The Microbiome-Gut-Brain Axis and Probiotic Supplementation: ...

Implications for Dementia and Alzheimer's Disease

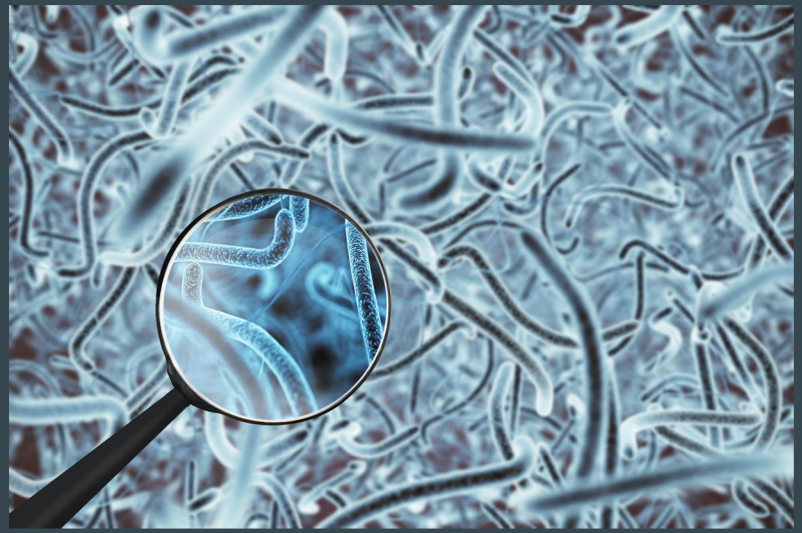
Hayley M MacLean, MS
Sodexo Dietetic Intern

Introduction[1]

- Gut microbiota ⇔ central and enteric nervous system
- Role in dementia and Alzheimer's disease still being investigated
- Dementia affects 50 million worldwide
- 60-70% of dementia cases are Alzheimer's disease
- Currently no known cause or cure
- Research focusing on delaying onset and slowing disease progression
- Differences in gut microbiome, dysbiosis, and potential of probiotic supplementation being studied

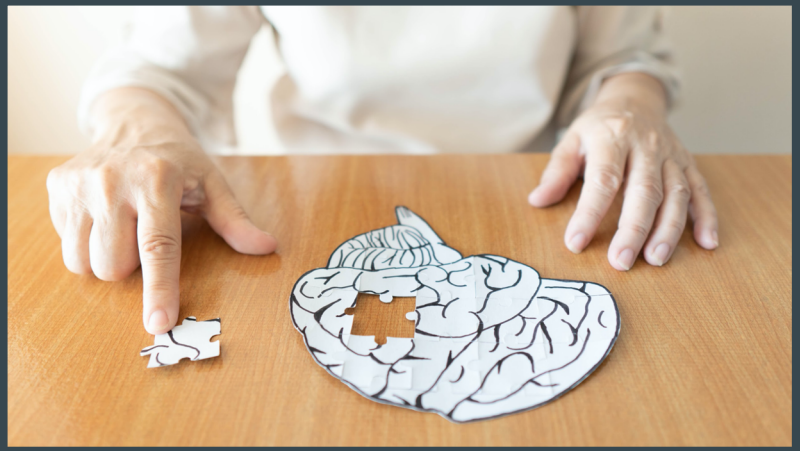
What is the Gut Microbiome?[2,3]

- Collection of microorganisms living in digestive tract
- At least 1000 strains of bacteria
  - ⅔ intrinsic in all people
  - ⅓ specific to the individual
- Responsible for specific physiological functions
  - Microbiota-gut-brain axis
- Many factors can influence composition
- Can directly affect the presence of cognitive issues
- Roles of specific microbial communities have yet to be defined



What is Alzheimer's Disease?[4,5,6]

- Progressive, long-term cognitive decline
- Associated with loss of neurons
- Microscopic changes in the brain
  - Amyloid plaques, tau proteins, neurofibrillary tangles
- Loss of connections and ability to send messages throughout the body
- Changes can occur years before symptoms
- Aging number one risk factor
- Treatment surrounds supporting the patient
- Looking into how dysbiosis of gut microbiota can shape prognosis



Objectives

- Participants will be able to explain the current research surrounding the differences in gut microbiota in patients with and without dementia and Alzheimer's disease.

- Participants will be able to describe the methods by which probiotic supplementation is thought to help with cognitive function.

- Participants will be able to provide future patients with evidence-based recommendations surrounding probiotic supplementation for the treatment of dementia and Alzheimer's disease.

Analysis of the relationship between the gut microbiome and dementia: a cross-sectional study conducted in Japan[7]

- Single-center observational study
- Investigated the associated between the composition of the gut microbiome and the clinical condition of the patient
- Assessment of cognitive function and fecal sample examination
- 128 participants, ages 68-82, placed into two groups - demented and non-demented (34 demented, 94 non-demented based cognitive function)
- All underwent a baseline assessment, comprehensive geriatric assessment, MRI brain imaging, and at-home fecal sample collection

Analysis of the relationship between the gut microbiome and dementia: a cross-sectional study conducted in Japan[7]

- Prevalence of Enterotype III in dementia group
  - More “other” bacteria than non-demented group
- Fewer Enterotype I in dementia group
  - Less *Bacteroides* than non-demented group
- Lactobacillales and *Bifidobacterium* slightly more frequent in dementia group

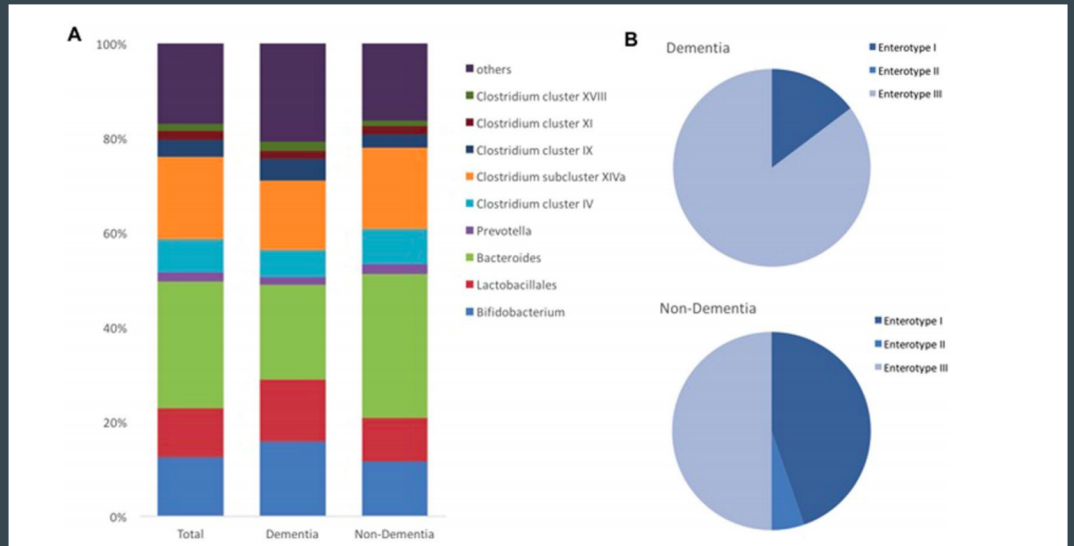


Figure 2. (**A**) Distribution of the gut microbiota. (**B**) Frequency of each enterotype in the dementia and non-dementia groups. Enterotype I (*Bacteroides* >30%) was enriched in the non-dementia group.

Saji N, Niida S, Murotani K, et al. Analysis of the relationship between the gut microbiome and dementia: a cross-sectional study conducted in Japan. *Sci Rep*. 2019;9:1008. doi: 10.1038/s41598-018-38218-7.

Analysis of the relationship between the gut microbiome and dementia: a cross-sectional study conducted in Japan[7]

- Firmicutes/Bacteroidetes ratio higher in dementia patients
- F/B ratio also higher in patients with silent lacunar infarcts in MRI
- No significant differences found with other types of brain abnormalities

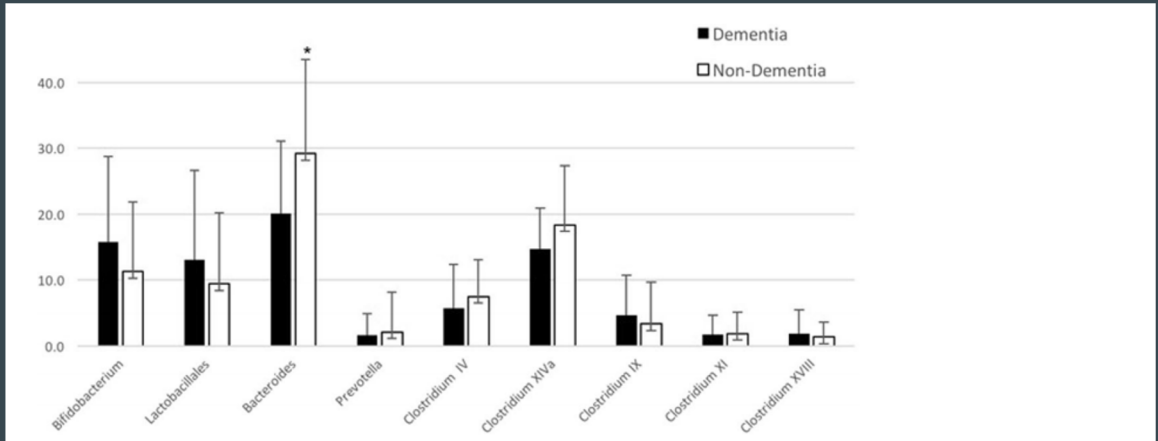


Figure 3. Comparison of the gut microbiota between the dementia and non-dementia groups. The percentages of each taxon of gut microbe was compared. The percentage of *Bacteroides* was significantly lower in the dementia than the non-dementia group.

Saji N, Niida S, Murotani K, et al. Analysis of the relationship between the gut microbiome and dementia: a cross-sectional study conducted in Japan. *Sci Rep*. 2019;9:1008. doi: 10.1038/s41598-018-38218-7.

Gut microbiome alterations in Alzheimer's Disease[8]

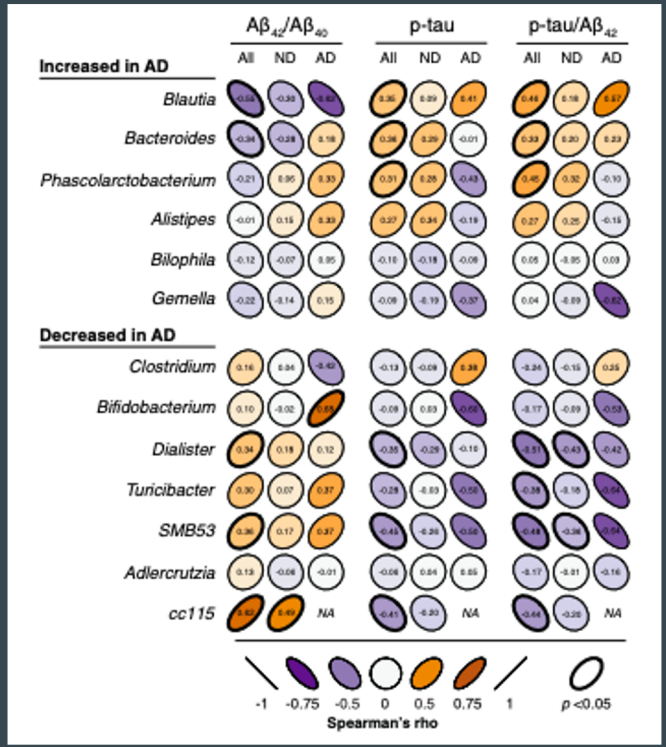
- Observational study
- 50 participants for primary microbiome analysis (25 with dementia due to AD, 25 age- and sex-controlled non-demented)
- 40 participants for secondary CSF analysis (9 AD cohort, 31 non-demented)
- Examined the relationship between gut microbiota and AD pathology as measured by cerebrospinal fluid biomarkers
    - Amyloid plaque burden ($A\beta_{42}/A\beta_{40}$), neurofibrillary tangle pathology (p-tau), overall AD pathology (p-tau/$A\beta_{42}$)
- Characterized the gut microbial communities in individuals with and without a clinical diagnosis of dementia due to AD
    - Bacterial 16S ribosomal RNA gene sequencing

Gut microbiome alterations in Alzheimer's disease[8]

- Decreased microbial richness and diversity found in AD patients
- Decreased Firmicutes
  - Also found in patients with DMII and obesity (risk factors for AD)
  - Insulin resistance increases the risk of developing AD
- Increased Bacteroidetes
  - Also seen increased in patients with DMII and Parkinson's disease
  - Gram-negative bacteria - outer membrane lipopolysaccharide (LPS) capable of triggering systemic inflammation and pro-inflammatory cytokines once in systemic circulation
  - LPS colocalized with amyloid plaques in the brain of deceased AD patients
- Decreased Actinobacteria
  - Certain species associated with anti-inflammatory properties and decreased intestinal permeability
  - Decreases LPS levels in the intestine and improves gut mucosal barrier properties in mice

Gut microbiome alterations in Alzheimer's disease[8]

- In general, genera identified as more abundant in AD were associated with greater AD pathology
  - Negative correlation between bacterial abundance and $A\beta_{42}/A\beta_{40}$
  - Predominantly positive correlation between bacterial abundance and p-tau and p-tau/$A\beta_{42}$
- Genera identified as less abundant in AD were associated with less AD pathology



Vogt NM, Kerby RL, Dill-McFarland KA, et al. Gut microbiome alterations in Alheimer's disease. *Sci Rep*. 2017;7:13527. doi: 10.1038/s41598-017-13601-y.

Effect of Probiotic Supplementation of Cognitive Function and Metabolic Status in Alzheimer's Disease: A Randomized, Double-Blind and Controlled Trial[9]

- Randomized, double-blind, controlled clinical trial
- 60 AD patients (30 probiotic group, 30 control group) - 12-week study
  - Probiotic mixture contained *Lactobacillus* strains and *Bifidobacterium bifidum*
- Assessed the effects of probiotic supplementation on cognitive function and metabolic status in the AD population
- Mini-mental state examination (MMSE) score recorded before and after treatment
- Fasting blood sample taken pre- and post-treatment to examine metabolic markers
  - Plasma malondialdehyde, serum high-sensitivity C-reactive protein, homeostasis model of assessment-estimated insulin resistance, beta cell function, serum triglycerides, and quantitative insulin sensitivity check index, fasting plasma glucose, other lipid profiles, and other biomarkers of oxidative stress and inflammation

Effect of Probiotic Supplementation of Cognitive Function and Metabolic Status in Alzheimer's Disease: A Randomized, Double-Blind and Controlled Trial[9]

- Probiotic supplementation for 12 weeks positively affected cognitive function and some metabolic statuses in the AD patients
- 52 subjects completed experiment, however all 60 included in final analysis
- Probiotic group showed an improvement in MMSE score compared to their control counterparts (difference between the two was statistically significant)
- Favorable effects found in MDA, hs-CRP, markers of insulin metabolism, and serum TGs and VLDL
- No changes found in other biomarkers of oxidative stress and inflammation, FPG, or other lipid profiles
- Gut microbiota could be expressing effects through neurotransmitter synthesis or receptor expression

Effect of Probiotic Supplementation of Cognitive Function and Metabolic Status in Alzheimer's Disease: A Randomized, Double-Blind and Controlled Trial[9]

TABLE 2 | Mean values of the behavioral test and the biomarkers measurements in the probiotic and control groups.

	Control group		Probiotic group		Difference between the two groups
	Baseline	End-of-trial	Baseline	End-of-trial	*P*-value[a]
MMSE (score out of 30)	8.47 ± 1.10	8.00 ± 1.08	8.67 ± 1.44	10.57 ± 1.64	< 0.001
TAC (mmol/L)	895.66 ± 25.96	915.35 ± 26.60	876.13 ± 26.48	922.42 ± 28.53	0.25
GSH (μmol/L)	390.78 ± 17.46	386.76 ± 20.33	377.26 ± 14.82	401.25 ± 16.68	0.19
MDA (μmol/L)	4.26 ± 0.30	4.32 ± 0.31	4.31 ± 0.26	3.21 ± 0.23	< 0.001
hs-CRP (μg/ml)	4.54 ± 1.30	6.59 ± 1.14	6.61 ± 1.24	5.44 ± 0.85	< 0.001
NO (imol/L)	44.76 ± 0.53	45.56 ± 0.82	43.68 ± 0.64	44.37 ± 1.14	0.93
FPG (mg/dl)	83.40 ± 2.36	86.77 ± 4.07	92.00 ± 7.92	94.13 ± 7.72	0.98
HOMA-IR	1.43 ± 0.24	2.08 ± 0.27	1.30 ± 0.13	1.60 ± 0.19	0.002
HOMA-B	25.04 ± 3.21	37.86 ± 4.64	27.36 ± 3.50	22.06 ± 2.43	0.001
QUICKI	0.38 ± 0.01	0.36 ± 0.01	0.38 ± 0.01	0.37 ± 0.01	0.006
Triglycerides (mg/dl)	84.32 ± 4.65	81.74 ± 4.76	119.60 ± 10.25	94.33 ± 10.04	0.003
VLDL (mg/dL)	16.86 ± 0.93	16.35 ± 0.95	23.92 ± 2.05	18.87 ± 2.01	0.003
LDL (mg/dl)	90.44 ± 4.58	94.34 ± 4.39	85.16 ± 4.14	90.64 ± 5.29	0.76
HDL (mg/dl)	51.27 ± 1.75	44.49 ± 1.97	45.81 ± 1.45	38.82 ± 1.35	0.93
Total cholesterol (mg/dl)	158.57 ± 5.75	155.17 ± 5.59	154.88 ± 4.91	148.32 ± 5.43	0.63
Total/ HDL-cholesterol	3.15 ± 0.12	3.62 ± 0.16	3.43 ± 0.12	3.95 ± 0.2	0.81

Data are mean ± SEM.[a] represents P-values obtained from the time × group interaction analysis. FPG, fasting plasma glucose; GSH, total glutathione; HOMA-IR, homeostasis model of assessment-estimated insulin resistance; HOMA-B, homeostasis model of assessment-estimated B cell function; hs-CRP, high-sensitivity C-reactive protein; MMSE, mini-mental state examination; MDA, malondialdehyde; NO, nitric oxide; QUICKI, quantitative insulin sensitivity check index; TAC, total antioxidant capacity.

Akbari E, Asemi Z, Kakhaki RD, et al. Effect of Probiotic Supplementation on Cognitive Function and Metabolic Status in Alzheimer's Disease: A Randomized, Double-Blind and Controlled Trial. *Front Aging Neurosci*. 2016;8:256. doi: 10.3389/fnagi.2016.00256.

Probiotic Supplementation in Patients with Alzheimer's Dementia - An Explorative Intervention Study[10]

- Explorative intervention study
- 20 outpatients with Alzheimer's dementia diagnosis
- 28 days of supplementation with multispecies probiotic
- Fecal samples collected before and after supplementation, with microbiota quantified and qualified
  - *Akkermansia muciniphila, Faecalibacterium prausnitzii, Clostridium cluster I*
- Measurements of fecal inflammation markers
  - Calprotectin, α_1-antitrypsin, and zonulin
- Biomarkers of immune activation measured in serum: neopterin, vitamin D, brain derived nerve growth factor (BDNF), aromatic amino acids (tryptophan:kynurenine, phenylalanine:tyrosine, nitrite)

Probiotic Supplementation in Patients with Alzheimer's Dementia - An Explorative Intervention Study[10]

Table 2. **Concentrations of fecal inflammation markers and fecal bacterial strains (mean ± SD, range in brackets) in patients with Alzheimer's dementia (n = 18) before and after 28 days of a multi-specific probiotic supplementation.**

	Before	After
	Mean ± SD (Range)	Mean ± SD (Range)
α1-Antitrypsin [mg/g]	37.9 ± 23.7 (9.6 - 282)	44.7 ± 35.8 (6.2 - 520)
Calprotectin [mg/L]	84.7 ± 71 (2.8 - 112)	119 ± 131 (3.8 - 123)
Zonulin [µg/L]	93.1 ± 56.3 (16 - 220)	66.6 ± 54.2 (19 - 213)**
S100A12 [µg/L]	3.5 + 6.0 (0 - 23)	not available
Clostridium cluster I*	7.76 ± 1.10 (5.46 - 9.26)	7.92 ± 1.28 (5.34 - 10.2)
*Faecalibacterium prausnitzii**	8.25 ± 1.47 (5.15 – 10.1)	9.04 ± 1.43 (5.83 - 10.9) ***
*Akkermansia muciniphila**	8.61 ± 1.67 (6.00 – 10.9)	8.47 ± 1.85 (6.00 - 10.8)

(*RNA copy/g feces, log10; **U = 2.461, p = 0.01; ***U = 3.375, p <0.001).

Leblhuber F, Steiner K, Schuetz B, Fuchs D, Gostner JM. Probiotic Supplementation in Patients with Alzheimer's Dementia - An Explorative Intervention Study. *Curr Alzheimer Res*. 2018;15(12):1106–1113. doi:10.2174/1389200219666180813144834.

Probiotic Supplementation in Patients with Alzheimer's Dementia - An Explorative Intervention Study[10]

Table 3. **Concentrations of serum inflammation markers (mean ± SD and range) and of serum neurotransmitter precursor amino acids before and after 28 days of a multi-specific probiotic supplementation in 15 patients with Alzheimer's dementia for whom pre- and follow-up data were available.**

	Before:		After:	
	Mean ± SD	Range	Mean ± SD	Range
Neopterin [nmol/L]	9.8 ± 4.9	6.0 - 23.7	12.8 ± 10.1	6.6 - 44.5
Kyn/Trp [µmol/mmol]	38.2 ± 13.8	17.8 - 80.3	39.4 ± 10.5	23.5 - 61.0
Kynurenine [µmol/L]	1.82 ± 0.29	1.4 - 2.5	2.06 ± 0.42*	1.3 - 2.6
Tryptophan [µmol/L]	51.9 ± 15.0	22.6 - 85.5	54.1 ± 11.6	37.8 - 82.2
Phe/Tyr [µmol/µmol]	0.77 ± 0.30	0.3 - 1.6	0.82 ± 0.24	0.5 - 1.26
Tyrosine [µmol/L]	133 ± 33.5	86.6 - 199	146 ± 65.0	71 - 280
Phenylalanine [µmol/L]	98.5 ± 29.1	32.1 - 143	111 ± 33.0	54.0 – 174
Nitrite [µmol/L]	238 ± 421	5.5 – 1050	442 ± 514	20.0 - 1050

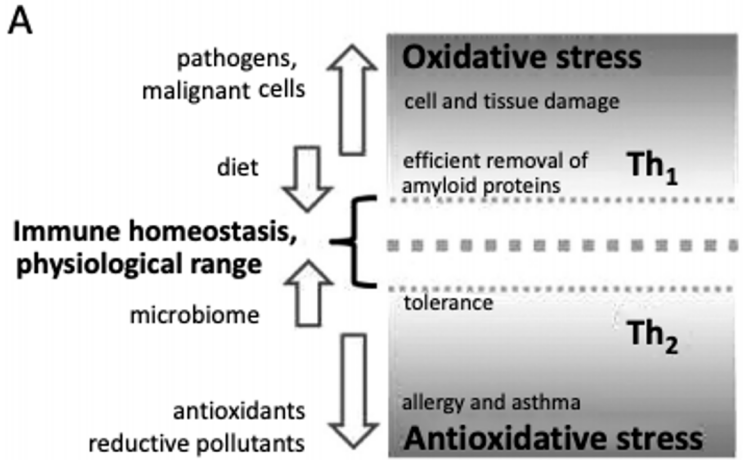
*U = 2.481, $p < 0.05$.

Leblhuber F, Steiner K, Schuetz B, Fuchs D, Gostner JM. Probiotic Supplementation in Patients with Alzheimer's Dementia - An Explorative Intervention Study. *Curr Alzheimer Res*. 2018;15(12):1106–1113. doi:10.2174/1389200219666180813144834.

Probiotic Supplementation in Patients with Alzheimer's Dementia - An Explorative Intervention Study[10]

- Increase in *Faecalibacterium prausnitzii*
- Decrease in fecal zonulin - modulates the permeability of the intestinal barrier
- Increase in serum kynurenine levels - probably caused by immune activation
- Before and after values of neopterin and the kynurenine:tryptophan ratios correlated significantly
  - Concentrations point to activation of macrophages or dendritic cells
- Supplementation influences gut bacteria composition and tryptophan metabolism
- Balance between oxidative stress (Th_1) and antioxidative stress (Th_2) needed to avoid cognitive issues like AD

Probiotic Supplementation in Patients with Alzheimer's Dementia - An Explorative Intervention Study[10]



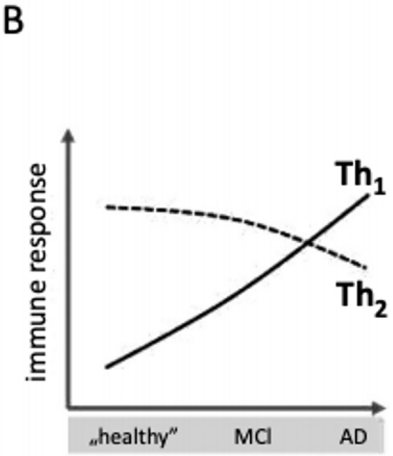


Fig. (1). The proposed role of immune activation arms in Alzheimer's disease (AD). (**A**) Oxidative stress is associated with Th1-type immunity and suppresses the Th2-arm, and *vice versa.* Both, the composition of diet and the microbiome, influence immune homeostasis in a physiological range. While the establishment of tolerance requires more Th2-like conditions, a deviation to pro-oxidative Th1 is necessary for an efficient removal of pathogens, tumor cells and amyloid proteins. The preponderance of a strong reductive milieu, *e.g.,* due to excessive intake of food antioxidants and likewise the presence of chronic oxidative stress are crucial in the progression of a variety of disorders. (**B**) Corresponding hypothesis: It is suggested that in early stages of AD there is an inefficient clearance from amyloid precursors, potentially due to overwhelming Th2 conditions which in the course of disease development from mild cognitive impairment (MCI) to AD promote an activation of counteracting Th1-type immune mechanisms that also lead to neuronal damage.

Leblhuber F, Steiner K, Schuetz B, Fuchs D, Gostner JM. Probiotic Supplementation in Patients with Alzheimer's Dementia - An Explorative Intervention Study. *Curr Alzheimer Res*. 2018;15(12):1106–1113. doi:10.2174/1389200219666180813144834.

Efficacy and Safety of *Lactobacillus Plantarum* C29-Fermented Soybean (DW2009) in Individuals with Mild Cognitive Impairment: A 12-Week, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Clinical Trial[11]

- Multi-center, randomized, double-blind, placebo-controlled clinical trial
- 100 participants with mild cognitive impairment (MCI) - 50 probiotic, 50 placebo
  - MCI = state of cognitive deterioration that precedes clinical AD diagnosis
- 12 week supplementation with *Lactobacillus plantarum* C-29-fermented soybean (DW2009)
- Outcomes assessed by computerized neurocognitive functions tests
- Changes in serum brain-derived neurotrophic factor (BDNF) and cognitive performance were evaluated

Efficacy and Safety of *Lactobacillus Plantarum* C29-Fermented Soybean (DW2009) in Individuals with Mild Cognitive Impairment: A 12-Week, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Clinical Trial[11]

- Those who received DW2009 showed greater cognitive improvement
  - Changes in attention composite score and combined cognitive function statistically significant

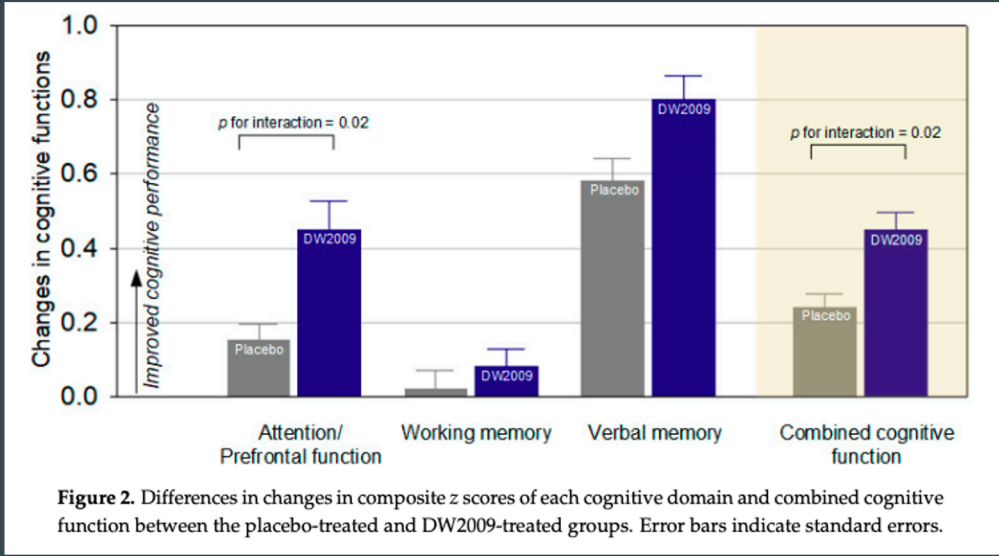


Figure 2. Differences in changes in composite *z* scores of each cognitive domain and combined cognitive function between the placebo-treated and DW2009-treated groups. Error bars indicate standard errors.

Hwang YH, Park S, Paik JW, et al. Efficacy and Safety of *Lactobacillus Plantarum* C29-Fermented Soybean (DW2009) in Individuals with Mild Cognitive Impairment: A 12-Week, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *Nutrients*. 2019;11(2):305. doi:10.3390/nu11020305.

Efficacy and Safety of *Lactobacillus Plantarum* C29-Fermented Soybean (DW2009) in Individuals with Mild Cognitive Impairment: A 12-Week, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Clinical Trial[11]

- For the DW2009 group, change in serum BDNF levels were positively associated with change in the combined cognitive function

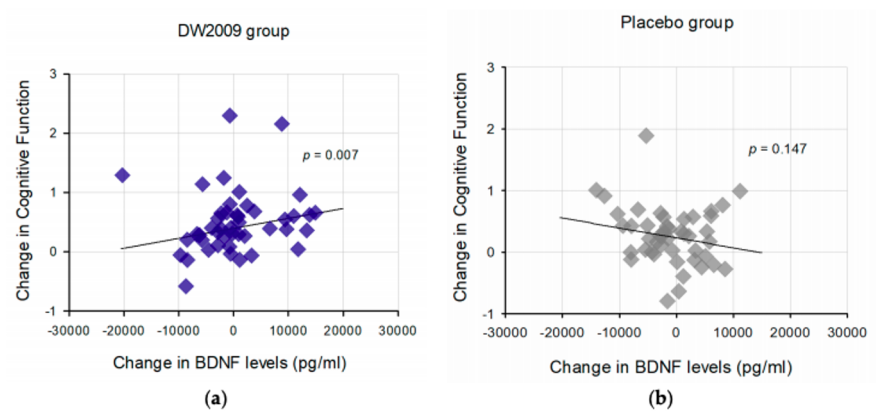


Figure 3. Association between change in brain-derived neurotrophic factor (BDNF) levels and combined cognitive function in (**a**) DW2009 treatment group and (**b**) placebo group. Composite z scores for the combined cognitive function were calculated by averaging z scores of the measured cognitive domains (attention, working memory, and verbal memory).

Hwang YH, Park S, Paik JW, et al. Efficacy and Safety of *Lactobacillus Plantarum* C29-Fermented Soybean (DW2009) in Individuals with Mild Cognitive Impairment: A 12-Week, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *Nutrients*. 2019;11(2):305. doi:10.3390/nu11020305.

Efficacy and Safety of *Lactobacillus Plantarum* C29-Fermented Soybean (DW2009) in Individuals with Mild Cognitive Impairment: A 12-Week, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Clinical Trial[11]

- Lactobacilli population was significantly increased in the DW2009 group
- No significant changes in bifidobacteria or clostridia populations

Table 3. Effect of DW2009 on the bifidobacteria, lactobacilli, and clostridia.

Gut Microbiota Composition	Placebo Group			DW2009 Group		
	Baseline	Follow-up	*n*	Baseline	Follow-up	*n*
Bifidobacterium spp.	2.99×10^{11} (1.13×10^{12})	4.46×10^{10} (1.11×10^{11})	40	4.16×10^{11} (1.16×10^{12})	5.04×10^{11} (1.75×10^{12})	38
Lactobacillus spp.	3.52×10^{10} (1.22×10^{11})	6.80×10^{10} (1.69×10^{11})	38	1.82×10^{10} (3.43×10^{10})	8.04×10^{10} * (1.82×10^{11})	37
Clostridium spp.	2.20×10^{11} (8.46×10^{11})	6.60×10^{10} (1.41×10^{11})	40	8.00×10^{10} (1.80×10^{11})	8.38×10^{10} (2.32×10^{11})	38

Asterisk denotes significant difference at $p < 0.05$, measured using one-way ANOVA. Data are presented as mean (standard deviation). Values represent number of bacteria (/g wet weight).

Hwang YH, Park S, Paik JW, et al. Efficacy and Safety of *Lactobacillus Plantarum* C29-Fermented Soybean (DW2009) in Individuals with Mild Cognitive Impairment: A 12-Week, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *Nutrients*. 2019;11(2):305. doi:10.3390/nu11020305.

Discussion: Differences in Microbiota Composition[12]

- Differences in gut microbiota have yet to be clearly defined
- Could be caused by differences in classification, disease progression, location, diet, etc
- Very few studies with small samples sizes - not applicable
- Control of brain-derived neurotrophic factor possible mechanism of action for prevention
    - Neurotransmitter production
- Dysbiosis causes disruption of the microbiome-gut-brain axis
    - Increases inflammation, disease progression
- Future research should focus on analyzing structural differences of gut microbiota and how they regulate AD pathology

Discussion: Probiotic Supplementation[13]

- Overall positive results in cognitive function with the use of probiotic supplementation
- Could be used as prevention or possible treatment for AD and dementia, though mechanisms of action still largely unclear
- Proposed methods include:
  - Modulation of immune reactions
  - Suppression of oxidative stress
  - Control of CNS function
- More research necessary to further define the relationship between probiotics and cognitive health

Conclusion

- Research still highly unverified and needs replication
- Further research important for Registered Dietitians, especially those working in long-term care or with the elderly population
- Understanding how the gut microbiota interact with our other bodily systems could provide insight into the prevention and treatment of many diseases
- Dementia and AD becoming more and more prevalent in society
- Finding out more about their pathogenesis and link with gut microbiome through the microbiome-gut-brain axis should be front and center

Discussion

- What are you opinions on the current research being done? Do you think supplementation with probiotics could be a viable treatment for dementia and AD?
- What further questions would you have about the effect of probiotic supplementation on the body in these patients?

Questions?

References

1. World Health Organization. Dementia: Key Facts. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/dementia. Updated September 19, 2019. Accessed November 30, 2019.
2. Cresci G, Izzo K. Gut Microbiome. In: Corrigan ML, Roberts K, Steiger E. *Adult Short Bowel Syndrome*. Amsterdam, Netherlands: Elsevier; 2019: Chapter 14.
3. Cryan JF, O'Riordan KJ, Cowan CSM, et al. The Microbiota-Gut-Brain Axis. *Physiol Rev*. 2019;99(4):1977-2013. doi: 10.1152/physrev.00018.2018.
4. Mahan KL, Raymond JL. *Krause's food & the nutrition care process, 14th edition*. St. Louis, MO: Elsevier; 2017.
5. National Institute on Aging. Basics of Alzheimer's Disease and Dementia. US Department of Health and Human Services. https://www.nia.nih.gov/health/what-alzheimers-disease. Reviewed May 16, 2017. Accessed December 1, 2019.
6. Centers for Disease Control and Prevention. Alzheimer's Disease. Centers for Disease Control and Prevention. https://www.cdc.gov/aging/aginginfo/alzheimers.htm. Reviewed September 20, 2019.
7. Saji N, Niida S, Murotani K, et al. Analysis of the relationship between the gut microbiome and dementia: a cross-sectional study conducted in Japan. *Sci Rep*. 2019;9:1008. doi: 10.1038/s41598-018-38218-7.
8. Vogt NM, Kerby RL, Dill-McFarland KA, et al. Gut microbiome alterations in Alheimer's disease. *Sci Rep*. 2017;7:13527. doi: 10.1038/s41598-017-13601-y.
9. Akbari E, Asemi Z, Kakhaki RD, et al. Effect of Probiotic Supplementation on Cognitive Function and Metabolic Status in Alzheimer's Disease: A Randomized, Double-Blind and Controlled Trial. *Front Aging Neurosci*. 2016;8:256. doi: 10.3389/fnagi.2016.00256.
10. Leblhuber F, Steiner K, Schuetz B, Fuchs D, Gostner JM. Probiotic Supplementation in Patients with Alzheimer's Dementia - An Explorative Intervention Study. *Curr Alzheimer Res*. 2018;15(12):1106–1113. doi:10.2174/1389200219666180813144834.

References

11. Hwang YH, Park S, Paik JW, et al. Efficacy and Safety of *Lactobacillus Plantarum* C29-Fermented Soybean (DW2009) in Individuals with Mild Cognitive Impairment: A 12-Week, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *Nutrients*. 2019;11(2):305. doi:10.3390/nu11020305.
12. Hu X, Wang T, Jin F. Alzheimer's disease and gut microbiota. *Sci China Life Sci*. 2016;59(10):1006-23. doi: 10.1007/s11427-016-5083-9.
13. Wong CB, Kobayashi Y, Xiao J. Probiotics for Preventing Cognitive Impairment in Alzheimer's Disease. In: Evrensel A, Unsalver BO. *Gut Microbiota-Brain Axis*. IntechOpen; 2018: Chapter 6. doi: 10.5772/intechopen.79088.

All photos used are from Adobe Stock Photos, unless otherwise marked.