifestyle that influences a person’s health status, including AD, based on the microbial interactions that exist within the gut of an individual.  The diet is a key player in molding an individual’s microbiome, and consuming particular food sources can modify the gut microbiota towards a predicted gut colonization (7).   AD is associated with overall decreased gut microbial diversity, and distinct variances in phyla (8).  High-salt diet strongly correlated with reduced Lactobacillus species, followed by other species, including Clostridium XIVa, Oscillibacter, and Pseudoflavonifractor in mice (9) and in a rat model of AD, treatment with Lactobacillus plantarum reduced AD pathology (10).  In a salt-sensitive rat model, when fed a high-salt diet, an increase in Christensenellaceae and Corynebacteriaceae and Erwinia taxa was observed (11).  While previous work suggests a role of the high-salt diet in modulating the microbiome in the AD animal model, no current evidence has been provided that there is an association of a high salt diet and the gut microbiota in impacting AD phenotypes.  Identifying the link between high salt diets and AD progression and neuropathology will help to determine how to manipulate the gut microbiota to benefit AD patients.

The goal of this research is to identify if the microbiome plays a role in AD.  Theobjectiveis to determine if there are modulatory effects from a high salt diet on AD through the microbiome.  It ishypothesizedthat high salt diet induced changes of the microbiome will enhance AD pathology.  Following this, when implicated taxa are individually administered to AD-mice, it is hypothesized that they have a protected effect in AD progression.

Establishment Aim: To determine if specific taxa will change in mice fed a high-salt diet.

Using wildtype C75Bl/6 mice fed either high salt diet (7% NaCl) (Liu et al., 2014) or control feed for 12 weeks, changes in the microbiome will be assessed to determine if the high salt diet is inducing differences in the microbial composition of the gut between control of diet manipulated conditions.  Based on previous findings, specific emphasis will be placed on Lactobacillus, Clostridium XIVa, Oscillibacter, Pseudoflavonifractor, Christensenellaceae and Corynebacteriaceae taxa.

Aim 1: To determine that AD pathology is more severe in high-salt diet models.

Derived germ-free (GF) J20 mice and control GF mice will be fed high-salt diet or control diet 2 months prior to onset of disease symptoms or at beginning of AD symptoms (4-6 months (12)).  Mice will be analyzed every 2 weeks via MRI for β-amyloid plaques, cognitive function (13) and neural tissue will be collected for histological staining.  In addition, J20 mice or control mice will be treated with broad spectrum antibiotics for 1 week, 2 months prior to unset of disease, or at onset of disease.  After antibiotic (Abx) treatment, mice will be fed either control or high salt diet and disease severity will be determined as previously described.  For both GF mouse models and Abx-treated mouse models, fecal pellets will be collected every month to determine changes in microbiome taxa with exposure to high salt diet on the AD background.  It is expected that mice fed the high salt diet will have increased beta amyloid plaques and decreased cognitive function, indicating an association with the high salt diet and AD disease severity.

Aim 2: To determine that AD pathology from a high-salt diet can be rescued by manipulating colonization of taxa implicated in the high-salt diet.

Using the same GF-J20 and Abx-J20 models as described above, probiotics will be administered to help reverse the phenotype of AD in these mice models.  Based on data obtained in the establishment aim, and previous literature, Lactobacillus taxa representatives and other relevant species will be added as an oral probiotic at the same time as high-salt diet introduction.  MRIs, cognitive function and histological staining will be conducted on neural tissue to confirm disease progression status.  It is expected that mice supplemented with probiotics will have a less severe AD phenotype, indicating that the altered taxa play a protective role in modulating AD.

Aim 3: To determine changes in metabolomics in GF-J20 mice treated with Lactobacillus representative species.

Lactobacillus is negatively regulated in the presence of high salt diet based on previous literature.  In order to understand mechanistically how this species may be playing a role in AD protection, metabolomics will be conducted to find potential metabolites that stem from Lactobacillus.  Baseline metabolomics will be conducted in GF-J20 mice and control mice, and Lactobacillus will be gavaged in both groups of mice.  Gastrointestinal tract tissue will be harvested from both groups 1 month and 2 months post gavage for metabolomic analysis.  It is expected that there will be correlative metabolic hits in conditions were Lactobacillus was introduced, providing insight into a mechanism of function for this group of commensal bacteria.

In conclusion, these experiments will help us determine the relative impact of gut microbial changes from a high salt diet and how that impacts AD progression.  This study will identify key taxa that may protect against the high salt diet and help to modulate AD via altering composition of the gut microbiota.

## References

1. Long JM, Holtzman DM. 2019. Alzheimer Disease: An Update on Pathobiology and Treatment Strategies. Cell 179: 312-339.

2. Pope SK, Shue VM, Beck C. 2003. Will a healthy lifestyle help prevent Alzheimer’s disease? Annu Rev Public Health 24: 111-32.

3. Pistollato F, Sumalla Cano S, Elio I, Masias Vergara M, Giampieri F, Battino M. 2016. Associations between Sleep, Cortisol Regulation, and Diet: Possible Implications for the Risk of Alzheimer Disease. Adv Nutr 7: 679-89.

4. Liu YZ, Chen JK, Li ZP, Zhao T, Ni M, Li DJ, Jiang CL, Shen FM. 2014. High-salt diet enhances hippocampal oxidative stress and cognitive impairment in mice. Neurobiol Learn Mem 114: 10-5.

5. Cheng XJ, Gao Y, Zhao YW, Cheng XD. 2015. Sodium Chloride Increases Abeta Levels by Suppressing Abeta Clearance in Cultured Cells. PLoS One 10: e0130432.

6. Taheri S, Yu J, Zhu H, Kindy MS. 2016. High-Sodium Diet Has Opposing Effects on Mean Arterial Blood Pressure and Cerebral Perfusion in a Transgenic Mouse Model of Alzheimer’s Disease. J Alzheimers Dis 54: 1061-1072.

7. Singh RK, Chang HW, Yan D, Lee KM, Ucmak D, Wong K, Abrouk M, Farahnik B, Nakamura M, Zhu TH, Bhutani T, Liao W. 2017. Influence of diet on the gut microbiome and implications for human health. J Transl Med 15: 73.

8. Vogt NM, Kerby RL, Dill-McFarland KA, Harding SJ, Merluzzi AP, Johnson SC, Carlsson CM, Asthana S, Zetterberg H, Blennow K, Bendlin BB, Rey FE. 2017. Gut microbiome alterations in Alzheimer’s disease. Sci Rep 7: 13537.

9. Wilck N, Matus MG, Kearney SM, Olesen SW, Forslund K, Bartolomaeus H, Haase S, Mahler A, Balogh A, Marko L, Vvedenskaya O, Kleiner FH, Tsvetkov D, Klug L, Costea PI, Sunagawa S, Maier L, Rakova N, Schatz V, Neubert P, Fratzer C, Krannich A, Gollasch M, Grohme DA, Corte-Real BF, Gerlach RG, Basic M, Typas A, Wu C, Titze JM, Jantsch J, Boschmann M, Dechend R, Kleinewietfeld M, Kempa S, Bork P, Linker RA, Alm EJ, Muller DN. 2017. Salt-responsive gut commensal modulates TH17 axis and disease. Nature 551: 585-589.

10. Nimgampalle M, Kuna Y. 2017. Anti-Alzheimer Properties of Probiotic, Lactobacillus plantarum MTCC 1325 in Alzheimer’s Disease induced Albino Rats. J Clin Diagn Res 11: Kc01-kc05.

11. Bier A, Braun T, Khasbab R, Di Segni A, Grossman E, Haberman Y, Leibowitz A. 2018. A High Salt Diet Modulates the Gut Microbiota and Short Chain Fatty Acids Production in a Salt-Sensitive Hypertension Rat Model. Nutrients 10.

12. Hall AM, Roberson ED. 2012. Mouse models of Alzheimer’s disease. Brain Res Bull 88: 3-12.

13. Wolf A, Bauer B, Abner EL, Ashkenazy-Frolinger T, Hartz AM. 2016. A Comprehensive Behavioral Test Battery to Assess Learning and Memory in 129S6/Tg2576 Mice. PLoS One 11: e0147733.