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Relationship between Alzheimer's Disease and the Human Microbiome

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Abstract: Alzheimer's disease (AD) is a neurodegenerative disease characterized by memory and language disorders, and the accumulation of amyloid-β and tau protein in the brain has been considered a feature of AD. The accumulation of amyloid-β has been reported to be observed 15 to 20 years before the onset by image analysis-based diagnostic methods. In addition, it has been reported that AD is associated with various diseases such as type 2 diabetes, periodontal disease, and obesity. It is conceivable that these diseases trigger the onset of AD. The human gut and brain form a network called "brain–gut–microbiota axis," and it is suggested that the gut microbiota is involved in brain diseases. Recently, the microbiota has also been reported to be involved in diseases such as depression and Parkinson's disease, and so attention is being paid to the relationship between AD and gut microbiota. This chapter outlines the relationship between AD and the human microbiome.

Keywords: amyloid-β; behavior; brain–gut–microbiota axis; gut microbiota; metabolome

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INTRODUCTION

The cause of Alzheimer's disease (AD) is presently unknown, but its onset has been shown to involve mainly genetic and environmental factors. About 700 risk genes (as of April 2019) are registered in Alzforum (https://www.alzforum.org/) as the genetic factors of AD. Other factors found to be involved include lifestyle habits such as sleep, exercise, diet, and educational history. Recently, it has been reported that sleep is related to the accumulation of amyloid-β, which is a characteristic of AD. In healthy middle-aged men, sleep reduced amyloid-β 42 in cerebrospinal fluid by 6%, while lack of sleep abolished that reduction (1). In a study investigating the relationship between the Mediterranean diet and dementia, it was noted that the traditional Mediterranean diet that consists of a large amount of fruits, vegetables, and cereals reduces the risk of developing dementia and AD (2). In addition, Ozawa, upon following more than 1000 subjects over 17 years, has reported that the incidence of AD decreased significantly with increased intake of milk and dairy products (3). Lifestyle plays an important role in the prevention of AD, and dysregulation of lifestyle leads not only to AD but also to various other diseases. This chapter first outlines the relationship between lifestyle diseases and AD, and then the relationship between gut microbiota and AD.

AD AND DIABETES

Association of AD to diabetes led to the classification of a new category of diabetes called type 3 diabetes (4). Ott et al. (5) examined the association between diabetes and dementia in 6330 people aged 55–99 years, and the results suggest an association between diabetes mellitus and dementia. In addition, in a prospective population-based cohort study among 6370 elderly subjects, diabetes mellitus reportedly doubled the risk of dementia and AD. The study also reported that patients treated with insulin had four times higher the risk of dementia. A cohort study of 2574 men reported that patients with type 2 diabetes are associated with dementia, AD, and vascular dementia (6). The same study concluded that these associations are stronger in patients carrying the APOE ε4 allele (7). Furthermore, borderline diabetes is also associated with the increased risk of dementia and AD (8). Conversely, Michal et al. (9) reported that in the hippocampus of AD patients, diabetics had significantly lower plaque ratings than the non-diabetics. In addition, inflammation in the brain by the intake of a high-fat diet promotes accumulation of amyloid in diabetes model mice, regardless of the decrease in insulin (10). Thus, prior studies suggest that the factors like eating habits, mild glucose intolerance, and onset of type 2 diabetes are involved in the onset of AD. On the other hand, amyloidosis is a key pathological feature of both AD and type 2 diabetes (11). Bacterial endotoxin lipopolysaccharide and bacterial cell wall peptidoglycan are involved in amyloidosis, suggesting that chronic bacterial inflammation may link the two diseases. In addition, recent advances in gene analysis technology have revealed the relationship between intestinal bacteria and diabetes. Adachi et al. (12) have reported the relationship between type 2 diabetes and short-chain fatty acids (SCFAs), the metabolites of the microbiota, in the

Japanese population. From these studies, it can be considered that changes in the microbiota affect the production of SCFAs, thereby promoting the onset of type 2 diabetes as well as AD.

AD AND PERIODONTAL DISEASE

Periodontitis is considered as a risk factor for dementia and AD. Periodontal disease is a chronic disease caused by gram-negative bacteria such as *Porphyromonas gingivalis, Treponema denticola,* and *Tannerella forsythia*. It has been clarified that this chronic inflammation is related to the accumulation of amyloid-β and cognitive impairment that are characteristic of AD (13). In addition, tumor necrosis factor-α and antibodies against periodontitis in plasma have been reported to be biomarkers of AD (14, 15), and periodontal disease has been suggested to be a probable trigger for AD. Recently, gingipain, a protease produced by *P. gingivalis*, has been detected in the brains of patients with AD (16). The concentration of gingipain is high in the brain of patients with AD, and the accumulation of tau protein is promoted, whereas the accumulation of amyloid-β is suppressed by the gingipain inhibitor. Furthermore, oral administration of *P. gingivalis* to mice promotes the accumulation of amyloid-β (17). Gingipain reportedly activates microglia and causes inflammation in the brain (18). These activated microglia cause accumulation of amyloid-β and cognitive decline (19). However, Noble et al. (20) have reported that, in a cohort study of 219 subjects (consisting of 110 patients with AD and 109 healthy volunteers), subjects with high serum IgG against *Actinomyces naeslundii* (which is associated with periodontal disease) were at a high risk of developing AD. Thus, the periodontitis bacteria have been linked to AD through the microbial toxins, inflammatory substances, and serum antibodies. Chronic inflammation developed by these bacteria is a predisposing factor for AD.

AD AND OBESITY

Obesity is considered as one of the risk factors associated with AD. Recently, the relationship between obesity and AD has been studied extensively. Animal studies have shown that mice fed with high-fat diet significantly increases the accumulation of amyloid-β in the hippocampus and are involved in cognitive decline (21–23). Another clinical study characterized by magnetic resonance imaging (MRI) scan of the brains of 700 patients having mild cognitive impairment (MCI) inferred that higher body mass index (BMI) is associated with brain volume deficits (24). Gustafson reported the relationship between BMI and risk of dementia as investigated in an 18-year follow-up of 392 Swedish adults (aged 70–88 years) without dementia. Higher body weight was observed in women who developed AD compared to women without dementia (70, 75, and 79 years). In particular, at the age of 70 years, every 1.0 increase in BMI showed a 36% increase in AD risk (25). In addition, Luchsinger's study has shown that the waist to hip ratio is related to a higher risk of AD (26). In the

Swedish, 8534 twin individuals over the age of 65 were assessed to detect cases of dementia. Overweight (BMI 25–30) and obesity (BMI over 30) at midlife were related to dementia with odds ratios of 1.71 and 3.88, respectively (27). However, the risk for dementia associated with obesity gradually reduced with increasing age (28). Obesity has been implicated as a risk factor for AD in middle age, whereas its associated risk decreases with increasing age. Conversely, weight loss and low BMI have been found to be associated with increased risk of AD in older adults (29).

MICROBIOTA AND AMYLOID ACCUMULATION

The relationship between microbiota and amyloid-β accumulation has been studied by Harach et al. (30). APPPS1, an AD mouse model, presents accumulation of amyloid-β in the brain in an age-dependent manner. The generation of germ-free APPPS1 mice was inhibited by the accumulation of amyloid-β. In addition, the microbiota of this mouse model is different from that of the wild type, and it has been reported that accumulation of amyloid-β increases in mice transplanted with the microbiota of an AD mouse model. Furthermore, Ho et al. (31) found that valeric acid and butyric acid, SCFAs produced by the microbiota, strongly inhibit the aggregation of amyloid-β in an in vitro test. Furthermore, bacterial endotoxin may be involved in the inflammations associated with amyloidosis and AD (32). Although some bacteria such as *Escherichia coli* produce amyloids (33), the relationship between the amyloid that is caused by neurodegenerative diseases such as AD and bacterial amyloids has not been clarified (34). However, bacterial amyloid has been shown to activate signaling pathways that play a role in the pathogenesis of neurodegenerative diseases and AD, and microbiota is a noted key player that enhances inflammation associated with the accumulation of amyloid-β (35). Furthermore, the lipopolysaccharide of gram-negative bacteria promotes accumulation of amyloid-β in mouse brain and induces cognitive dysfunction (36, 37). Hence, it has been suggested that microbiota is involved in the accumulation of amyloids, which is known to be a pathological feature of AD, via metabolites such as extracellular components and SCFAs. In addition, bacteria that produce amyloids are also present in the enteric bacterial groups, but it is thought that further research is necessary to clarify whether amyloids derived from the bacteria are involved in AD progression.

EFFECTS OF DAIRY PRODUCTS AND PROBIOTICS IN AD

Acute and chronic inflammation is associated with neurodegenerative diseases such as AD and Parkinson's disease (38–41). Probiotics such as lactic acid bacteria and *Bifidobacterium* have attracted attention as tools to suppress this inflammation. In the Bonfili study, administration of the probiotic cocktail SLAB 51 (*Streptococcus thermophilus*, *Bifidobacterium longum*, *B. breve*, *B. infantis*, *Lactobacillus acidophilus*, *L. plantarum, L. paracasei*, and *L. delbrueckii* subsp. *bulgaricus*, *L. brevis*) in AD model mice (3xTg-ADmouse) affected changes in the microbiota, thus

affecting the content of metabolites of enteric bacteria such as SCFAs and cognitive function (42). Kobayashi et al. (31) also reported that oral administration of *B. breve* A1 led to behavior impairment to the same level as donepezil, a centrally acting cholinesterase inhibitor, in AD model mice injected with amyloid-β into the ventricles. Acetic acid, which is a metabolite of *Bifidobacterium*, is known to play an important role in the improvement of AD. However, there have been cases where improvement in memory due to probiotics was not observed. Benton et al. (43) confirmed the cognitive function by following 3 weeks of probiotic milk drink or placebo control consumption in 124 healthy volunteers (mean age 61.8 years), and the cognitive function was higher in the placebo consuming group than the probiotic drinking group upon 20 days of consumption. Furthermore, recent research has shown that consumption of not only these probiotics but also yogurt and cheese has been linked to AD and dementia. David et al. (44) reviewed that bioactive peptides in dairy products improve cognitive function. Ano et al. (45, 46) have also shown that in vivo experiments the peptides present in Camembert cheese improve the decline in memory and cognitive function. On the contrary, Rahman et al. (47), in an epidemiological study of 1056 subjects, reported that dietary intake of cheese is associated with a lower prevalence of cognitive impairment. Also, a study conducted on a total of 1006 community-dwelling Japanese subjects without dementia, aged 60–79 years (followed up for a median of 15 years), reported that high intake of milk and milk products reduced the risk of dementia (48). Although many model animals for AD and dementia are produced and their application to this field is advanced, further studies are needed to establish the influence of probiotics and dairy products on brain function.

AD AND GUT MICROBIOTA

Recently, the development of next-generation sequencing technology has made it possible to estimate the gut microbiota rapidly at a low cost, and the relationship between various diseases and the gut microbiota has been studied extensively. The Vogt study compared the microbiota in 50 subjects (Healthy control HC: n = 25 and AD: n = 25) and noted decreased microbial diversity in the AD subjects. It also reported a decrease in *Firmicutes* and increase in *Bacteroidetes* percentage abundance (49). Saji et al. (50) compared the microbiota of non-demented patients (n = 49) with demented patients (n = 34) among 128 Japanese subjects and found that *Bacteroides* decreased in demented patients compared to non-demented patients (Figure 1). Furthermore, Nguyen et al. (51) reported that butyrate-producing bacteria involved in cognitive function have been isolated from the microbiota of patients with AD. Liu et al. (52) reported that in a study of 97 subjects (AD: n = 33, MCI: n = 32, and HC: n = 32), the fecal microbial diversity was decreased in AD patients compared with MCI patients and healthy volunteers. In addition, it also reported a decrease in *Firmicutes* and increase in *Proteobacteria* abundance. There are similar reports on the relationship between gut microbiota and AD as the studies stated above. Therefore, further research is needed to clarify the difference. With the growing research in this field, future boom in AD cure research might as well be directed toward microbiome research.

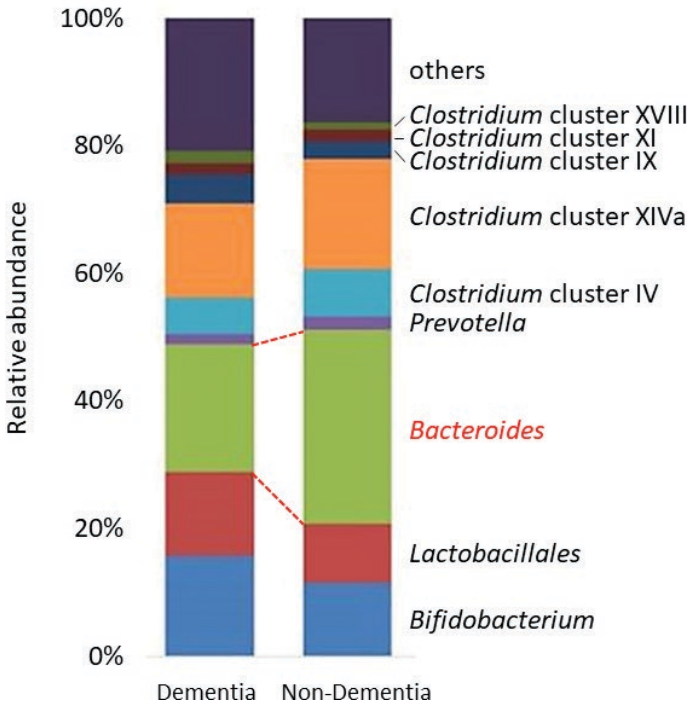

Figure 1 Relative bacterial abundance in the gut microbiota of dementia and non-dementia patients. It was suggested that a lower prevalence of *Bacteroides* is seen in the gut of dementia patients than non-dementia patients (50).

GUT MICROBIOTA AND BEHAVIOR

Human intestine and brain form a network called the "brain–gut–microbiota axis" through physiologically active substances. The gut microbiota has been shown to play an important role in this network. Researchers have transplanted mice with different microbiota and compared their response to stress with adrenocorticotropic hormone and corticosterone as indicators (53). Specifically, as compared with specific pathogen-free mice, adrenocorticotropic hormone and corticosterone levels have been reported to significantly increase in germ-free mice due to restraint stress. In addition, the effect is also seen in mice transplanted with *B. infantis*, suggesting that the effect differs depending on the microbe transplanted and that the microbiota also affects neurotransmitters in the brain (54, 55). Kim et al. (56) reported that pregnant mice colonized with the human commensal bacteria (a mix of 20 human bacterial strains), which induce intestinal Th17 cells due to poly (I:C)-induced inflammation, produced offspring that were found to have increased anxiety behaviors such as increased ultrasonic vocalization, enhanced repetitive behavior with marble burying test, and shortened time in the center of the open-field arena. In contrast, these anxiety behaviors were not observed if the mothers were pre-treated with interleukin-17a blocking antibody, since interleukin-17 production of intestinal Th17 cells induced by human

commensal bacteria contributes to the development of anxiety behaviors in mouse offspring. Thus, it was revealed that the gut microbiota of the mother mouse is involved in the behavior of the offspring mouse. In addition, the authors previously reported cognitive behavior decline in germ-free mice transplanted with the microbiota of AD patients (57). Cognitive behavior was assessed by Object Location Test (OLT) and Novel Object Recognition Test (ORT). A significant deterioration of cognitive function was observed through both OLT (70 and 75 weeks of age vs. 10 weeks of age; 55, 70, and 75 weeks of age vs. 15 weeks of age) and ORT (70 weeks of age vs. 10 weeks of age; 35, 55, 65, 70, and 75 weeks of age vs. 15 weeks of age) in mice transplanted with microbiota from affected patients. Moreover, significant reduction of cognitive function of these mice was confirmed by both OLT (55 and 70 weeks of age) and ORT (55, 60, 65, and 70 weeks of age) in comparison with cognitive function of mice transplanted with microbiota of healthy volunteers (Figure 2). In this article, these data were re-analyzed by linear regression analysis (Figure 3). A significant decrease in cognitive function was confirmed in mice transplanted with microbiota from affected donors in relation

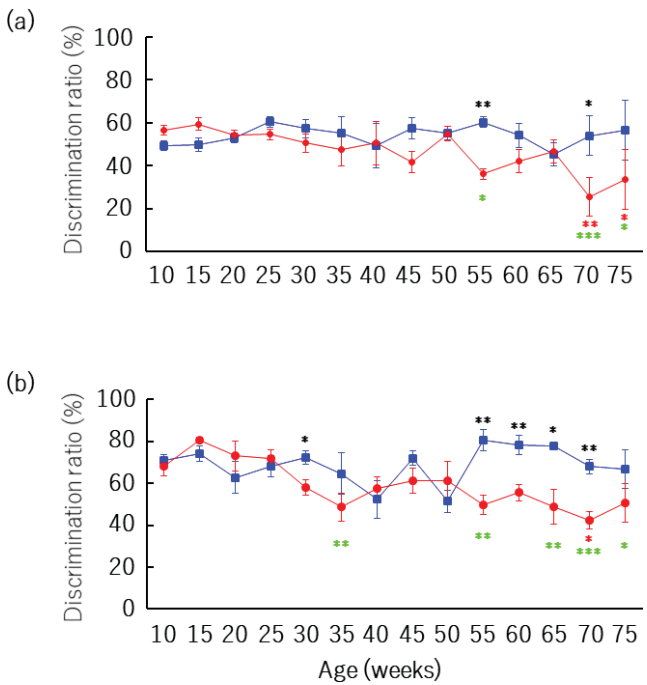

Figure 2 Novel object recognition test in mice transplanted with microbiota. (A) Ratio of time spent exploring a familiar object in a new location to time spent exploring a familiar object in an old location. (B) Ratio of time spent exploring a novel object to time spent exploring a familiar object. Blue and red lines indicate the ratio of time spent by mice transplanted with microbiota from a healthy donor and a patient with Alzheimer's disease, respectively. Black, * and ** indicate comparison between groups; red,* and ** indicate mice transplanted with microbiota from a patient with Alzheimer's disease had significantly altered cognitive function at respectively weeks of age compared with that at 10 weeks of age; green, *, **, and *** indicate mice transplanted with microbiota from a patient with Alzheimer's disease had significantly altered cognitive function at respectively weeks of age compared with that at 15 weeks of age. Data are mean ± SEM. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$ (57).

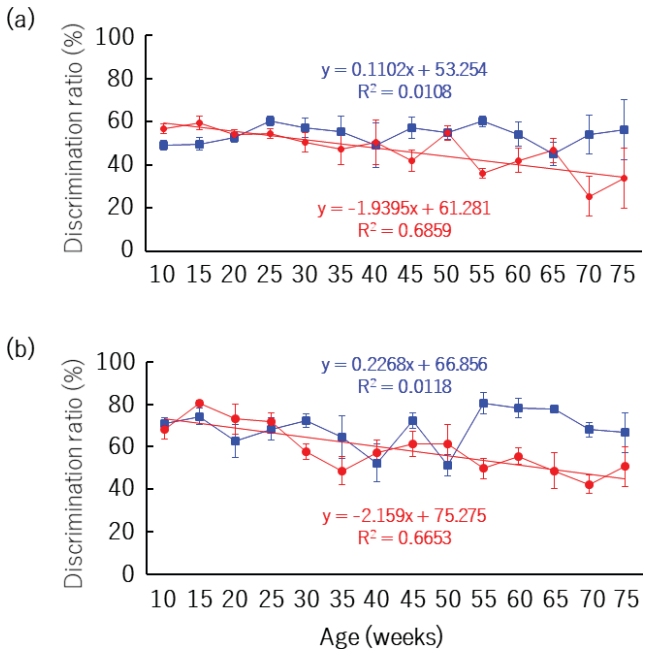

Figure 3 Regression analysis of two behavior tests. (A) Ratio of exploring novel objects in the 5 min of OLT. Blue square and red circle indicate healthy control (HC) group and Alzheimer's disease (AD) group, respectively. (B) Ratio of exploring for novel objects in the 5 min of object recognition test. In both panels means ± SEM are shown (57).

with age. The regression analysis results showed association between cognitive decline and age in mice transplanted with microbiota from affected patients, but not in mice transplanted with microbiota of healthy volunteers. Therefore, it was clear that mice transplanted with microbiota from affected patients had reduced cognitive function. This was further investigated by fecal metabolome analysis. The principal component analysis of the metabolites from individual mice exhibits separate clusters representing each of the mice categories (Figure 4). And the different metabolites from affected donors to mice transplanted with microbiota included gamma-aminobutyric acid, taurine, and valine, all of which are involved in central nervous system function. In addition, a difference in the concentration of other amino acids such as tryptophan, tyrosine, propionic acid, and SCFAs was also reported. Thus, it was suggested that the microbiota influences host behavior through its metabolites.

CONCLUSION

AD is known to cause deposition of amyloid-β, which is the main component of senile plaques in the brain. This deposition of amyloid-β is caused by the accumulation of amyloid generated from the amyloid precursor protein (APP) by the action of two enzymes β-secretase and γ-secretase in the cerebral cortex of the brain.

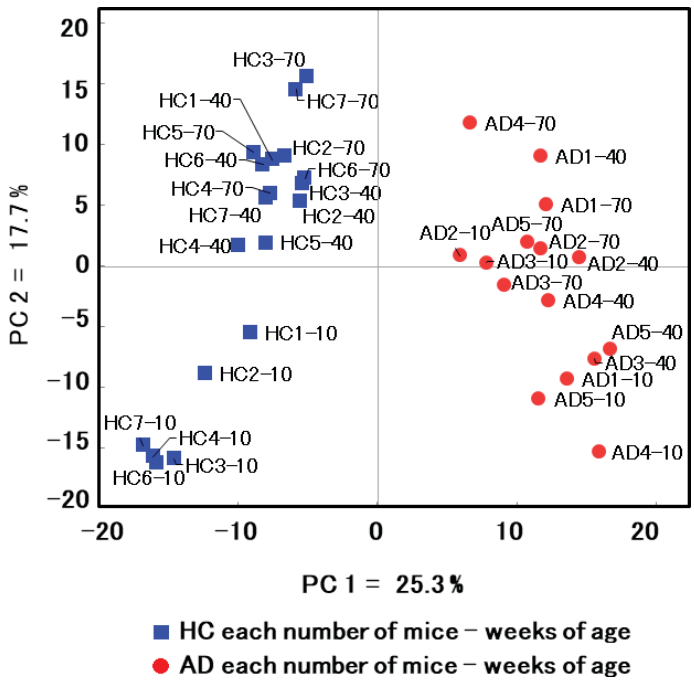

Figure 4 Comparison of metabolites in HC and AD mice feces. Principal component analysis of fecal metabolites in mice transplanted with microbiotas from a healthy volunteer (blue) and a patient with Alzheimer's disease (red) (57).

It has been clarified that this accumulation of amyloid-β starts 15–20 years before the onset of AD. At the same time, after a decrease in cognitive function is observed, there is not much change in the accumulation of amyloid-β, and no effect is seen in a drug targeting amyloid-β. Hence, some investigators have questioned the involvement of amyloid-β in AD. However, further studies are needed to investigate whether AD caused changes in the gut microbiota or vice versa.

Conflict of interest: The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this chapter.

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REFERENCES

1. Ooms S, Overeem S, Besse K, Rikkert MO, Verbeek M, Claassen JAHR. Effect of 1 night of total sleep deprivation on cerebrospinal fluid β-amyloid 42 in healthy middle-aged men: A randomized clinical trial. JAMA Neurol. 2014 Aug 1;71(8):971–7. http://dx.doi.org/10.1001/jamaneurol.2014.1173

2. Lourida I, Soni M, Thompson-Coon J, Purandare N, Lang IA, Ukoumunne OC, et al. Mediterranean diet, cognitive function, and dementia: A systematic review. Epidemiology. 2013 Jul;24(4):479–89. http://dx.doi.org/10.1097/EDE.0b013e3182944410
3. Ozawa M, Ohara T, Ninomiya T, Hata J, Yoshida D, Mukai N, et al. Milk and dairy consumption and risk of dementia in an elderly Japanese population: The Hisayama Study. J Am Geriatr Soc. 2014 Jul;62(7):1224–30. http://dx.doi.org/10.1111/jgs.12887
4. Steen E, Terry BM, Rivera EJ, Cannon JL, Neely TR, Tavares R, et al. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease – Is this type 3 diabetes? J Alzheimers Dis. 2005 Jan 1;7(1):63–80. http://dx.doi.org/10.3233/JAD-2005-7107
5. Ott A, Stolk RP, Hofman A, van Harskamp F, Grobbee D, Breteler MM. Association of diabetes mellitus and dementia: The Rotterdam Study. Diabetologia. 1996 Nov;39(11):1392–7. http://dx.doi.org/10.1007/s001250050588
6. Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: The Rotterdam Study. Neurology. 1999 Dec;53(9):1937–42. http://dx.doi.org/10.1212/WNL.53.9.1937
7. Peila R, Rodriguez B, Launer L. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: The Honolulu-Asia Aging Study. Diabetes. 2002 Apr;51(4):1256–62. http://dx.doi.org/10.2337/diabetes.51.4.1256
8. Xu W, Qiu C, Winblad B, Fratiglioni L. The effect of borderline diabetes on the risk of dementia and Alzheimer's disease. Diabetes. 2007 Jan;56(1):211–16. http://dx.doi.org/10.2337/db06-0879
9. Michal SB, Jeremy MS, Kenneth LD, Deborah M, Hillel ZG, James S, et al. Type 2 diabetes is negatively associated with Alzheimer's disease neuropathology. J Gerontol A Biol Sci Med Sci. 2005 Apr;60(4):471–5.
10. Wakabayashi T, Yamaguchi K, Matsui K, Hashimoto T, Mano A, Yamada K. Differential effects of diet- and genetically-induced brain insulin resistance on amyloid pathology in a mouse model of Alzheimer's disease. Mol Neurodegener. 2019 Apr;14:15. http://dx.doi.org/10.1186/s13024-019-0315-7
11. Judith M, Patrick LM. Common mechanisms involved in Alzheimer's disease and type 2 diabetes: A key role of chronic bacterial infection and inflammation. Aging. 2016 Apr;8(4):575–88. http://dx.doi.org/10.18632/aging.100921
12. Adachi K, Sugiyama T, Yamaguchi Y, Tamura Y, Izaw S, Hijikata Y, et al. Gut microbiota disorders cause type 2 diabetes mellitus and homeostatic disturbances in gut-related metabolism in Japanese subjects. J Clin Biochem Nutr. 2019 May;63(3):231–23. http://dx.doi.org/10.3164/jcbn.18-101
13. Kamer AR, Pirraglia E, Tsui W, Rusinek H, Vallabhajosula S, Mosconi L, et al. Periodontal disease associates with higher brain amyloid load in normal elderly. Neurobiol Aging. 2015 Feb;36(2):627–33. http://dx.doi.org/10.1016/j.neurobiolaging.2014.10.038
14. Farhad SZ, Amini S, Khalilian A, Barekatain M, Mafi M, Barekatain M, et al. The effect of chronic periodontitis on serum levels of tumor necrosis factor-alpha in Alzheimer disease. Dent Res J (Isfahan). 2014 Sep;11(5):549–52.
15. Kamer AR, Craig RG, Pirraglia E, Dasanayake AP, Norman RG, Boylan RJ, et al. TNF-α and antibodies to periodontal bacteria discriminate between Alzheimer's disease patients and normal subjects. J Neuroimmunol. 2009 Nov 30;216(1–2):92–7. http://dx.doi.org/10.1016/j.jneuroim.2009.08.013
16. Dominy SS, Lynch C, Ermini F, Benedyk M, Marczyk A, Konradi A, et al. *Porphyromonas gingivalis* in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. Sci Adv. 2019 Jan 1;5(1):eaau3333. http://dx.doi.org/10.1126/sciadv.aau3333
17. Ilievski V, Zuchowska PK, Green SJ, Toth PT, Ragozzino ME, Le K, et al. Chronic oral application of a periodontal pathogen results in brain inflammation, neurodegeneration and amyloid beta production in wild type mice. PLoS One. 2018 Oct 3;13(10):e0204941. http://dx.doi.org/10.1371/journal.pone.0204941
18. Liu Y, Wu Z, Zhang X, Ni J, Yu W, Zhou Y, et al. Leptomeningeal cells transduce peripheral macrophages inflammatory signal to microglia in reponse to *Porphyromonas gingivalis* LPS. Mediators Inflamm. 2013 Dec;2013:407562. http://dx.doi.org/10.1155/2013/407562
19. Wu Z, Ni J, Liu Y, Teeling JL, Takayama F, Collcutt A, et al. Cathepsin B plays a critical role in inducing Alzheimer's disease-like phenotypes following chronic systemic exposure to lipopolysaccharide

from *Porphyromonas gingivalis* in mice. Brain Behav Immun. 2017 Oct;65:350–61. http://dx.doi.org/10.1016/j.bbi.2017.06.002
20. Noble JM, Scarmeas N, Celenti RS, Elkind MSV, Wright CB, Schupf N, et al. Serum IgG antibody levels to periodontal microbiota are associated with incident Alzheimer disease. PLoS One. 2014 Dec;9(12):e114959. http://dx.doi.org/10.1371/journal.pone.0114959
21. Barron AM, Rosario ER, Elteriefi R, Pike CJ. Sex-specific effects of high fat diet on indices of metabolic syndrome in 3xTg-AD mice: Implications for Alzheimer's disease. PLoS One. 2013 Oct;8:10. http://dx.doi.org/10.1371/journal.pone.0078554
22. Julien C, Tremblay C, Phivilay A, Berthiaume L, Emond V, Julien P, et al. High-fat diet aggravates amyloid-beta and tau pathologies in the 3xTg-AD mouse model. Neurobiol Aging. 2010 Sep;31(9):1516–31. http://dx.doi.org/10.1016/j.neurobiolaging.2008.08.022
23. Knight EM, Martins IVA, Gümüsgöz S, Allan SM, Lawrence CB. High-fat diet-induced memory impairment in triple-transgenic Alzheimer's disease (3xTgAD) mice is independent of changes in amyloid and tau pathology. Neurobiol Aging. 2014 Aug;35(8):1821–32. http://dx.doi.org/10.1016/j.neurobiolaging.2014.02.010
24. Ho AJ, Raji CA, Becker JT, Lopez OL, Kuller LH, Hua X, et al. Obesity is linked with lower brain volume in 700 AD and MCI patients. Neurobiol Aging. 2010 Aug;31(8):1326–39. http://dx.doi.org/10.1016/j.neurobiolaging.2010.04.006
25. Gustafson D, Rothenberg E, Blennow K, Steen B, Skoog I. An 18-year follow-up of overweight and risk of Alzheimer disease. Arch Intern Med. 2003 Jul;163(13):1524–8. http://dx.doi.org/10.1001/archinte.163.13.1524
26. Luchsinger J, Cheng D, Tang M, Schupf N, Mayeux R. Central obesity in the elderly is related to late onset Alzheimer's disease. Alzheimer Dis Assoc Disord. 2012 Apr;26(2):101–5. http://dx.doi.org/10.1097/WAD.0b013e318222f0d4
27. Xu WL, Atti AR, Gatz M, Pedersen NL, Johansson B, Fratiglioni L. Midlife overweight and obesity increase late-life dementia risk: A population-based twin study. Neurology. 2011 May;76(18):1568–74. http://dx.doi.org/10.1212/WNL.0b013e3182190d09
28. Wotton CJ, Goldacre MJ. Age at obesity and association with subsequent dementia: Record linkage study. Postgrad Med J. 2014 Oct;90(1068):547–51. http://dx.doi.org/10.1136/postgradmedj-2014-132571
29. Moser VA, Pike CJ. Obesity and sex interact in the regulation of Alzheimer's disease. Neurosci Biobehav Rev. 2016 Aug;67:102–18. http://dx.doi.org/10.1016/j.neubiorev.2015.08.021
30. Harach T, Marungruang N, Duthilleul N, Cheatham V, Mc Coy KD, Frisoni G, et al. Reduction of Abeta amyloid pathology in APPPS1 transgenic mice in the absence of gut microbiota. Sci Rep. 2017 Feb 8;7:41802. http://dx.doi.org/10.1038/srep41802
31. Ho L, Ono K, Tsuji M, Mazzola P, Singh R, Pasinetti GM. Protective roles of intestinal microbiota derived short chain fatty acids in Alzheimer's disease-type beta-amyloid neuropathological mechanisms. Expert Rev Neurother. 2018 Jan;18(1):83–90. http://dx.doi.org/10.1080/14737175.2018.1400909
32. Asti A, Gioglio L. Can a bacterial endotoxin be a key factor in the kinetics of amyloid fibril formation? J Alzheimers Dis. 2014;39(1):169–79. http://dx.doi.org/10.3233/JAD-131394
33. Syed AK, Boles BR. Fold modulating function: Bacterial toxins to functional amyloids. Front Microbiol. 2014 Aug 1;5:401. http://dx.doi.org/10.3389/fmicb.2014.00401
34. Bhattacharjee S, Lukiw WJ. Alzheimer's disease and the microbiome. Front Cell Neurosci. 2013 Sep 17;7:153. http://dx.doi.org/10.3389/fncel.2013.00153
35. Pistollato F, Sumalla Cano S, Elio I, Masias Vergara M, Giampieri F, Battino M. Role of gut microbiota and nutrients in amyloid formation and pathogenesis of Alzheimer disease. Nutr Rev. 2016 Oct 1;74(10):624–34. http://dx.doi.org/10.1093/nutrit/nuw023
36. Zhan X, Stamova B, Jin L-W, DeCarli C, Phinney B, Sharp FR. Gram-negative bacterial molecules associate with Alzheimer disease pathology. Neurology. 2016 Nov;87(22):2324–32. http://dx.doi.org/10.1212/WNL.0000000000003391
37. Lee JW, Lee YK, Yuk DY, Choi DY, Ban SB, Oh KW, et al. Neuro-inflammation induced by lipopolysaccharide causes cognitive impairment through enhancement of beta-amyloid generation. J Neuroinflamm. 2008 Aug;5:37. http://dx.doi.org/10.1186/1742-2094-5-37
38. Holmes C, Cunningham C, Zotova E, Woolford J, Dean C, Kerr S, et al. Systemic inflammation and disease progression in Alzheimer disease. Neurology. 2009 Sep 8;73(10):768–74. http://dx.doi.org/10.1212/WNL.0b013e3181b6bb95

39. Tan ZS, Beiser AS, Vasan RS, Roubenoff R, Dinarello CA, Harris TB, et al. Inflammatory markers and the risk of Alzheimer disease: The Framingham study. Neurology. 2007 May;68(22):1902–8. http://dx.doi.org/10.1212/01.wnl.0000263217.36439.da
40. Swardfager W, Lanctôt K, Rothenburg L, Wong A, Cappell J, Herrmann N. A meta-analysis of cytokines in Alzheimer's disease. Biol Psychiatry. 2010 Nov;68(10):930–41. http://dx.doi.org/10.1016/j.biopsych.2010.06.012
41. Chen H, O'Reilly EJ, Schwarzschild MA, Ascherio A. Peripheral inflammatory biomarkers and risk of Parkinson's disease. Am J Epidemiol. 2008 Jan;167(1):90–5. http://dx.doi.org/10.1093/aje/kwm260
42. Bonfili L, Cecarini V, Berardi S, Scarpona S, Suchodolski JS, Nasuti C, et al. Microbiota modulation counteracts Alzheimer's disease progression influencing neuronal proteolysis and gut hormones plasma levels. Sci Rep. 2017 May 25;7:2426. http://dx.doi.org/10.1038/s41598-017-02587-2
43. Benton D, Williams C, Brown A. Impact of consuming a milk drink containing a probiotic on mood and cognition. Eur J Clin Nutr. 2007 Mar;61(3):355–61. http://dx.doi.org/10.1038/sj.ejcn.1602546
44. Camfield DA, Owen L, Scholey AB, Pipingas A, Stough C. Dairy constituents and neurocognitive health in ageing. Br J Nutr. 2011 Jul;106(2):159–74. http://dx.doi.org/10.1017/S0007114511000158
45. Ano Y, Yoshino Y, Kutsukake T, Ohya R, Fukuda T, Uchida K, et al. Tryptophan-related dipeptides in fermented dairy products suppress microglial activation and prevent cognitive decline. Aging (Albany NY). 2019 May 23;11(10):2949–67. http://dx.doi.org/10.18632/aging.101909
46. Ano Y, Ayabe T, Kutsukake T, Ohya R, Takaichi Y, Uchida S, et al. Novel lactopeptides in fermented dairy products improve memory function and cognitive decline. Neurobiol Aging. 2018 Dec;72:23–31. http://dx.doi.org/10.1016/j.neurobiolaging.2018.07.016
47. Rahman A, Sawyer Baker P, Allman RM, Zamrini E. Dietary factors and cognitive impairment in community-dwelling elderly. J Nutr Health Aging. 2007 Feb;11(1):49–54.
48. Ozawa M, Ninomiya T, Ohara T, Doi Y, Uchida K, Shirota T, et al. Dietary patterns and risk of dementia in an elderly Japanese population: The Hisayama Study. Am J Clin Nutr. 2013 May;97(5):1076–82. http://dx.doi.org/10.3945/ajcn.112.045575
49. Vogt NM, Kerby RL, Dill-McFarland KA, Harding SJ, Merluzzi AP, Johnson SC, et al. Gut microbiome alterations in Alzheimer's disease. Sci Rep. 2017 Oct 19;7(1):13537. http://dx.doi.org/10.1038/s41598-017-13601-y
50. Saji N, Niida S, Murotani K, Hisada T, Tsuduki T, Sugimoto T, et al. Analysis of the relationship between the gut microbiome and dementia: A cross-sectional study conducted in Japan. Sci Rep. 2019 Jan;9(1):1008. http://dx.doi.org/10.1038/s41598-018-38218-7
51. Nguyen TTT, Fujimura Y, Mimura I, Fujii Y, Nguyen NL, Arakawa K, et al. Cultivable butyrate-producing bacteria of elderly Japanese diagnosed with Alzheimer's disease. J Microbiol. 2018 Oct 1;56(10):760–71. http://dx.doi.org/10.1007/s12275-018-8297-7
52. Liu P, Wu L, Peng G, Han Y, Tang R, Ge J, et al. Altered microbiomes distinguish Alzheimer's disease from amnestic mild cognitive impairment and health in a Chinese cohort. Brain Behav Immun. 2019 May;80:633–43. http://dx.doi.org/10.1016/j.bbi.2019.05.008
53. Sudo N, Chida Y, Aiba Y, Sonoda J, Oyama N, Yu X-N, et al. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. J Physiol (Lond). 2004 Jul;558(Pt 1):263–75. http://dx.doi.org/10.1113/jphysiol.2004.063388
54. Liang S, Wu X, Jin F. Gut-brain psychology: Rethinking psychology from the microbiota–gut–brain axis. Front Integr Neurosci. 2018 Sep;12:33. http://dx.doi.org/10.3389/fnint.2018.00033
55. Sudo N. Stress and gut microbiota: Does postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response? Int Congr Ser. 2006 Apr;1287:350–4. http://dx.doi.org/10.1016/j.ics.2005.12.019
56. Kim S, Kim H, Yim YS, Ha S, Atarashi K, Tan TG, et al. Maternal gut bacteria promote neurodevelopmental abnormalities in mouse off spring. Nature. 2017 Sep 28;549(7673):528–532. http://dx.doi.org/10.1038/nature23910
57. Fujii Y, Nguyen TTT, Fujimura Y, Kameya N, Nakamura Y, Arakawa K, et al. Fecal metabolite of a gnotobiotic mouse transplanted with gut microbiota from a patient with Alzheimer's disease. Biosci Biotechnol Biochem. 2019 Nov;83(11):2144–2152. http://dx.doi.org/10.1080/09168451.2019.1644149