



## Research article

## Associations between constipation, overeating, and depression: A survey of Chinese oldest-old and centenarians

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## ABSTRACT

**Objectives:** Depression is a common disease of elderly population, with a global prevalence of more than 20%. Few studies have involved the associations of constipation and overeating with depression, especially in the elderly population. We aimed to address these associations in Chinese oldest-old and centenarians.

**Methods:** A total of 1863 elderly individuals from 18 regions of Hainan, China, were investigated from July 2014 to December 2016. Health survey, physical examination, and blood analyses were performed through structured questionnaires and standard procedures. The Geriatric Depression Scale (GDS-15) was used to measure depression.

**Results:** The proportions of elderly individuals with depression, constipation, and overeating were 20.80% (349), 15.14% (254), and 26.52% (445), respectively. The prevalence of constipation and overeating was significantly higher in the elderly group with depression than in those without depression ( $P < 0.05$ , all). In the multiple linear regression analyses, higher prevalence of constipation and overeating had positive and significant associations with the GDS-15 ( $P < 0.05$ , all). In the multiple logistic regression analyses, constipation (odds ratio [OR]: 2.328; 95% confidence interval [CI]: 1.540–3.521) and overeating (OR: 2.735; 95% CI: 1.920–3.898) had positive and significant associations with depression ( $P < 0.05$ , in all).

**Conclusions and Implications:** This study provides epidemiological evidence that constipation and overeating have positive associations with depression in Chinese oldest-old and centenarians. The interventions for constipation and overeating should be improved to promote prevention and treatment for depression and achieve successful aging and healthy longevity.

## 1. Introduction

Depression is a common disease of elderly population, with a global prevalence of more than 20% [1, 2]. It is closely related to the decline in

cognitive function and life quality in the elderly population. In severe cases, it can lead to suicidal behavior; thus, its prevention is important. Depression is not an inevitable manifestation of aging, but most studies have shown that age and sex (female) is an important risk factor for

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depression [3, 4]. More importantly, age-related life factors such as living alone, pain, visual impairment, and auditory impairment will further increase the probability of depression in the elderly population [5, 6, 7, 8, 9, 10]. Additionally, improper or long-term use of drugs, such as proton-pump inhibitors, may lead to neuropsychological side effects and promote the development of depression [11, 12]. Previous study has also shown that concomitant use of benzodiazepines with antipsychotics increases the risk of neurological dysfunction in older people [13]. The current risk factors that were discovered can improve our ability to identify older people who are at higher risk of depression, but they are still not comprehensive.

Recently, with the continuous exploration of the gut-brain axis, people have gradually realized close relationships between the intestinal and central nervous system and discovered that normal activities of the intestine play a vital role in the neuroactive potential [14]. Conversely, constipation caused by abnormal gut movements can change the structure of intestinal microbiota, such as bifidobacteria and lactobacilli [15], and induce central nervous system diseases by influencing neurogenesis,  $\alpha$ -synuclein, neurotransmitter content, antioxidant defense, and immune regulation [16, 17]. Numerous clinical studies have shown that constipation and overeating are closely related to the occurrence of central neuropathy, and it is a risk factor for Parkinson's and Alzheimer's diseases [18, 19]. However, the clinical research on depression is relatively insufficient compared with the aforementioned diseases. Studies have shown that constipation and overeating are more common in depressed individuals than in non-depressed individuals [20], but there is no clear conclusion on the associations of constipation and overeating with depression, especially in the elderly population.

Therefore, based on the China Hainan Centenarian Cohort Study, the current study aimed to address the associations of constipation and overeating with depression in Chinese oldest-old and centenarians to provide a reference for the prevention and treatment of depression.

## 2. Material and methods

### 2.1. Study design and population

According to the age information provided by the Civil Affairs Department of Hainan, the structured questionnaires of 1863 elderly individuals from 18 regions of Hainan, China, were investigated from June 2014 to December 2016. Physical examination and blood analyses were performed through the standard procedures. The research designation and investigation methods have been described in a previous article [21]. Excluding those with incomplete data, 1678 older people were eventually included in the study. All participants provided informed consent, and the protocol (no. 301HNLL-2016-01) was approved by the local ethics committee.

### 2.2. Depression and overeating

The Geriatric Depression Scale (GDS-15) was used to measure the participants' depressive symptoms. The scale has a total of 15 dichotomous items, and higher scores indicate more depressive symptoms. The scores >6 (possible range 0–15) indicated depression. Constipation and overeating were determined through a questionnaire answered by the participants and recorded by the investigator. Constipation was when the interval between defecation was more than 3 days. Overeating was determined when feeling fullness after eating.

### 2.3. Definitions of the study variables

Investigators conducted household interviews after rigorous training and collected data including age, sex, illiteracy, smoking (every week), drinking (every week), the presence of cerebrovascular disease, visual impairment, auditory impairment, dementia, pain, duration of outdoor activities (more than an hour a day), living alone and life satisfaction. A

life satisfaction questionnaire was used to assess the state of their life satisfaction. Visual impairment, auditory impairment, and pain were defined based on whether they affected the participant's daily life.

Body mass index (BMI) was computed using the following standard formula:  $BMI (kg/m^2) = \text{weight}/\text{height}^2$ . Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice using calibrated desktop sphygmomanometer (Yuwell medical equipment and supply Co., Ltd., Jiangsu, China), and the values used in the analyses were the average of the two measurements. Samples of venous blood were obtained from the participants by professional nurses, and blood specimens were transported within 4 h in cold storage (4 °C) to a clinical laboratory. Total cholesterol (TC), triglyceride (TG), glucose (GLU) and vitamin D<sub>3</sub> were determined by enzyme colorimetry using a fully automatic biochemical autoanalyzer (COBAS c702; Roche Products, Ltd.).

### 2.4. Statistical analyses

The mean  $\pm$  standard deviation is used to describe continuous variables that were analyzed using the t-test, and number (percentage) is used to describe categorical variables that were analyzed using the chi-square test. Multiple linear and logistic regression analyses were used to evaluate the associations between constipation, overeating, and depression, which were adjusted for age, sex, illiteracy, smoking, drinking, cerebrovascular disease, visual impairment, auditory impairment, dementia, pain, duration of outdoor activities, living alone, life satisfaction, BMI, SBP, DBP, TC, TG, GLU, and vitamin D<sub>3</sub>. Residual error was normally distributed as shown in p-p plot, and the criteria of multiple normality was met in our analyses. Statistical analyses were performed with SPSS 17.0 software package (IBM Corp.). A P-value <0.05 was considered as statistically significant.

## 3. Results

In total, 1678 elderly individuals participated in this study. Participants' mean age was  $94.45 \pm 9.51$  years, ranging between 80 and 116 years, and 71.57% were female. The proportions of elderly individuals with depression, constipation, and overeating were 20.80% (349), 15.14% (254), and 26.52% (445), respectively. As Table 1 shows the prevalence of constipation and overeating in the participants with depression were statistically significantly higher than in those without depression ( $P < 0.05$ , all). Compared to participants without depression, those with depression had a statistically significantly older age; female predominance; higher prevalence of illiteracy, cerebrovascular disease, visual impairment, auditory impairment, dementia, and pain; lower prevalence of drinking and outdoor activities; and lower levels of life satisfaction, BMI, TC, TG, and vitamin D<sub>3</sub> ( $P < 0.05$ , all; Table 1).

In the multiple linear regression analyses, older age; higher prevalence of constipation, overeating, illiteracy, dementia, pain, and living alone; higher levels of DBP; and lower levels of life satisfaction, had positive and statistically significant associations with the GDS-15 ( $P < 0.05$ , all; Table 2). In the multiple logistic regression analyses, constipation (odds ratio [OR]: 2.328; 95% confidence interval [CI]: 1.540–3.521) and overeating (OR: 2.735; 95% CI: 1.920–3.898) had positive and statistically significant associations with depression ( $P < 0.05$ , all; Table 3). Moreover, participants who were older, female and illiterate, had statistically significant higher prevalence of dementia, pain and living alone, higher levels of DBP, and lower levels of life satisfaction tended to have more depression ( $P < 0.05$ , all).

## 4. Discussion

In this study, higher prevalence of overeating and constipation had positive and significant associations with depression in Chinese oldest-old and centenarians. These associations remained unchanged after adjusting for demographic characteristics and potential confounders. Based on this large sample study, we provided the evidence of the

**Table 1.** Characteristics of all participants with and without depression.

Characteristic	Total (n = 1678)	With depression (n = 349)	Without depression (n = 1329)	P-value
Constipation <sup>†</sup>	254 (15.14%)	98 (28.08%)	156 (11.74%)	<0.001
Overeating <sup>†</sup>	445 (26.52%)	146 (41.83%)	299 (22.50%)	<0.001
Age, years*	94.45 ± 9.51	98.93 ± 8.02	93.3 ± 9.53	<0.001
Female sex <sup>†</sup>	1201 (71.57%)	298 (85.39%)	903 (67.95%)	<0.001
Illiteracy <sup>†</sup>	1430 (85.2%)	319 (91.4%)	981 (73.81%)	<0.001
Smoking <sup>†</sup>	94 (5.60%)	14 (4.01%)	80 (6.02%)	0.147
Drinking <sup>†</sup>	142 (8.46%)	19 (5.44%)	123 (9.26%)	0.023
Cerebrovascular disease <sup>†</sup>	34 (2.03%)	14 (4.01%)	20 (1.50%)	0.003
Visual impairment <sup>†</sup>	324 (19.31%)	91 (26.07%)	233 (17.53%)	<0.001
Auditory impairment <sup>†</sup>	342 (20.38%)	88 (25.21%)	254 (19.11%)	0.012
Dementia <sup>†</sup>	277 (16.51%)	110 (31.52%)	167 (12.57%)	<0.001
Pain <sup>†</sup>	664 (39.57%)	208 (59.60%)	456 (34.31%)	<0.001
Outdoor activities >1 h/d <sup>†</sup>	617 (36.77%)	82 (23.50%)	535 (40.26%)	<0.001
Living alone <sup>†</sup>	263 (15.67%)	58 (16.62%)	205 (15.43%)	0.585
Life satisfaction*	22.58 ± 5.65	20.455 ± 6.454	23.132 ± 5.282	<0.001
BMI (kg/m <sup>2</sup> )*	19.57 ± 3.87	18.54 ± 4.18	19.79 ± 3.77	<0.001
SBP (mmHg)*	150.24 ± 24.75	151.148 ± 25.468	150.008 ± 24.571	0.455
DBP (mmHg)*	78.37 ± 22.05	77.372 ± 13.543	78.633 ± 23.754	0.354
TC (mg/dL)*	4.86 ± 1.07	4.68 ± 1.02	4.91 ± 1.08	0.001
TG (mg/dL)*	1.21 ± 0.64	1.14 ± 0.657	1.23 ± 0.639	0.025
GLU (mmol/L)*	4.99 ± 1.94	5.132 ± 1.597	4.959 ± 2.014	0.156
Vitamin D <sub>3</sub> (ng/mL)*	24.56 ± 9.58	22.32 ± 8.8	25.16 ± 9.7	<0.001

Notes: \* Data are presented as mean ± standard deviation. †Data are presented as number (percentage).

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; GLU, glucose.

associations between overeating, constipation, and depression among the elderly population.

Physical status is closely related to healthy life of elderly population. As one study found, body fat was positively associated with poorer health-related life quality and depression [22], while lower extremity muscle strength was negatively associated with depression [23]. In recent years, with high-protein diet trend, gastrointestinal symptoms such as constipation, as an unhealthy physical state, are an important manifestation of aging and have a high prevalence in the elderly population [24, 25, 26]. The evidence provided by previous studies has shown that constipation may be related to depressive symptoms. Dore et al. revealed that constipation is related to an increased risk of depression in a representative sample of elderly

**Table 2.** Multiple linear regression analyses between constipation, overeating, and GDS-15.

Variable	Beta	95% confidence interval	P-value
<b>Constipation</b>			
Crude Model	1.528	1.127–1.928	<0.001
Model 1	1.134	0.741–1.528	<0.001
Model 2	0.827	0.380–1.273	<0.001
Model 3	0.848	0.403–1.294	0.001
<b>Overeating</b>			
Crude Model	1.351	1.027–1.675	0.001
Model 1	1.015	0.695–1.335	<0.001
Model 2	1.125	0.777–1.473	<0.001
Model 3	1.324	0.981–1.667	<0.001

Crude model: none adjusted.

Model 1: adjusted for age and sex.

Model 2: model 1 plus body mass index, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, and glucose.

Model 3: model 2 plus illiteracy, cerebrovascular disease, smoking, drinking, visual impairment, auditory impairment, dementia, pain, outdoor activities, living alone, life satisfaction, and vitamin D<sub>3</sub>.

population from Northern Sardinia aged from 65 to 94 years [27]. Chang et al. reported that constipation was significantly and positively correlated with depression in patients with Parkinson's disease [28]. Rajindrajith et al. found that compared to teenagers without functional constipation, those with functional constipation were more likely to have isolated psychological problems, such as depression and social problems, with a negative impact on their health-related life quality [29]. Additionally, previous research has indicated that a high proportion of individuals with depression meet the criteria for overeating, and are also at an increased risk of weight gain and chronic disease [30]. Consistent with previous studies, our study showed that constipation and overeating were significantly associated with depression after full adjustment.

**Table 3.** Multiple logistic regression analyses between constipation, overeating, and depression.

Variable	Odds ratio	95% confidence interval	P-value
<b>Constipation</b>			
Crude Model	2.936	2.203–3.912	<0.001
Model 1	2.324	1.721–3.138	<0.001
Model 2	2.112	1.451–3.074	<0.001
Model 3	2.328	1.540–3.521	<0.001
<b>Overeating</b>			
Crude Model	2.478	1.932–3.177	<0.001
Model 1	1.998	1.540–2.593	<0.001
Model 2	2.270	1.656–3.111	<0.001
Model 3	2.735	1.920–3.898	<0.001

Crude model: none adjusted.

Model 1: adjusted for age and sex.

Model 2: model 1 plus body mass index, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, and glucose.

Model 3: model 2 plus illiteracy, cerebrovascular disease, smoking, drinking, visual impairment, auditory impairment, dementia, pain, outdoor activities, living alone, life satisfaction, and vitamin D<sub>3</sub>.

The mechanism by which constipation influences neurological function has not been clearly understood, but evidence is accumulating to support the view that it may be related to the microecological-gut-brain axis [31, 32]. Gut microbes are capable of producing most of the neurotransmitters found in the human brain, such as 5-hydroxytryptamine, norepinephrine, and diaminobenzoic acid [33, 34, 35]. Israelyan et al. reported that mice with a variant of tryptophan hydroxylase have significant depression-like behaviors and gastrointestinal motor function defects. The administration of slow-release formulation of 5-hydroxytryptophan can restore the development of the enteric nervous system and reverse abnormal behavior, indicating that the deficiency of neurotransmitters, such as 5-hydroxytryptamine, may be a key link in constipation leading to emotional disorders [36]. Through fecal metabolomics and network pharmacology, Liu et al. discovered that choline, betaine, and glycine were significantly associated with constipation and depression [37].

Meanwhile, the association between depression and overeating may be related to neuroendocrine abnormalities. Previous study [30] has found that dopamine levels correlated positively with disordered eating behaviors in females, and negatively in males. The results provide evidence that depressogenic overeating and weight gain are associated with dopamine levels. Animal studies have also shown that corticosterone basal levels were significantly elevated in binge-eating rats with depressive-like behaviors while corticosterone increase to acute stress was attenuated [38]. These findings also provide some potential targets and ideas for early prevention and treatment of depression and overeating [39].

## 5. Conclusions and Implications

The current study provides epidemiological evidence that constipation and overeating have positive associations with depression in Chinese oldest-old and centenarians. Based on these findings, the interventions for constipation and overeating should be improved to promote prevention and treatment for depression and achieve successful aging and healthy longevity.

## Declarations

### Author contribution statement

Zhigao Sun; Xin Su; Xiaoqian Zhao; Yao Yao; Yali Zhao; Pei Zhang; Zhirui Li; Shihui Fu: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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## Data availability statement

Data will be made available on request.

## Declaration of interest's statement

The authors declare no conflict of interest.

## Additional information

Supplementary content related to this article has been published online at <https://doi.org/10.1016/j.heliyon.2022.e12432>.

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## References

- [1] P. Zis, A. Daskalaki, I. Bountouni, P. Sykioti, G. Varrassi, A. Paladini, Depression and chronic pain in the elderly: links and management challenges, *Clin. Interv. Aging* 12 (2017) 709–720.
- [2] M. Vazquez Roque, E.P. Bouras, Epidemiology and management of chronic constipation in elderly patients, *Clin. Interv. Aging* 10 (2015) 919–930.
- [3] M. Luppá, C. Sikorski, T. Luck, L. Ehreke, A. Konnopka, B. Wiese, et al., Age- and gender-specific prevalence of depression in latest-life—systematic review and meta-analysis, *J. Affect. Disord.* 136 (3) (2012) 212–221.
- [4] D.J. Sassarini, Depression in midlife women, *Maturitas* 94 (2016) 149–154.
- [5] G.S. Alexopoulos, Depression in the elderly, *Lancet* 365 (9475) (2005) 1961–1970.
- [6] H. Shimada, H. Park, H. Makizako, T. Doi, S. Lee, T. Suzuki, Depressive symptoms and cognitive performance in older adults, *J. Psychiatr. Res.* 57 (2014) 149–156.
- [7] E.L. Whitlock, L.G. Diaz-Ramirez, M.M. Glymour, W.J. Boscardin, K.E. Covinsky, A.K. Smith, Association between persistent pain and memory decline and dementia in a longitudinal cohort of elders, *JAMA Intern. Med.* 177 (8) (2017) 1146–1153.
- [8] R. Scott, D. Paulson, Cerebrovascular burden and depressive symptomatology interrelate over 18 years: support for the vascular depression hypothesis, *Int. J. Geriatr. Psychiatr.* 33 (1) (2018) 66–74.
- [9] R. Rubin, Exploring the relationship between depression and dementia, *JAMA* 320 (10) (2018) 961–962.
- [10] X. Zhao, D. Zhang, M. Wu, Y. Yang, H. Xie, Y. Li, et al., Loneliness and depression symptoms among the elderly in nursing homes: a moderated mediation model of resilience and social support, *Psychiatr. Res.* 268 (2018) 143–151.
- [11] M. Novotny, B. Klimova, M. Valis, PPI long term use: risk of neurological adverse events? *Front. Neurol.* 9 (2019) 1142.
- [12] G. Onder, S. Giovannini, F. Sganga, E. Manes-Gravina, E. Topinkova, H. Finne-Soveri, et al., Interactions between drugs and geriatric syndromes in nursing home and home care: results from Shelter and IBenC projects, *Aging Clin. Exp. Res.* 30 (9) (2018) 1015–1021.
- [13] American Geriatrics Society Beers Criteria® Update Expert Panel, American Geriatrics Society 2019 Updated AGS Beers Criteria® for potentially inappropriate medication use in older adults, *J. Am. Geriatr. Soc.* 67 (4) (2019) 674–694.
- [14] M. Valles-Colomer, G. Falony, Y. Darzi, E.F. Tigchelaar, J. Wang, R.Y. Tito, et al., The neuroactive potential of the human gut microbiota in quality of life and depression, *Nat. Microbiol.* 4 (2019) 623–632.
- [15] E. Dimidi, S. Christodoulides, S.M. Scott, K. Whelan, Mechanisms of action of probiotics and the gastrointestinal microbiota on gut motility and constipation, *Adv. Nutr.* 8 (2017) 484–494.
- [16] K. Gao, C.L. Mu, A. Farzi, W.Y. Zhu, Tryptophan metabolism: a link between the gut microbiota and brain, *Adv. Nutr.* 11 (2020) 709–723.
- [17] M. Coggrave, C. Norton, J.D. Cody, Management of faecal incontinence and constipation in adults with central neurological diseases, *Cochrane Database Syst. Rev.* 13 (2014) CD002115.
- [18] A. Mukherjee, A. Biswas, S.K. Das, Gut dysfunction in Parkinson's disease, *World J. Gastroenterol.* 22 (2016) 5742–5752.
- [19] P. Fu, M. Gao, K.K.L. Yung, Association of intestinal disorders with Parkinson's Disease and Alzheimer's Disease: a systematic review and meta-analysis, *ACS Chem. Neurosci.* 11 (2020) 395–405.
- [20] S. Ballou, J. Katon, P. Singh, V. Rangan, H.N. Lee, C. McMahon, et al., Chronic diarrhea and constipation are more common in depressed individuals, *Clin. Gastroenterol. Hepatol.* 17 (2019) 2696–2703.
- [21] S. Fu, J. Hu, X. Chen, B. Li, H. Shun, J. Deng, et al., Mutant single nucleotide polymorphism rs189037 in Ataxia-Telangiectasia Mutated gene is significantly associated with ventricular wall thickness and human lifespan, *Front Cardiovasc Med* 8 (2021), 658908.
- [22] S. Giovannini, C. Macchi, R. Liperoti, A. Laudisio, D. Coraci, C. Loreti, et al., Association of body fat with health-related quality of life and depression in

- nonagenarians: the Mugello Study, *J. Am. Med. Dir. Assoc.* 20 (5) (2019) 564–568.
- [23] J. Kim, S. Kang, H. Hong, H. Kang, J.H. Kim, S.K. Woo, Muscle strength moderates the relationship between nutritional health risk and depression in Korean older adults, *Nutrients* 14 (3) (2022) 665.
- [24] I. Dumić, T. Nordin, M. Jecmenica, M. Stojkovic Lalosevic, T. Milosavljevic, et al., Gastrointestinal tract disorders in older age, *Chin. J. Gastroenterol. Hepatol.* 17 (2019), 6757524.
- [25] A. Tsapanou, G.S. Vlachos, S. Cosentino, Y. Gu, J.J. Manly, A.M. Brickman, et al., Sleep and subjective cognitive decline in cognitively healthy elderly: results from two cohorts, *J. Sleep Res.* 28 (2019), e12759.
- [26] B. Bulut Çakmak, G. Özkula, S. Işık, İ. Özkan Göncüoğlu, S. Öcal, A.E. Altınöz, et al., Anxiety, depression, and anger in functional gastrointestinal disorders: a cross-sectional observational study, *Psychiatr. Res.* 268 (2018) 368–372.
- [27] M.P. Dore, G.M. Pes, S. Bibbò, P. Tedde, G. Bassotti, Constipation in the elderly from Northern Sardinia is positively associated with depression, malnutrition and female gender, *Scand. J. Gastroenterol.* 53 (2018) 797–802.
- [28] T.Y. Chang, Y.H. Chen, M.H. Chang, C.H. Lin, Is there a close association of depression with either constipation or dysosmia in Parkinson's disease? *Sci. Rep.* 10 (2020), 15476.
- [29] S. Rajindrajith, N. Ranathunga, N. Jayawickrama, M. van Dijk, M.A. Benninga, N.M. Devanarayana, Behavioral and emotional problems in adolescents with constipation and their association with quality of life, *PLoS One* 15 (2020), e0239092.
- [30] G.M. Jessica, J.T. Susan, Al Theresa, D. Chao, Overeating and food addiction in major depressive disorder: links to peripheral dopamine, *Appetite* 148 (2020), 104586.
- [31] S. Rajindrajith, N. Ranathunga, N. Jayawickrama, M. van Dijk, M.A. Benninga, N.M. Devanarayana, Behavioral and emotional problems in adolescents with constipation and their association with quality of life, *PLoS One* 15 (2020), e0239092.
- [32] F. Stocchi, M. Torti, Constipation in Parkinson's disease, *Int. Rev. Neurobiol.* 134 (2017) 811–826.
- [33] J.D. Wood, Enteric nervous system: sensory physiology, diarrhea and constipation, *Curr. Opin. Gastroenterol.* 26 (2010) 102–108.
- [34] D. Bagga, J.L. Reichert, K. Koschutnig, C.S. Aigner, P. Holzer, K. Koskinen, et al., Probiotics drive gut microbiome triggering emotional brain signatures, *Gut Microb.* 9 (2018) 486–496.
- [35] P. Strandwitz, Neurotransmitter modulation by the gut microbiota, *Brain Res.* 1693 (2018) 128–133.
- [36] N. Israelyan, A. Del Colle, Z. Li, Y. Park, A. Xing, J.P.R. Jacobsen, et al., Effects of serotonin and slow-release 5-Hydroxytryptophan on gastrointestinal motility in a mouse model of depression, *Gastroenterology* 157 (2019) 507–521.
- [37] X. Liu, H. Liu, F. Wei, D. Zhao, Y. Wang, M. Lv, et al., Fecal metabolomics and network pharmacology reveal the correlations between constipation and depression, *J. Proteome Res.* 20 (2021) 4771–4786.
- [38] W.J. Jeong, B.Y. Sang, R. Vitaly, H.L. Jong, Hyperphagia and depression-like behavior by adolescence social isolation in female rats, *Int. J. Dev. Neurosci.* 30 (1) (2012) 47–53.
- [39] L. Feng, Z. Chu, X. Quan, Y. Zhang, W. Yuan, Y. Yao, et al., Malnutrition is positively associated with cognitive decline in centenarians and oldest-old adults: a cross-sectional study, *EClinicalMedicine* 47 (2022), 101336.