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**FROM THE ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE 2023**

**CONSTIPATION ASSOCIATED WITH  
COGNITIVE AGING AND DECLINE**

*Plus, Gut Bacteria Linked to Alzheimer's Biomarkers, Dementia Risk*

**Key Takeaways:**

- **Chronic constipation — one bowel movement every three days or more — could signal worsening cognition.**
- **People who were chronically constipated had worse cognition equal to three years of aging, according to the study, which is the first to look at constipation's potential impact on the aging brain.**
- **The new findings add to mounting research aligning a healthy gut with a healthy brain.**

**AMSTERDAM, JULY 19, 2023** — Experiencing less frequent bowel movements is associated with cognitive decline, according to new research reported today at the [Alzheimer's Association International Conference](#)<sup>®</sup> (AAIC<sup>®</sup>) 2023, in Amsterdam, Netherlands, and online.

Two additional studies define specific gut bacteria that are associated with increased dementia risk, as well as gut bacteria that may be neuroprotective. Previous research has connected the health and makeup of the gut microbiome, which is the community of microorganisms that live in our digestive tracts, with a number of other vital body functions.

“Our body systems are all interconnected,” said Heather M. Snyder, Ph.D., Alzheimer's Association vice president of medical and scientific relations. “When one system is malfunctioning, it impacts other systems. When that dysfunction isn't addressed, it can create a waterfall of consequences for the rest of the body.”

“Still, there are a lot of unanswered questions about the connection between the health of our digestive system and our long-term cognitive function,” Snyder said. “Answering these questions may uncover novel therapeutic and risk-reduction approaches for Alzheimer's and other dementias.”

To study this relationship further, the Alzheimer's Association [U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk](#) (U.S. POINTER), with support from the U.S. National Institutes of Health, is examining the impact of behavioral interventions on the [gut-brain axis](#) to better understand how engaging in healthier habits impacts microorganisms in the gut and how changes in gut bacteria relate to brain health.

“While we await the results of the POINTER-Microbiome study, people should talk to their doctor about their digestive health and ways to alleviate constipation, such as increasing dietary fiber and drinking more water,” Snyder said. “Eating well and taking care of your gut may be a pathway to reduce risk of dementia.”

**Constipation Associated with Worse Cognition, More Cognitive Aging**

Approximately [16% of the world's population](#) struggles with constipation. That prevalence is even higher among older adults due to age-related factors like fiber-deficient diets, lack of exercise and the use of certain constipating drugs to treat other medical conditions. Chronic constipation — defined by having bowel movements every 3+ days — has been associated with long-term health issues like inflammation, hormonal imbalances and anxiety/depression.

To study this relationship, Chaoran Ma, M.D., Ph.D., former research fellow at Brigham and Women's Hospital and Harvard Medical School and current Assistant Professor at University of Massachusetts Amherst, assessed three prospective cohort studies of more than 110,000 people in the Nurses' Health Study, the Nurses' Health Study II, and the Health Professionals Follow-up Study. Ma and team collected data on all participants' bowel movement frequency in 2012-2013 and their self-assessments of cognitive function from 2014 to 2017; objective cognitive function was measured between 2014 and 2018 in a subgroup of 12,696 participants.

The researchers found that less frequent bowel movements were associated with poorer cognitive function. Compared to those with bowel movements once daily, constipated participants (bowel movements every three days or more) had significantly worse cognition, equivalent to 3.0 years more of chronological cognitive aging. Bowel movement frequency of every three days or less was associated with 73% higher odds of subjective cognitive decline. They also found:

- A slightly increased risk of cognitive decline in those who had bowel movements more than twice a day.
- Study participants with certain specific levels of microbes in the gut — fewer bacteria that can produce butyrate and fewer bacteria responsible for digesting dietary fibers — had both less frequent bowel movements and worse cognitive function.

“These results stress the importance of clinicians discussing gut health, especially constipation, with their older patients,” said senior investigator of this study, Dong Wang, M.D., Sc.D., an assistant professor at Harvard Medical School, Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health. “Interventions for preventing constipation and improving gut health include adopting healthy diets enriched with high-fiber and high-polyphenol foods such as fruits, vegetables and whole grains; taking fiber supplementation; drinking plenty of water every day; and having regular physical activity.”

### **A Novel Connection Between Gut Bacteria and Alzheimer's Biomarkers**

Mouse models of Alzheimer's have demonstrated connections between beta amyloid buildup and levels of certain gut microbiota. However, whether the buildup of Alzheimer's biomarkers is associated with shifts in the human gut microbiota is largely unknown.

To study this, Yannick Wadop, Ph.D., postdoctoral fellow at the Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases at UT Health San Antonio, and colleagues used fecal samples and cognitive measures from 140 cognitively healthy middle-aged individuals from the Framingham Heart Study (mean age=56, 54% female) to assess the relationship between gut microbiome composition with amyloid- and tau-PET measures.

They found that elevated levels of amyloid and tau as detected by brain scans were associated with lower levels of gut bacteria *Butyricoccus* and *Ruminococcus*, and higher amounts of *Cytophaga* and *Alistipes*. The researcher's functional analysis suggested that *Butyricoccus* and *Ruminococcus* may have neuroprotective effects.

“These findings begin to reveal more specific connections between our gut and our brain,” Wadop said. “For example, we believe that the reduction of certain identified bacteria may increase gut permeability and the transport of toxic metabolites in the brain, thus increasing amyloid-beta and tau deposition.”

“One plausible next step is to test whether introducing, increasing or reducing specific gut microbes might beneficially change levels of amyloid and tau,” Wadop added. “This could help us identify potential new therapeutic approaches for Alzheimer's.”

## Low Levels of Healthy Gut Bacteria Linked to Poor Cognition

To better understand the link between the gut microbiome and cognition in middle-aged and older adults, Jazmyn Muhammad, B.S., research associate at the Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases at UT Health San Antonio, and colleagues, examined fecal samples and cognitive test scores from more than 1,000 participants in the Framingham Heart Study (mean age=52, 55% female).

The researchers divided the study group based on participants' cognitive test scores and compared the microbiomes of participants scoring in the lowest 20% (i.e., poorer cognition) to those who scored higher. They found individuals with poorer cognition had lower levels of Clostridium and Ruminococcus. The bacteria Alistipes and Pseudobutyrvibrio were found to be highly abundant in those with poor cognition compared to other study participants.

“Further research is needed to better understand the possible neuroprotective effects of some of these bacteria,” Muhammad said. “In the future, it may be possible to manipulate the abundance of these bacteria through diet and pre/probiotics to preserve brain health and cognitive function.”

### About the Alzheimer's Association International Conference® (AAIC®)

The Alzheimer's Association International Conference (AAIC) is the world's largest gathering of researchers from around the world focused on Alzheimer's and other dementias. As a part of the Alzheimer's Association's research program, AAIC serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community.

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### About the Alzheimer's Association®

The Alzheimer's Association is a worldwide voluntary health organization dedicated to Alzheimer's care, support and research. Our mission is to lead the way to end Alzheimer's and all other dementia — by accelerating global research, driving risk reduction and early detection, and maximizing quality care and support. Our vision is a world without Alzheimer's and all other dementia®. Visit [alz.org](http://alz.org) or call 800.272.3900.

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- Chaoran Ma, M.D., Ph.D., et al. Bowel movement frequency, the gut microbiome, and cognitive function in women and men. (Funder: U.S. National Institutes of Health - R01AG077489 and K99/R00DK119412 to Dong D. Wang; UM1 CA186107 to the Nurses' Health Study; U01 CA176726 to the Nurses' Health Study II; U01 CA167552 to the Health Professionals Follow-Up Study)
- Yannick Joel Wadop Ngouongo, Ph.D., et al. Elevated Amyloid-β and Tau Levels in the Brain are Associated with a Reduced Abundance of Neuroprotective Gut Bacteria. (Funder: U.S. National Institutes of Health P30AG066546, P30AG059305, K01NS126489)
- Jazmyn A Muhammad, B.S., et al. Poor cognition is associated with increased abundance of Alistipes and decreased abundance of Clostridium genera in the gut. (Funder: U.S. National Institutes of Health P30AG066546, P30AG059305, K01NS126489)

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**Proposal ID:** 73719

**Bowel movement frequency, the gut microbiome, and cognitive function in women and men**

**Background:** Bowel movement frequency and the gut microbiome may be associated with the risk of dementia.

**Method:** We examined the association between bowel movement frequency and cognitive function in 112,753 women and men from Nurses' Health Study (NHS), Nurses' Health Study II (NHSII), and Health Professionals Follow-Up Study (HPFS) and explored the role of the gut microbiome in explaining these associations in a sub-cohort of 515 NHSII and HPFS participants. We collected data on bowel movement frequency in 2012/13 and subjective cognitive function from 2014 to 2017 in all participants and objective cognitive function using a neuropsychological battery between 2014 and 2018 in 12,696 NHSII participants. We profiled the gut microbiome using shotgun metagenomics.

**Result:** Bowel movement frequency was associated with overall objective cognitive function and learning and working memory in an inverse J-shape dose-response manner (both  $P_{non-linearity} < 0.05$ ). Compared to those with once daily bowel movements, participants with bowel movement frequency of every 3+ days had significantly worse cognition, equivalent to 3.0 (95% confidence interval (CI), 1.2, 4.7) years of additional aging. We observed similar J-shape dose-response relationships of bowel movement frequency with the odds of subjective cognitive decline and the likelihood of having more subjective cognitive complaints over time. Bowel movement frequencies of every 3+ days and  $\geq$ twice/day, compared to once daily bowel movement, were associated with odds ratios of subjective cognitive decline of 1.73 (95% CI, 1.60, 1.86) and 1.37 (95% CI, 1.33, 1.44), respectively. These relationships were generally consistent across three cohorts and subgroups. Bowel movement frequency and subjective cognition were significantly associated with the overall variation of the gut microbiome (both  $P < 0.005$ ) and specific microbial species. Butyrate producers were depleted in those with less frequent bowel movements and worse cognitive function, while a higher abundance of dysbiosis-related, pro-inflammatory species was associated with bowel movement frequency of  $\geq$ twice/day and worse cognitive function.

**Conclusion:** Less frequent bowel movements were associated with worse cognitive function. The gut microbiome may be a mechanistic link underlying the association between intestinal motility patterns and cognitive function.

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**Proposal ID:** 74962

## **Elevated Amyloid- $\beta$ and Tau Levels in the Brain are Associated with a Reduced Abundance of Neuroprotective Gut Bacteria**

**Background:** Recent research suggests that differences in the gut microbiome composition may contribute to the pathogenesis of neurological disorders, including Alzheimer's disease (AD). Animal studies have shown that fecal microbiota transplantation reduces amyloid plaques in mouse AD models. However, whether the buildup of A $\beta$  and tau deposits in the brain are associated with shifts in the human gut microbiota composition is understudied.

**Method:** We used stool specimens and neuropathological measures from 140 middle-aged individuals (Table 1: mean age 56, 54% Female) from the Framingham Heart Study (FHS) to assess the link between the gut microbiome composition and A $\beta$  Positron Emission Tomography (A $\beta$ -PET) in a global composite brain measure, and tau-PET deposits in the rhinal cortex and the inferior temporal cortex. We quantified gut microbiome composition using 16S rRNA sequencing. We performed multivariable association and differential abundance analyses, adjusting for age, sex, body mass index, and other confounders.

**Result:** Multivariable association results (Figure 1) indicated significant associations (adjusted p-value < 0.001) between both A $\beta$ -PET and tau-PET levels with abundance of genera *Butyricoccus* and *Ruminococcus*. Moreover, differential abundance analysis (Figure 2) showed that these bacteria have lower than expected abundance in individuals with elevated A $\beta$ -PET and tau-PET measures (A $\beta$ -PET, *Ruminococcus*: OR = 0.89, [0.88, 0.91]; *Butyricoccus*: OR = 0.77, [0.72, 0.81]); (tau-PET in the rhinal cortex: *Ruminococcus*: OR = 0.82, [0.8, 0.83]; *Butyricoccus*: OR = 0.91 [0.88, 0.94]); (tau-PET in the inferotemporal cortex: *Ruminococcus*: OR = 0.79 [0.78, 0.81]; *Butyricoccus*: OR = 0.83 [0.81, 0.86]). Conversely, we observed an increased abundance of genera *Cytophaga* (tau-PET in the rhinal cortex, OR = 1.78, [1.15, 2.75]) and *Alistipes* (tau-PET in the rhinal cortex, OR = 1.19, [1.17, 1.22]) in individuals with high A $\beta$ -PET and tau-PET levels. Finally, functional analysis showed that *Butyricoccus* and *Ruminococcus* are butyrate-producing bacteria harboring neuroprotective effects.

**Conclusion:** We showed that elevated measures of A $\beta$ -PET and tau-PET in the rhinal and the inferior temporal cortex are associated with a reduced abundance of butyrate-producing *Butyricoccus* and *Ruminococcus* in the gut of middle-aged individuals from the FHS. As these bacteria harbor neuroprotective effects, further studies are needed to elucidate underlying mechanisms and assess their therapeutic potential.

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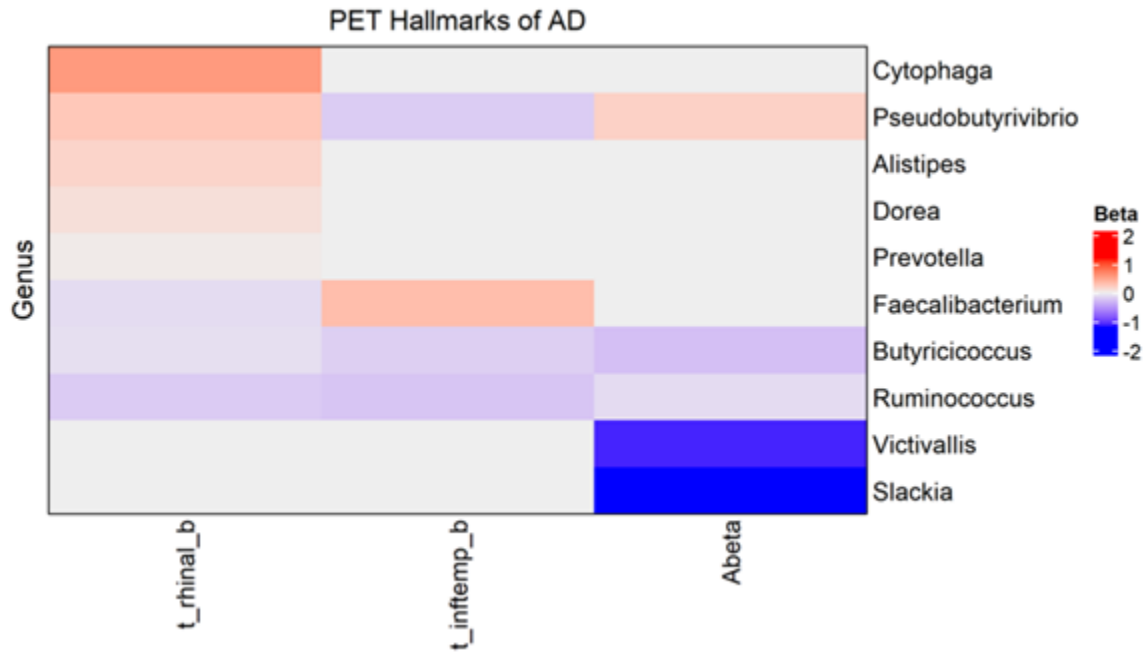


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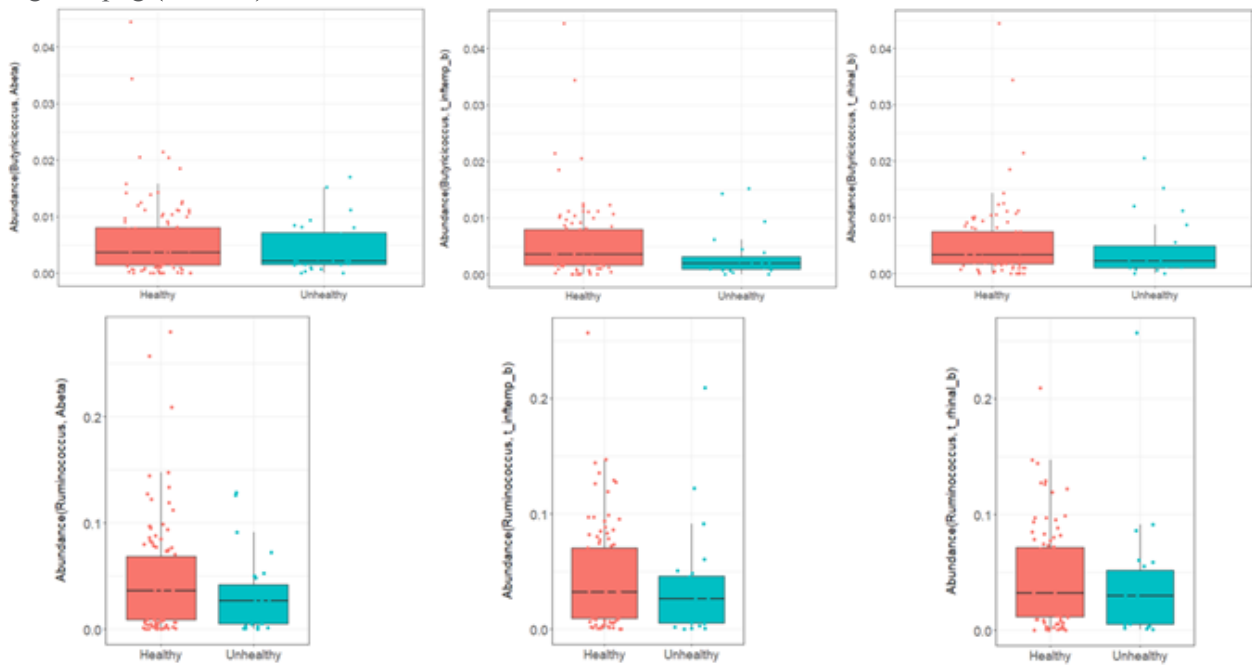


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Characteristic	<b>N = 140</b>
<b>AGE</b>	56 [32, 72]
<b>BMI</b>	28 [19, 44]
<b>SEX, F</b>	76 (54%)
<b>CAM</b>	
D_GE_S	37 (26%)
HR+	103 (74%)
<b>Dt_ amy</b>	72 [1, 197]
<b>A<math>\beta</math>-PET</b>	
Range	1.07 [0.87, 1.60]
Unhealthy (high burden)	28 (20%)
Healthy (low burden)	111 (80%)
<b>tau-PET in the rhinal cortex</b>	
Range	1.11 [0.77, 1.38]
Unhealthy (high burden)	23 (20%)
Healthy (low burden)	91 (80%)
<b>tau-PET in the inferior temporal cortex</b>	
Range	1.13 [0.89, 1.32]
Unhealthy (high burden)	24 (20%)
Healthy (low burden)	97 (80%)
<b>Dt_ tau</b>	61 [1, 191]

**Table 1:** study demographics. Participants were recruited from the third generation, the New Offspring Spouse, and the OMNI2 cohorts of the Framingham Heart Study during their third examination.

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**Proposal ID:** 76520

**Poor cognition is associated with increased abundance of Alistipes and decreased abundance of Clostridium genera in the gut**

**Background:** Brain and gut health are intricately connected via the gut-microbiota-brain axis. Studies have shown that gut dysbiosis is associated with neurodegenerative diseases, including Alzheimer's disease. However, how cognitive changes affects the gut microbiome structure is currently understudied. We aimed to assess the association between the gut microbiome and global cognitive scores in the Framingham Heart Study (FHS).

**Method:** Our sample included 1,014 participants (mean age 52, 55% female) of the third generation FHS cohort with available stool samples, cognitive assessments, and no history of dementia or stroke (Table 1). We quantified the gut microbiome composition using 16S rRNA sequencing and performed multivariable association and differential abundance analyses, adjusting for age, sex, education, BMI, and other confounders. The global cognitive score (GCS) was built using neuropsychological assessments of four cognitive domains: Executive function (trails-making B); Processing speed (visual reproduction immediate and delayed); Language (similarity test); and Memory (logical memory immediate and delayed). Participants were additionally stratified by GCS with lower and higher scores indicating poor and normal cognition, respectively.

**Result:** Our results (Figure 1) showed that individuals with poor cognition have a decreased abundance of genera Clostridium (OR = 0.69, 95% CI [0.55, 0.86]) and Ruminococcus (0.93, [0.93, 0.94]). Meanwhile, the genus Alistipes, previously connected to anxiety, chronic fatigue syndrome, depression, and hypertension, was more abundant (1.06, [1.05, 1.06]) in the poor cognition group. Moreover, the genus Pseudobutyrvibrio, a butyrate-producing bacteria from the rumen, was also found to be highly abundant (1.12, [1.11, 1.14]) in the poor cognition compared to normal. Finally, there was no difference in alpha and beta diversity between cognitive groups (Figure 2).

**Conclusion:** Our study suggests that the abundance of several genera, including Pseudobutyrvibrio, Alistipes, Ruminococcus, and Clostridium is associated with cognition in middle-age. Clostridium was previously proposed as novel probiotics for human health, and increasing its abundance was viewed as an effective strategy to regulate and maintain the homeostasis of the gut microbiota. As all these bacteria have neuroprotective effects, manipulating their abundance through diet and pre/pro-biotics could be a research path for preserving global cognitive function in the future.

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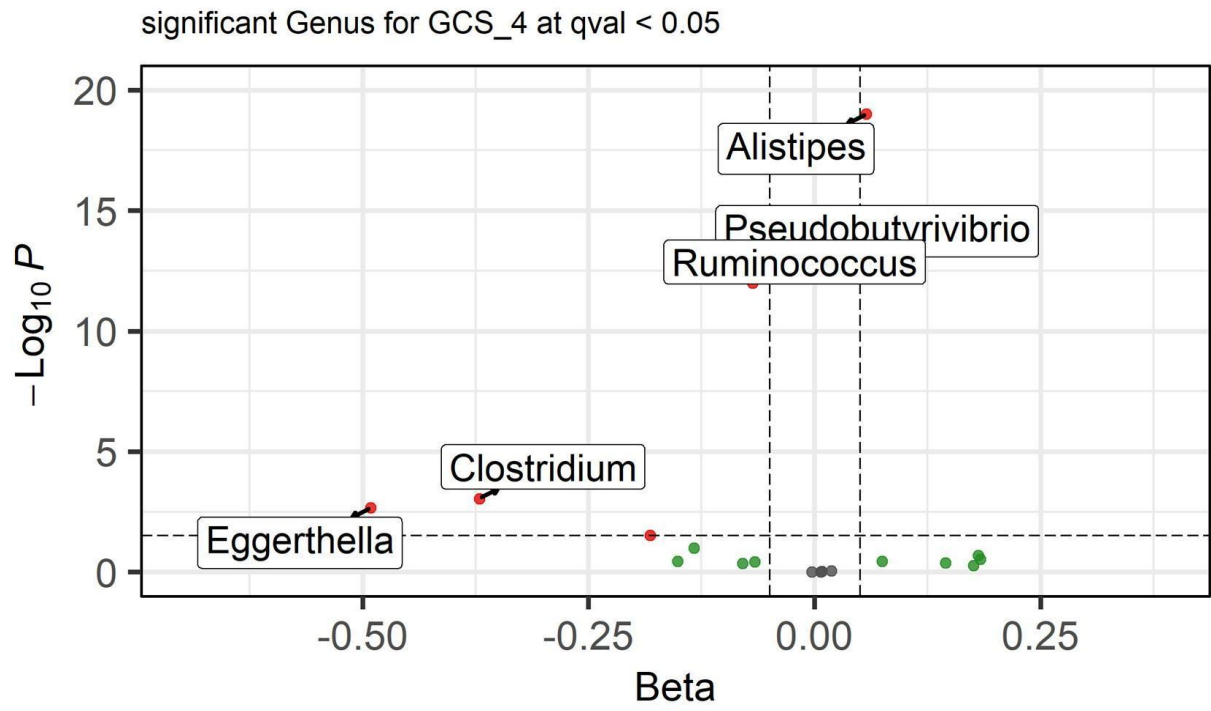
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Tables and Figures:

<b>Characteristics</b>	<b>Normal Cognition (N = 813)</b>	<b>Poor Cognition (N = 201)</b>
<b>Age (mean, min, max)</b>	54.4 (32, 82)	59.5 (33, 89)
<b>BMI</b>	27.8 (15.5, 51.4)	28.2 (16.9, 51)
<b>Sex, Female (n,%)</b>	460 (56.8%)	104 (51.2%)
<b>Education (n,%)</b>		
<b>Some college</b>	183 (22.6%)	77 (38.7%)
<b>College Graduate</b>	571 (70.5%)	77 (38.7%)
<b>High School degree</b>	56 (6.9%)	45 (22.6%)
<b>Time interval</b>	141.2 (0.03, 456.7)	132.4 (0.03, 464.5)
<b>GCS</b>		
<b>Range</b>	0.8 (-0.092, 2.8)	-0.6 (-2.2, -0.098)

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