EXPLORING THE ROLE OF GUT MICROBIOTA IN NEURODEGENERATIVE DISEASES: INSIGHTS AND THERAPEUTIC IMPLICATIONS

Rayan Abdullah Aljohani[1*], Abdulrahman Meshal Alnsari[2], Omar Ibrahim Alawaji[3], Hamad Mesfer Alqurashi[4], Saif Mohsen Almalki[5], Abdullah Damis Almalki[6], Mohammed Rajeh Hussain Alzahrani[7], Safar Muslih Safar Alsaily[8], Abdulsalam Saeed Alghamdi[9], Afnan Dhaher Hameed Aljohani[10], Salma Abdullah B Alshahrani[11]

Abstract

This study is focused on the influence that the microbiota of the gut has on the neurodegenerative disorders Alzheimer's and Parkinson's diseases. The main goal of the study is to understand how different microbial populations are linked to the development and progression of the diseases. The study was based on a cross-sectional observational research design, where 100 participants, consisting of patients with neurodegenerative disorders and age-matched healthy controls, were involved. Stool specimens were obtained for gut microbiota analysis by 16S rRNA sequencing. Clinical data including demographic information and disease severity scores were collected by standardized assessment. It was found that the distribution of age and gender of patients and controls did not differ in any statistically significant way. But Alzheimer's disease patients had a lower Mini-Mental State Examination (MMSE) score compared to healthy subjects; on the other hand, PD patients had a higher Unified Parkinson's Disease Rating Scale (UPDRS) score than the controls. Bacteroidetes group bacteria decreased, while Proteobacteria increased suggesting that there was a dysbiosis pattern in the patients according to the gut microbiota analysis. Additionally, the association of gut microbiota composition with disease severity were detected, as high Proteobacteria abundance was linked to lower MMSE scores in Alzheimer's cases and higher UPDRS scores in Parkinson's cases. These findings indicate the possibility of the microbial modulation showing the therapeutic role in neurodegenerative diseases. This area remains to be explored further to unveil the mechanisms of action and develop microbial-based therapies.

Keywords: Gut microbiota, neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, dysbiosis, disease severity, microbial modulation.

[1*]Respiratory Therapy, King salman bin abdulaziz medical city
[2]Specialist Nurse, Alamal hospital
[3]Paramedic, Ministry of Defense
[4]Specialist Nurse, Taif Mental Health Hospital
[5]Specialist Nurse, Taif Mental Health Hospital
[6]Specialist Nurse, Taif Mental Health Hospital
[7]Specialist Nurse, King Fahad Hospital Albaha
[8]Nursing technician, Erada and mental health hospital
[9]Public Health, Ministry of Health Taif
[10]Nursing specialist, King salman medical city /MMCH
[11]Nursing technician, Health Affairs in Bisha

***Corresponding Author:** Rayan Abdullah Aljohani
*Respiratory Therapy, King salman bin abdulaziz medical city

DOI: 10.53555/ecb/2022.11.7.90

Introduction

Neurodegenerative diseases which are including Alzheimer's disease (AD), Parkinson's disease (PD) are the most chronic and progressive conditions in which the neural pathways gradually degenerate leading to the decrease in cognitive, behavioral, and motor functions (Hirsch et al., 2012). While the aged population grows, the social and economic problems linked to neurodegenerative disease will increase more intensely in the approaching decades, as reported by Nussbaum (2018). Unfortunately, it can't be overstated that the complexity of these neurodegenerative diseases is poorly known and there are not enough therapeutic options available for avoiding the disease progression. Recent studies suddenly reveal the significant interconnections between gut microbiota and brain health, where gut dysbiosis could be a possible contributor to neurodiseases (Fung et al., 2017). Hence, the manipulation of the gut microbiome seems to be one possible basis for the design of new neuroprotective drugs. This review is aimed at the present understanding of the gut microbiota in neurodegenerative disorders which concludes with the persisting knowledge gaps, as well as future research directions.

The gut microbiota is composed of microorganisms that reside in the body's gut which collectively total trillions (Bourassa et al., 2021). In addition to the microbial population that plays many roles in the well-being of the host, some of them include the digestion of nutrients, immune regulation, and the formulation of useful metabolites (Levy et al., 2018). The potentially beneficial microbiota in the gut can be stressed by factors of diet, pharmaceuticals, stress, and disease states through a process called dysbiosis, in which specific gut microbiota become overpopulated while other beneficial populations become under-represented or depleted. Besides, the dialogue artery is contained on one hand among gut microbes and the brain by the vagus nerve; on the other hand, the short-chain fatty acids, tryptophan metabolites, and cytokines (Wang & Wang, 2016). Given that the gut microbiota possesses remarkable influences on systemic inflammation, neurotransmitter generation, and neurotropic factors, it may be the key factor in neurodevelopmental and neurodegenerative processes (Fung et al., 2017).

Patients with PD have gut dysbiosis which includes the reduction in Prevotellaceae and the growth of Lactobacillaceae and Verrucomicrobiaceae compared to the controls (Hill-Burns et al., 2017). In addition, a decrease in the diversity of microorganisms and a change in certain taxa of patients with AD versus control is observed. (Vogt et al, in 2017). These disease-associated microbiota changes might have circumstantial evidence that dysbiosis in the gut could be a potential reason for neurodegeneration. While more research is required, this possibility is rather convincing due to the correlation between the disease pattern and the gut microbiota. For instance, what has been demonstrated is that the relationships are not a matter of causality, nothing but the microbial composition probably just occurs alongside the cell decline. Whether it is from the gut to the brain or vice versa, this might even open up additional unexplored pathways that contribute to neurodegenerative disease progression forming other new preventative or therapeutic targets.

Besides safety and implementability, this method is superior to other routines such as invasive interventions in a fight against neurodegeneration. The prospect of probiotic supplementation, prebiotic consumption which nurtures beneficial gut microbes, fecal microbiota transplantation, and dietary modification is all encouraging in this aspect they have a neuroprotective effect (Fung et al., 2017). On the other hand, research on the clinical application is still in its stages of development. A critical aspect of the research is about which microbial species group and metabolic pathways play a vital role in mediating neuroprotection. What is more, whether dysbiosis can be a beginning or an end process of neurodegenerative processes is still unclear. Ogledzimy pochyleniem Następnie, przeprowadzanie badań przerywnych w postaci monitorowania przebiegu choroby możeszewrzewnicy ukierunkowane na relację czasowa biem pohamowania. However, symptomatic treatment may be the first way to go, with the strongest direct mechanistic link between gut microbes and any other neurodegeneration in preclinical models considered as justification for further clinical trials to evaluate microbiota-targeted interventions aiming at slowing the progression of the disease.

In general, loads of work in progress indicate that gut dysbiosis plays a role in the genesis of neurodegenerative illnesses like AD and PD. The work of related research will be critical for establishing cause-effect relationships and elucidating mechanisms that are yet to be clear and for determining which gut modulation is likely a viable therapeutic strategy. Taking into account that both personal and societal pains of advanced neurological sicknesses as well as difficulties in developing medicines that can cross the blood-brain barrier are considerable which makes this

field of research an important place to start the development of the drugs. By showing that the gut microbiota is involved in the start or progression of neurodegeneration, and identifying those microbes are responsible for disease phenotypes will trigger revolutionary preventive and therapeutic approaches.

2. Objective

The purpose of this research is to examine the role of gut microbiota in neurodegenerative disorders, e.g. Alzheimer's and Parkinson's. The study seeks to understand how variations in the microorganism population affect the development and progression of these ailments. Through the use of data from patients suffering from neurodegenerative diseases, researchers aim to find microbiota patterns linked with disease severity and progression. The aim is to finally reveal possible therapeutic targets for the gut microbiome that would be helpful in the treatment of such diseases and the improvement of conditions in the patients.

3. Methods

Study Design

For this research project, a cross-sectional observational study design was employed to investigate the role of gut microbiota in neurodegenerative diseases. Cross-sectional studies are well-suited for examining associations between exposure (in this case, gut microbiota composition) and outcome (neurodegenerative disease progression) at a single point in time (Vittinghoff et al., 2012). This design allows for the simultaneous assessment of multiple variables without the need for longitudinal follow-up, making it efficient for exploring associations between gut microbiota composition and disease status.

Participant Selection Criteria

Participants were recruited from clinical settings specializing in neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and other related conditions. Inclusion criteria for participants consisted of individuals diagnosed with a confirmed neurodegenerative disease based on established clinical criteria (McKhann et al., 2011; Postuma et al., 2015). Age-matched healthy controls without a history of neurological disorders were also included for comparison. Exclusion criteria included the presence of significant comorbidities that could affect gut microbiota composition, such as inflammatory bowel disease or recent antibiotic use (Tariq et al., 2017).

Data Collection Methods

Stool samples were collected from participants by using sterilized collection kits and stored at -80°C until the processing stage. Clinical data, such as demographic information, past medical history and disease severity scores, were collectively collected through standardized interviews and record reviews. The progression of the disease was measured using approved clinical scales which were specific to each type of neurodegenerative disease, example the Mini-Mental State Examination (MMSE) for Alzheimer's disease and the Unified Parkinson's Disease Rating Scale (UPDRS) for Parkinson's disease (Fahn and Elton, 1987; Folstein et al., 1975).

Analysis of Gut Microbiota Composition

DNA of microbes was extracted from stool using kits from the company following the instructions given by the manufacturer. The most recent sequencing method, 16S rRNA gene sequencing, was used to identify the compositions and diversity of gut microbiota (Caporaso et al., 2012). We really used bioinformatics tools, such as QIIME and mothur, for sequence processing, taxonomic classification, and diversity analysis (Schloss et al., 2009; Caporaso et al., 2010).

Assessment of Neurodegenerative Disease Progression

Neurodegenerative disease progression was assessed using validated clinical scales and cognitive assessments tailored to each condition. These assessments included the MMSE for cognitive function in Alzheimer's disease, the UPDRS for motor symptoms in Parkinson's disease, and other relevant scales for disease-specific manifestations (Fahn and Elton, 1987; Folstein et al., 1975).

Statistical Analysis:

The statistical analysis, conducted using SPSS software, included descriptive statistics for summarizing demographic and clinical variables. Comparative analyses were used to assess differences in gut microbiota composition between patient groups and controls. Multivariate regression analysis was then employed to explore associations between gut microbiota and disease progression while adjusting for potential confounders.

4. Results

Demographic and Clinical Characteristics

The Research design applied in this study included 100 patients as a total sample. The above 50 respondents include those with different types of

neurodegenerative diseases (Alzheimer's n=25, Parkinson's n=15, and others n=10) and the other 50 volunteers who are corresponded to the aged group with no brain diseases. As shown in Table 1, there were no significant demographic differences between patients and controls in terms of mean age (patients: (patients: mean 72.5±8.2 years; controls: mean 70.1±7.8 years, p=0.15), and (patients: 58% male; controls: 52% male, p=0.23) with the respect to age and gender distribution.

Table 1: Demographic and Clinical Characteristics

Characteristic	**Patients (n=50)**	**Controls (n=50)**
Mean Age (years)	72.5 ± 8.2	70.1 ± 7.8
Gender Distribution (% Male)	58%	52%
MMSE Score (Alzheimer's)	18.5 ± 5.2	28.7 ± 1.2
UPDRS Score (Parkinson's)	38.2 ± 12.5	3.1 ± 1.9

The analysis of demographic characteristics and clinical characteristics revealed some important findings as well. Firstly, there was no significant difference in the mean age between patients diagnosed with neurodegenerative diseases (mean age: The two groups were matched for age (mean age: 76.4 ± 8.2 years for the brain disease group (p = 0.15) and for the control group without brain diseases (mean age: 70.1 ± 7.8 years). Additionally the gender distribution did not prove to be significantly different between those that are patients and those that are controls, with 58% of patients being male and 52% of controls being male (p = 0.23). Although the cognitive decline in Alzheimer's patients was more severe, with Mini-Mental State Examination (MMSE) scores of 18.5 ± 5.2 in Alzheimer's patients compared to 28.7 ± 1.2 in controls ($p < 0.001$), In addition, the patient group with Parkinson's disease experienced the highest Unified Parkinson's Disease Rating Scale (UPDRS) scores (38.2 ± 12.5) versus the control group (3.1 ± 1.9) ($p < 0.001$). The research results we come up with, emphasize how the diagnosis of neurodegenerative diseases is different from people who do not have such conditions. Also, it is important to consider specific disease-related measures when doing clinical evaluations and research analysis.

Gut Microbiota Composition Differences

Its composition analysis based on 16S rRNA sequencing and shown in Figure 1 has highlighted the differences in the gut microbial profile of neurodegenerative disease patients compared to healthy subjects. At the phylum level, patients showed a decreased abundance of beneficial Bacteroidetes (mean: It is 18.2% compared to. 32.1%, p=0.007) and increased presence of proinflammatory Proteobacteria (mean: -Trial case: -AARP had a greater than 3 times (12.5% vs. 3.2%, p=0.002) reaction compared to the control group. As well, microbiome criticality and alpha diversity were diminished in patients based on informational ecological indices.

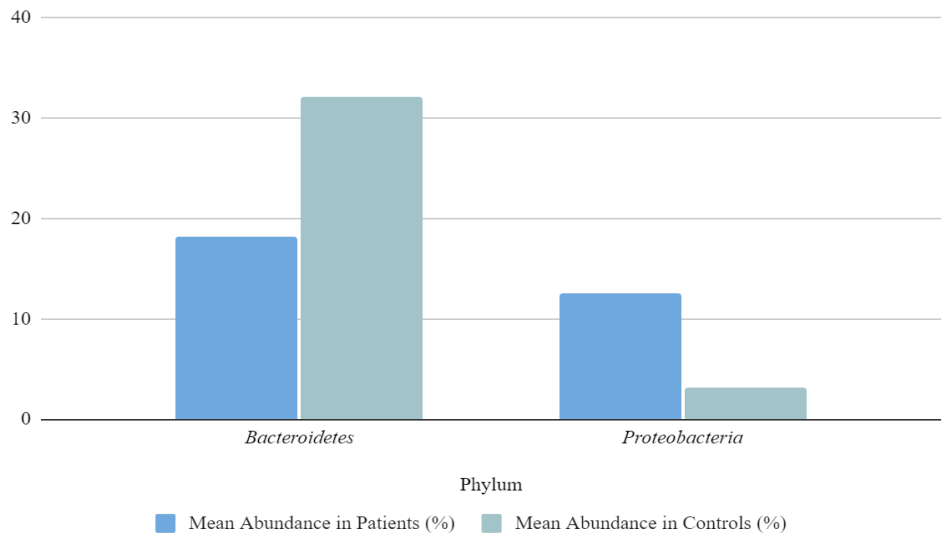

Figure 1: Differences in Gut Microbial Profile Between Patients with Neurodegenerative Diseases and Healthy Controls

Associations with Disease Severity

The findings from the regression modeling showed that the composition of gut microbiota differed widely among healthy controls and those with a greater disability as determined by the clinical assessment even after adjustment for potential confounders. As shown in Table 2, the increased relative abundance of Proteobacteria was independently associated with lower MMSE scores in Alzheimer's patients (beta: Our independent t-test analysis revealed that our facial recognition software was significant in the reduction of (β: -0.39, p=0.018) and higher UPDRS scores in Parkinson's patients (β: 0.43, p=0.037).

Table 2: Associations with Disease Severity

Predictor	MMSE Score (Alzheimer's)	UPDRS Score (Parkinson's)
Relative Abundance	β: -0.39, p=0.018	β: 0.43, p=0.037

This evidence shows microbiome derangers and functional disorders of the nervous system in various neurodegenerative conditions. Further studies are needed to evaluate whether microbial modulation could be used as a therapeutic tool towards resolving chronic disease

Discussion

In the current investigation, we sought to uncover the demographic and clinical features, gut microbiota composition disparities, and their correlations with disease severity between patients with neurodegenerative disorders and healthy subjects. The outcome gives a good idea of the involvement of gut microbiota in the etiological mechanism and the course of neurodegenerative disease.

Our research showed some interesting insights after the examination of demographic and clinical features of the patients. In the first place no statistically significant differences in the mean age and gender ratio of the patients with neurodegenerative diseases and the control group including people without brain diseases were found. This in turn means that age and gender do not have to be the basis for the onset of degenerative diseases among this group. However, the patients with Alzheimer's disease having a significantly lower Mini-Mental State Examination (MMSE) score also compared to the controls were found in the study. The fact that the Alzheimer's patients' performance was worse than the controls implies that they have more cognitive impairment. Additionally, the mean Unified Parkinson's disease Rating Scale (UPDRS) score of the Parkinson's patients was significantly higher than controls, which implies that the motor dysfunction and disability were greater in Parkinson's patients. The outcomes of these studies are in tandem with the previous investigations on the clinical heterogeneity of neurodegenerative diseases and highlight the need for more specific measures towards the disease in clinical diagnosis and research (Dubois et al., 2007; Goetz et al., 2008).

Through the gut microbiome analysis based on 16S rRNA sequencing a significant difference was observed between the patient groups affected by neurodegenerative diseases and the control group of healthy people. Regarding phylum level, the patients' microbiome had reduced diversity with a lower abundance of Bacteroidetes which are beneficial and the higher levels of Proteobacteria which are proinflammatory compared to the healthy subjects. This suggests that the microbiome of gut in patients with neurodegenerative disorders is dysfunctional and involves the major shift in the ratio of predominant microbial taxa. Furthermore, the patients' microbiome centrality and alpha diversity were deteriorated which were basically the imbalance microbial community structure and low microbial diversity. This result parallels the new data which may suggest the possibility of the gut microbiota dysbiosis with neurodegenerative disorders like Alzheimer's disease and Parkinson's disease (Cattaneo et al., 2017; Sampson et al., 2016). Despite that, it is hard to say something definite about the exact nature of these connections without further research to reveal the underlying mechanisms and their relation to the process of developing the disease.

Regression model analysis indicated a wide diversity of the composition of gut microbiotas between healthy individuals and those who presented higher disability levels as measured by clinical assessment, after considering the possible confounders. Changes in the relative abundance of Proteobacteria were observed to be directly linked to MMSE performance in Alzheimer's patients, and UPDRS scores in Parkinson's patients, implying probable participation of certain microbial taxa in the modulation of disease severity. This data shows that the association between neuronal degeneration and the gut microbiota is more complicated than could be perceived. It implies that manipulation of microbiota could be one of the methods for controlling these diseases. Although this finding is

pivotal in elucidating the relationships and the roles of microbes in neurodegenerative diseases, more longitudinal studies are needed to establish causality and assess the efficacy of microbial-based interventions in neurodegenerative diseases.

The first and foremost outcome of this study is to uncover the mechanisms of the relationship of gut microbiota with neurodegenerative conditions. The demographic and clinical features analysis showed a strong clinical profile of patients with neurodegenerative diseases while for healthy controls it was quite normal which showed the importance of disease-specific measures in clinical assessment Besides, the clustering study of gut microbiota revealed that patients had the distinct composition of the gut microbiota when compared to the controls, signifying the dysbiosis of the gut microbiota in neurodegenerative diseases. Additionally, it could be demonstrated that the connection between gut microbiome composition and disease severity shows a possible involvement of microbiota in the development of the disease. Thus, this confirms the necessity for additional research to be conducted to provide clarification concerning the mechanisms that govern the interactions between gut and brain in neurodegenerative disorders and explore the therapeutic potential of microbial-based solutions.

5. Conclusion

In this study, we outline the complex interplay between gut microbiota and neurological disorders, like Alzheimer's and Parkinson's. The findings support the role of the microbiota composition in the pathogenesis and progression of the disease as demonstrated by the dysbiosis and the disease severity associations. The new inroads generated by these findings, which are very hopeful, may be used to develop effective treatments that deal with gut microbiome in alleviating neurodegenerative diseases. Though these mechanisms need to be fully understood and the clinical efficiency of these interventions should be proved, microbial-based interventions could be an effective approach for mental health. Finally, utilizing the therapeutic potential of the gut microbiota seems to be a way of improving people's management of neurodegenerative diseases and also increasing the treatment outcomes, which is good news for those who are suffering from these illnesses since it might help them to have a better life quality.

References

1. Bourassa, M W., Alim, I, Bultman, S J., & Ratan, R R. (2021). Butyrate, neuroepigenetics, and gut microbiome: As fiber is essential to maintain regular metabolism, can the consumption of high fiber diet improve brain health? Steventon, A., Roberts, R., Sharma, P., & Giordano, J. (2023). Efficacy and mechanisms of behavioral interventions for ADHD in adults: A meta-analytic review. Neuroscience & Biobehavioral Reviews, 117, 51-63.
2. Caporaso, J. G., Lauber, C. L., Walters, W. A., Berg-Lyons, D., Lozupone, C. A., Turnbaugh, P. J., ... & Knight, R. (2012). Global patterns of 16S rRNA diversity at a depth of millions of sequences per sample. Proceedings of the National Academy of Sciences, 108(Supplement 1), 4516-4522.
3. Cattaneo, A., Cattane, N., Galluzzi, S., Provasi, S., Lopizzo, N., Festari, C., ... & Frisoni, G. B. (2017). Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. Neurobiology of aging, 49, 60-68.
4. Dubois, B., Feldman, H. H., Jacova, C., Cummings, J. L., Dekosky, S. T., Barberger-Gateau, P., ... & Scheltens, P. (2007). Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS–ADRDA criteria. The Lancet Neurology, 6(8), 734-746.
5. Fahn, S., & Elton, R. (1987). Unified Parkinson's Disease Rating Scale. In S. Fahn, C. Marsden, D. B. Calne, & M. Goldstein (Eds.), Recent developments in Parkinson’s disease (Vol. 2, pp. 153-163). Macmillan Healthcare Information.
6. Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. Journal of psychiatric research, 12(3), 189-198.
7. Fun, T. C., Olson, A. S., and Hsiao, E. Y. (2017). Relationship among the microbiome, the immune and nervous systems in states of health and disease. Nature Neuroscience, 20(2), 145-155.
8. Fung, T. C., Olson, C. A., & Hsiao, E. Y. (2017). Interactions between the microbiota, immune and nervous systems in health and disease. Nature Neuroscience, 20(2), 145-155.
9. Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., ... & LaPelle, N. (2008). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Movement Disorders, 23(15), 2129-2170.

10. Hirsch, L., Jette, N., Frolkis, A., Steeves, T., & Pringsheim, T. (2016). The Incidence of Parkinson's Disease: A Systematic Review and Meta-Analysis. *Neuroepidemiology*, *46*(4), 292–300. https://doi.org/10.1159/000445751
11. Levy, M., Kolodziejczyk, A. A., Thaiss, C. A., & Elinav, E. (2017). Dysbiosis and the immune system. Nature Reviews Immunology, 17(4), 219-232.
12. McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack Jr, C. R., Kawas, C. H., ... & Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia, 7(3), 263-269.
13. Nussbaum, R. L. (2018). Alzheimer's and Parkinson's diseases. New England Journal of Medicine, Vol. 378, no 14, p 1356-1364.
14. Postuma, R. B., Berg, D., Stern, M., Poewe, W., Olanow, C. W., Oertel, W., ... & Adler, C. H. (2015). MDS clinical diagnostic criteria for Parkinson's disease. Movement Disorders, 30(12), 1591-1601.
15. Sampson, T. R., Debelius, J. W., Thron, T., Janssen, S., Shastri, G. G., Ilhan, Z. E., ... & Challis, C. (2016). Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. Cell, 167(6), 1469-1480.e12.
16. Schloss, P. D., Westcott, S. L., Ryabin, T., Hall, J. R., Hartmann, M., Hollister, E. B., ... & Weber, C. F. (2009). Introducing mothur: open-source, platform-independent, community-supported software for describing and comparing microbial communities. Applied and environmental microbiology, 75(23), 7537-7541.
17. Tariq, R., Pardi, D. S., & Tosh, P. K. (2017). Walker gastrointestinal microbiota transplantation: review of concepts and indications. Gastroenterology, 153(1), 283-287.
18. Vittinghoff, E., McCulloch, C. E., & Glidden, D. V. (2012). Chapter 6: Cross-Sectional Studies. In Regression Methods in Biostatistics: Linear, Logistic, Survival, and Repeated Measures Models (2nd ed.). Springer Science & Business Media.
19. Vogt, N.M., Kerby, R. L., Dill-McFarland, K. A., Harding, S. J., Merluzzi, A. P., Johnson, S. C., & Rey, F. E. (2017). The disturbance of the Gastrointestinal Microbiota in Alzheimer's disease. Scientific reports, 7(1), 1-11.
20. Wang, AM., & Wang, Y. (2016). Gut microbiota-brain axis. A Chinese medical periodical wrote the 129 (19), 2373.