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RESEARCH ARTICLE

Antibiotic exposure and potential risk of depression in the Chinese elderly: a biomonitoring-based population study

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Abstract

Objective To examine the associations between urinary antibiotics from various sources and depression in the elderly using the biomonitoring method.

Methods In the current study, we investigated 990 elderly individuals (≥ 60 years old) from a community-based elderly cohort in West Anhui, China. The participants were interviewed by the Geriatric Depression Scale and self-developed questionnaires. A total of 45 antibiotics belonging to nine categories were screened in urine samples by the developed liquid chromatography electrospray tandem mass spectrometry method. Creatinine-corrected concentrations of antibiotics in urines were used to assess their exposure. Logistic regression analysis was employed to test the relationships between exposure to antibiotics and depression.

Results Compared to the control group, the multinomial logistic regression analyses showed the elderly exposed to higher concentrations of azithromycin (*OR* = 1.81, 95% *CI*: 1.09–3.00) and sulfaclozine (*OR* = 1.54, 95% *CI*: 1.05–2.28) had increased risks of depression, respectively. After categorizing the detected antibiotics, tetracyclines (*OR* = 1.48, 95% *CI*: 1.02–2.16) and veterinary antibiotics (VAs) (*OR* = 1.53, 95% *CI*: 1.06–2.20) were positively correlated with increased risks of depression. After stratified by sex, the VAs (*OR* = 2.04, 95% *CI*: 1.13–3.71) at higher concentrations were associated with elevated risks of depression in males, while the associations between depression and antibiotic exposures were observed in tetracyclines (*OR* = 1.74, 95% *CI*: 1.04–2.85) and all antibiotics (*OR* = 2.24, 95% *CI*: 1.01–2.94) at higher levels in females, respectively. Notably, after the stratification by age, the significant associations were mainly present in the subjects under the age of 70.

Conclusions Our findings reveal that azithromycin, sulfaclozine, tetracyclines, and the VAs were significantly associated with elevated risks of depression in the elderly. Importantly, sex- and age-specific differences were observed in the associations between antibiotic exposures and depression.

Keywords Depression · Elderly · Antibiotics · Biomonitoring · Urine · China

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Introduction

With the increase in the aging population in many countries in recent years, depression in older adults has become a global public health challenge. The prevalence of depression among older adults in China increased from 32 to 37% between 2008 and 2015 (Wang and Tian 2018). The continual annual increase in the incidence of depression not only imposes an increasingly heavy burden on healthcare services but also is a potential risk factor for disability (Yang et al. 2020). Although the etiology of depression remains poorly understood, the gut microbiota is recognized for playing a central role in depression in both animals and humans (Guida et al. 2018; Wang et al. 2020). Antibiotic residues, emerging contaminants in a class of well-known disruptors of gut microbiota function, have also attracted growing attention for their effects on human mental health, such as the pathogenesis of depression through the gut–brain axis (Hao et al. 2020). Almost 80 types of antibiotics and their active metabolites have been detected in food and drinking water, confirming that antibiotic residues can be ingested, potentially contributing to mental health risks (Feng et al. 2020; Kang et al. 2018; Schutzius et al. 2019).

In the past several years, biomonitoring studies have found that China's general population is widely exposed to multiclass antibiotics. In Shanghai, more than 20 types of antibiotics were found in children's urine, with an overall detection frequency of 79.6% (Wang et al. 2016). Another study reported the detection of nine types of VAs in 77.4% of preschool children in Hong Kong (Li et al. 2017). In addition, 18 types of antibiotics were detected in the urine of 822 adults in China between the ages of 21 and 75 years, with detection frequencies for individual compounds ranging between 0.1 and 15.2% (Wang et al. 2018b). Subsequent studies have provided compelling evidence that antibiotic exposure poses risks to human mental health, including by increasing the risk of Alzheimer disease (Abrams et al. 2019; Dutta et al. 2019), and depressive disorders (Lurie et al. 2015). Notably, a study conducted in eastern China reported that 7.2% of the general adult population had a health risk associated with gut microbiota dysbiosis under antibiotic challenge (Wang et al. 2018b). A nested case–control study based on patient records from a medical database demonstrated an association between antibiotic exposure and depression risk. The study further indicated that therapy with a single antibiotic, such as penicillin or quinolones, can increase the risk of depression (Lurie et al. 2015). A similar finding was reported by a study on fluoroquinolones: 93 of 94 participants who took fluoroquinolones reported psychiatric events, including depression (62%), insomnia (48%), and cognitive impairment (33%) (Kaur et al. 2016). Conclusions of epidemiological studies on the relationship between antibiotic exposure and depression have also been inconsistent, and even conflicting. A prospective study demonstrated a link between antibiotic exposure and postpartum depression in 124 mothers during and after pregnancy. However, the link between antibiotic exposure and postpartum depression was not significant at 3 or 6 months postpartum, indicating that the clinical use of antibiotics is not necessarily associated with depression (Murphy et al. 2018). Additional multisample and prospective cohort studies must examine the linkages between the onset and duration of antibiotic exposure and the risk of depressive symptoms or development of depression.

Experimental studies have demonstrated that antibiotic exposure can induce depressive disorders in mammals through disruption of gut homeostasis. In male mice, long-term exposure to a mixture of ampicillin, streptomycin, and clindamycin altered their gut microbiota composition. Concentration levels of Lachnospiraceae were significantly associated with depression-like behavior in these mice (Guida et al. 2018). In another study, a considerable increase in depression-like behaviors were observed in rats exposed to ciprofloxacin for approximately 2 weeks (Ilgin et al. 2015). Notably, our previous study revealed that perinatal exposure to sulfamonomethoxine induces persistent upregulation of the hippocampal mammalian target of the rapamycin pathway related to gut–brain axis dysfunction, potentially contributing to depression-like behavior in male mice offspring (Zhang et al. 2017).

Several noteworthy studies have been published on the relationship between antibiotic exposure and depression among different populations. However, assessments of antibiotic exposure in previous population studies have been based only on clinical utilization or self-medication. To the best of our knowledge, no studies have reported an association between the body burden of antibiotic exposure and the risk of depression in older adults. We hypothesized the existence of an association between antibiotic exposure from various sources, such as contaminated food or the environment, and depression in older adults. We employed a biomonitoring approach to monitor the concentrations of multiple antibiotics in the urine of 990 older adults in China.

Materials and methods

Study population

The baseline data were collected from our previous study, a cohort study conducted in Lu'an City, Anhui, China, from June to September 2016. The inclusion and exclusion criteria were as follows: (1) aged 60 years and above, (2) had lived in the area for at least 6 months prior to the survey, (3) did not have mental illness that could affect normal communication, (4) signed an informed consent and voluntarily participated (Li et al. 2019). In brief, of the 1,080 participants initially included in the present study, a small number of participants

were excluded because of their lack of depression data or urine samples. A total of 990 older adults between the ages of 60 and 92 years were enrolled. All participants provided written informed consent. The study was approved by the Ethics Committee of Anhui Medical University (the ethical clearance number for the population study: 20170284) and was conducted in accordance with the principles of the Declaration of Helsinki (Anonymous 1997).

Antibiotic Selections

With reference to the usage amount or detection frequency of antibiotics in animal-derived food (Chen et al. 2019), drinking water (Li et al. 2017), or urine samples in previous studies (Zhang et al. 2020; Zhu et al. 2020), 45 types of antibiotics and their two metabolites (acetyl metabolite of sulfamonomethoxine and metabolite of florfenicol) were selected from nine antibiotic categories—10 fluoroquinolones, 9 sulfonamides, 8 β-lactams, 7 macrolides, 4 tetracyclines, 3 phenicols, 2 quinoxalines, lincomycin, and 1 aminoglycoside. The antibiotics were grouped into four new categories according to their use: human antibiotics (HAs), VAs, antibiotics preferred as human antibiotics (PHAs), and antibiotics preferred as veterinary antibiotics (PVAs).

Antibiotic exposure assessment

The sample preparation and analytical process of the targeted antibiotics were performed as described in our previous study (Zhu et al. 2020). In brief, the urine samples were stored at − 80 °C for 12 h and kept frozen until analysis. Urinary creatinine level was measured at the local hospital after urine collection. The selected antibiotics were identified through high-performance liquid chromatography–tandem mass spectrometry. All urine sample analyses were performed by the same laboratory team. The matrix validation curve constructed for each analyte in a concentration range of 0.5−200 ng/mL demonstrated a good fit with correlation coefficients ranging from 0.990 to 0.999. The limits of detection (LODs) and limits of quantity ranged from 0.03 to 2.15 ng/mL and from 0.11 to 6.02 ng/mL, respectively. The recovery rate of the targeted antibiotic compounds ranged from 73.5 to 112.2%, and the matrix effects of the targets in urine ranged from 57.5 to 123.7%.

Outcome variables

Depression assessment

The 30-item Geriatric Depression Scale is a self-report measure of depressive symptoms in older adults (Chan 1996). Each item is a "yes" or "no" question. Scale items 1, 5, 7, 9, 15, 19, 21, 27, 29, and 30 are scored as 1 point for "no" and 0 for "yes." The remaining 20 items are scored as 1 point for "yes" and 0 for "no." Thus, the total score ranges from 0 to 30 points. A score of ≥ 11 was considered to indicate *depression*.

The activities of daily living

Activities of daily living (ADL) are behaviors associated with self-care, including functional mobility and eating. ADL scores range from 0 to 100, with 60 as a cutoff value. A higher score indicates a better ability to perform ADLs (Dong et al. 2018).

Mini-mental state examination

Cognitive function was evaluated using the Chinese version of the Mini-Mental State Examination (MMSE; Katzman et al. 1988). The MMSE evaluates five items: orientation, registration, attention and calculation, recall, and language. Total scores range from 0 to 30, with higher scores indicating better cognitive function. Because education level has a considerable effect on MMSE scores, cognitive impairment was evaluated according to the optimal cutoff points of the MMSE for elderly Chinese adults (Li et al. 2016).

Covariates

Data on sociodemographic and behavioral characteristics, including age (60–70 years, > 70 years), sex, marital status (widowed, non-widowed), education level (illiterate, primary school, middle school, and above), and living status, were obtained through face-to-face interviews. Health indices consisted of six questions: currently a smoker (yes or no), currently consume alcohol (yes or no), engage in regular physical exercise in the last 3 months (yes or no), history of chronic diseases (yes or no), height (m), and body weight (kg). The participants were divided into three groups according to body mass index (BMI): underweight (BMI < 18.5 kg/m^2), healthy weight (BMI = 18.5–23.9 kg/m^2), and overweight (BMI > 23.9 kg/m^2) (Hou et al. 2013). Smoking was defined as smoking at least three cigarettes a week over the past 6 months. Drinking was defined as drinking one glass of wine or more in the past 30 days. Physical exercise was defined as routine physical activity (e.g., jogging or hiking). History of chronic diseases was defined as the self-report of diagnosis as having chronic diseases such as hypertension, diabetes, chronic obstructive pulmonary disease, coronary heart disease, cancer/malignant tumor, or stroke.

Statistical analysis

The selected antibiotics were divided into six classes (macrolides, β-lactams, sulfonamides, fluoroquinolones, tetracyclines, and phenicols) according to their antibacterial

mechanisms. Because of their low detection frequencies, lincosamides and quinoxalines were excluded from the data analysis. Creatinine-corrected concentrations (μg/g) were calculated by dividing the urinary concentration (μg/L) of antibiotics by the urinary concentration of creatinine (g/L). In the present study, participants with urinary concentrations below the LODs were classified into the control group. Those with LODs equal to or higher than the 50th percentile P_{50} were classified into the low-concentration and high-concentration group, respectively (Wang et al. 2016).

A chi-square test was performed to examine the differences between the participants' demographic characteristics. Univariate logistic regression analysis was performed to identify differences in the prevalence of depression according to sex, age, marital status, education level, smoking, drinking, physical exercise, BMI, and history of chronic diseases. Associations between exposure to antibiotics and depression were analyzed using multinomial logistic regression analysis. Binary logistic regression models were used to examine the relationship between individual antibiotics and between antibiotic classes (detection frequency > 10%) and the risk of depression. Analyses stratified by sex and age were conducted to test the relationships between exposure to different antibiotic classes and depression. Demographic variables were considered in the model to be confounding factors if their associations with depression were significant ($p < 0.05$). Model A was a crude model, and model B contained the confounders: sex, age, marital status, guardian education level, previous occupation, living alone or with others, drinking, physical exercise, dietary structure, ADL score, cognitive impairment, and BMI. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA). A p value of <0.05 was considered to indicate statistical significance.

Results

Detection frequencies and concentrations of antibiotics

The distribution of detection frequencies and concentrations of 34 detected antibiotics in the normal and depression groups were illustrated in Table 1. Thirty-four antibiotics were observed in 93.0% of the elderly. It is noteworthy that 12 antibiotics were found in more than 10% of urine samples. The concentration of some antibiotics varied greatly in urines, with the extreme value exceeding 10,000 ng/mL. Additionally, through the rank sum test, the concentration levels of VAs, PVAs, and all antibiotics were significantly higher in depression group than those in normal group (Table S1).

Characteristics of study population

As shown in Table S2, the females were more likely to suffer from depression than the males. The elderly who were widowed, living alone, or illiterate had higher risks for depression. Significant differences in depression prevalence were also observed in the groups of ADL and cognitive impairment. In addition, smoking, drinking, physical activity, diet structure, and BMI were all influencing factors for depression. Interestingly, we found that the level of antibiotic residues in the elderly mainly engaged in physical activities was higher than that in the elderly with mental activities.

Associations of exposure to antibiotics with the risk of depression

Table 2 demonstrates the relationships between antibiotic exposures and the risk of depression. In model A, multinomial logistic regression indicated that the elderly exposed to higher concentrations of sulfaclozine (*OR* = 1.50, 95% *CI*: 1.05–2.14), oxytetracycline (*OR* = 1.80, 95% *CI*: 1.15–2.80), and lower concentrations of florfenicol (*OR* = 1.55, 95% *CI*: 1.02–2.34) were positively associated with the increased risks of depression. For antibiotic categories by antibacterial mechanism or usage, phenicols were associated with elevated risks of depression with the corresponding OR of 1.59 (95% *CI*: 1.06–2.37) at lower concentrations. However, the elderly exposed to HAs at lower concentrations with OR of 0.56 (95% *CI*: 0.37–0.84) had a lower risk of depression. After adjusting for potential confounders, some changes were discovered in the significant association of antibiotic exposure with depression. In model B, azithromycin (*OR* = 1.81, 95% *CI*: 1.09–3.00), sulfaclozine (*OR* = 1.54, 95% *CI*: 1.05–2.28), tetracyclines (*OR* = 1.48, 95% *CI*: 1.02–2.16), and VAs (*OR* = 1.53, 95% *CI*: 1.06–2.20) were associated with increased risks of depression. Nevertheless, the significant associations of oxytetracycline, florfenicol, phenicols, and HAs with depression disappeared, separately.

Sex- and age- specific associations of exposure to antibiotics with depression

Table 3 illustrates the relationships between antibiotic exposure and depression after stratified by sex. In the males, only exposure to higher levels of VAs (OR = 2.04, 95% *CI*: 1.13–3.71) presented a higher risk of depression. While the associations between depression and antibiotic exposures were observed in tetracyclines (*OR* = 1.74, 95% *CI*: 1.04–2.85) and all antibiotics (*OR* = 2.24, 95% *CI*: 1.01–2.94) at higher levels in the females, respectively. In addition, sulfaclozine (*OR* = 2.10, 95% *CI*: 1.15–3.82) was positively associated with depression in the males, whereas azithromycin (*OR* = 2.25, 95% *CI*: 1.20–4.21) and norfloxacin (*OR* = 2.41, 95% *CI*: 1.01–5.78)

Table 1 Detection frequency and urinary concentration (ng/mL) of antibiotics in different categories of depression (n = 990)

Antibiotics	Usage	All (n = 990)	Normal (n = 713)				Depression (n = 277)			
		N (%)[a]	N (%)	Percentiles			N (%)	Percentiles		
				P_{95}	P_{99}	Maximum		P_{95}	P_{99}	Maximum
Macrolides[b]		282 (28.5)	210 (29.5)	2.37	25.24	4966.18	72 (26.0)	3.32	40.80	981.49
Azithromycin	HA	180 (18.2)	131 (18.4)	0.23	6.71	431.88	49 (17.9)	0.28	40.80	981.49
Clarithromycin	HA	27 (2.7)	25 (3.5)	–	0.36	4.26	2 (0.7)	–	0.02	0.20
Erythromycin	PHA	85 (8.6)	63 (8.8)	1.20	15.45	4965.25	22 (7.9)	1.44	17.76	25.43
Roxithromycin	HA	27 (2.7)	20 (2.8)	–	0.67	1661.98	7 (2.5)	–	0.21	0.59
β-Lactams[b]		253 (25.6)	188 (26.4)	5.29	284.95	13520.02	65 (23.5)	8.62	757.10	10876.13
Cefaclor	HA	3 (0.3)	2 (0.3)	–	–	1.81	1 (0.4)	–	–	9.60
Cefotaxime	HA	8 (0.8)	4 (0.6)	–	–	23.31	4 (1.4)	–	9.16	24.00
Penicillin V	PHA	176 (17.8)	134 (18.8)	2.39	9.48	163.63	42 (15.2)	2.28	11.54	19.71
Amoxicillin	PHA	77 (7.8)	56 (7.9)	1.02	284.79	13520.02	21 (7.6)	1.14	757.10	10876.13
Tetracyclines[b]		440 (44.4)	307 (43.1)	7.21	510.91	29202.89	133 (48.0)	7.80	3364.96	30574.33
Oxytetracycline	PVA	187 (18.9)	126 (17.7)	1.28	254.86	28988.58	61 (22.0)	2.40	3088.97	36108.85
Chlortetracycline	PVA	77 (7.8)	57 (8.0)	0.98	9.26	36.32	20 (7.2)	0.98	11.35	906.36
Tetracycline	PVA	193 (19.5)	132 (18.5)	2.11	15.67	1042.67	61 (22.0)	1.94	70.78	385.00
Doxycycline	PVA	182 (18.4)	135 (18.9)	1.58	10.20	80.34	47 (17.0)	1.55	13.76	16.40
Fluoroquinolones[b]		496 (50.1)	344 (48.2)	58.68	657.65	179829.84	152 (54.9)	66.59	6171.67	21856.36
Pefloxacin	PVA	40 (4.0)	31 (4.3)	–	7.02	342.50	9 (3.2)	–	2.58	4.34
Danofloxacin	VA	40 (4.0)	27 (3.8)	–	19.78	158397.90	13 (4.7)	–	18.13	32.09
Lomefloxacin	PVA	14 (1.4)	8 (1.1)	–	0.23	108.36	6 (2.2)	–	0.80	3565.44
Sarafloxacin	VA	16 (1.6)	14 (2.0)	–	0.34	214.82	2 (0.7)	–	0.08	0.41
Ofloxacin	PVA	235 (23.7)	161 (22.6)	4.09	45.33	106.20	74 (26.7)	3.81	41.42	113.95
Levofloxacin	HA	33 (3.3)	28 (3.9)	–	157.50	179826.37	5 (1.8)	–	127.58	5459.14
Enrofloxacin	VA	103 (10.4)	75 (10.5)	0.63	7.52	13.81	28 (10.1)	0.83	8.97	22.43
Difloxacin	PVA	7 (0.7)	6 (1.8)	–	–	13.00	1 (0.4)	–	–	6.37
Ciprofloxacin	PVA	163 (16.5)	111 (15.6)	4.16	28.73	64.75	52 (18.8)	7.14	60.64	122.53
Norfloxacin	PVA	118 (11.9)	78 (10.9)	3.88	112.65	62670.01	40 (14.4)	8.28	2486.58	21862.55
Sulfonamides[b]		552 (55.8)	397 (55.7)	23.61	57.51	51770.05	155 (56.0)	33.82	3063.76	14301.41
Trimethoprime[c]	PVA	201 (20.3)	152 (21.3)	1.76	7.68	29803.34	49 (17.7)	1.21	1108.19	10572.11
Sulfamethoxazole	PVA	26 (2.6)	17 (2.4)	–	3.30	21964.17	9 (3.2)	–	913.33	8612.11
Sulfaclozine	VA	351 (35.5)	244 (34.2)	17.87	50.64	680.56	107 (38.6)	27.29	98.56	190.06
Sulfamethazine	VA	6 (0.6)	4 (0.6)	–	–	5.90	2 (0.7)	–	0.20	1.72
Sulfadiazine	PVA	28 (2.8)	17 (2.4)	–	1.32	5.30	11 (4.0)	–	4.48	120.19
Sulfachloropyridazine	VA	45 (4.5)	33 (4.6)	–	1.64	28.71	12 (4.3)	–	5.30	8.77
Sulfamonomethoxine[d]	VA	65 (6.6)	51 (7.2)	1.05	6.50	68.61	14 (5.1)	0.16	3.32	17.07
Phenicols[b]		247 (24.9)	168 (23.6)	7.28	88.09	1532.31	79 (28.5)	6.26	153.32	1811.49
Chloramhenicol		27 (2.7)	20 (2.8)		75.63	1532.31	7 (2.5)		135.32	1811.49
Thiamphenicol	VA	2 (0.2)	2 (0.3)	–	–	203.85	–	–	–	
Florfenicol	HA	228 (23.0)	154 (21.6)	5.06	15.38	111.93	74 (26.7)	4.36	8.31	11.21
Lincosamides[b]		36 (3.6)	26 (3.6)	–	291.33	151.51	10 (3.6)	–	107.41	1191.52
Lincomycin	PVA	36 (3.6)	26 (3.6)	–	291.33	194642.29	10 (3.6)	–	107.41	1191.52
Quinoxalines[b]		30 (3.0)	18 (2.5)		9.93	79.30	12 (4.3)		25.35	58.01
Cyadox	VA	30 (3.0)	18 (2.5)	–	9.93	79.30	12 (4.3)	–	25.35	58.01
All antibiotics[e]		921 (93.0)	660 (92.6)	4191.67	43312.28	194972.47	261 (94.2)	1296.72	5115.51	30587.75
HAs		271 (27.4)	206 (28.9)	27.32	644.15	179826.41	65 (23.5)	12.19	1164.11	5483.31
VAs		623 (62.9)	435 (61.0)	28.11	109.69	158437.71	188 (67.9)	33.72	98.56	190.06
PHAs		306 (30.9)	227 (31.8)	8.91	576.19	13520.02	79 (28.5)	296.96	17038.75	10876.13
PVAs		720 (72.7)	511 (71.7)	449.41	56156.57	194972.47	209 (75.5)	908.75	18032.84	30574.33

HAs, human antibiotics; *VAs*, veterinary antibiotics; *PHAs*, antibiotics preferred as HAs; *PVAs*, antibiotics preferred as VAs

[a] Positive detection (detection frequency, %)

[b] Sum of concentrations of antibiotics in corresponding category for individual

[c] Due to the similar antibacterial mechanisms, trimethoprim was included in the sulfonamides

[d] The urinary levels of sulfamonomethoxine and florfenicol were separately considered to be the sum of their prototypes and metabolites (sulfamonomethoxine-N4-acetyl and florfenicol amine)

[e] Sum of concentrations of all antibiotics

were separately associated with depression in females (Fig S1). Subsequently, a stratification analyses by age was also performed. Notably, there were significant associations primarily presented in the elderly under the age of 70. As shown

Table 2 Associations of creatinine-adjusted urinary antibiotics with depression in the elderly by multinomial logistic regression (less than LODs was used as the control) (n = 990)

Antibiotics	Model A[a]		Model B[b]	
	Low	High	Low	High
Individuals				
Azithromycin	0.64 (0.37, 1.09)[c]	1.34 (0.85, 2.13)	0.88 (0.49, 1.58)	**1.81 (1.09, 3.00)***
Sulfaclozine	0.96 (0.65, 1.34)	**1.50 (1.05, 2.14)***	0.93 (0.61, 1.41)	**1.54 (1.05, 2.28)***
Trimethoprim	0.78 (0.48, 1.26)	0.81 (0.50, 1.31)	0.88 (0.52, 1.51)	0.88 (0.52, 1.48)
Oxytetracycline	0.93 (0.57, 1.52)	**1.80 (1.15, 2.80)***	0.94 (0.56, 1.59)	1.56 (0.96, 2.54)
Tetracycline	1.09 (0.69, 1.74)	1.41 (0.90, 2.21)	1.02 (0.61, 1.71)	1.37 (0.84, 2.25)
Doxycycline	0.80 (0.48, 1.33)	0.95 (0.59, 1.55)	0.93 (0.53, 1.62)	0.92 (0.53, 1.57)
Ofloxacin	1.36 (0.90, 2.06)	1.15 (0.75, 1.76)	1.09 (0.69, 1.71)	1.07 (0.67, 1.71)
Enrofloxacin	0.79 (0.41, 1.53)	1.14 (0.62, 2.09)	0.84 (0.41, 1.75)	1.04 (0.54, 2.00)
Ciprofloxacin	1.17 (0.72, 1.92)	1.34 (0.82, 2.18)	1.16 (0.67, 2.00)	1.55 (0.91, 2.63)
Norfloxacin	1.27 (0.72, 2.24)	1.48 (0.85, 2.58)	1.50 (0.81, 2.80)	1.27 (0.69, 2.35)
Penicillin V	0.63 (0.37, 1.09)	0.92 (0.56, 1.51)	0.90 (0.50, 1.61)	0.70 (0.41, 1.21)
Florfenicol	**1.55 (1.02, 2.34)***	1.12 (0.73, 1.73)	1.47 (0.93, 2.32)	1.19 (0.74, 1.92)
Groups by antibacterial mechanism				
Macrolides	0.78 (0.51, 1.19)	0.91 (0.60, 1.36)	1.15 (0.72, 1.82)	1.00 (0.64, 1.56)
β-Lactams	0.68 (0.43, 1.06)	1.06 (0.70, 1.60)	0.82 (0.50, 1.35)	0.87 (0.55, 1.35)
Sulfonamides	0.80 (0.56, 1.13)	1.25 (0.90, 1.74)	0.87 (0.59, 1.27)	1.22 (0.85, 1.74)
Tetracyclines	1.11 (0.78, 1.57)	1.34 (0.96, 1.89)	1.12 (0.76, 1.64)	**1.48 (1.02, 2.16)***
Fluoroquinolones	1.28 (0.91, 1.80)	1.33 (0.95, 1.86)	1.22 (0.85, 1.77)	1.23 (0.85, 1.77)
Phenicols	**1.59 (1.06, 2.37)***	1.04 (0.68, 1.59)	1.46 (0.94, 2.27)	1.01 (0.63, 1.61)
Groups by usage				
HAs	**0.56 (0.37, 0.84)***	0.81 (0.58, 1.15)	0.77 (0.49, 1.20)	0.81 (0.56, 1.18)
VAs	1.23 (0.87, 1.73)	1.48 (1.06, 2.07)	1.22 (0.84, 1.77)	**1.53 (1.06, 2.20)***
PHAs	0.73 (0.48, 1.10)	0.99 (0.67, 1.46)	0.88 (0.56, 1.38)	0.84 (0.55, 1.29)
PVAs	1.08 (0.75, 1.55)	1.36 (0.95, 1.94)	1.19 (0.80, 1.77)	1.39 (0.95, 2.05)
All antibiotics	1.10 (0.63, 1.92)	1.45 (0.83, 2.51)	1.21 (0.66, 2.21)	1.57 (0.87, 2.85)

The bold, $p < 0.05$, indicates that the difference was statistically significant

LODs, less than limits of detection; *HAs*, human antibiotics; *VAs*, veterinary antibiotics; *PHAs*, antibiotics preferred as HAs; *PVAs*, antibiotics preferred as VAs

*$0.001 \le p < 0.05$; **$p < 0.001$

[a] Model A was the crude model

[b] Model B was adjusted for gender, age, marital status, educational level, previous occupation, living alone, drinking, physical activity, dietary structure, ADL, cognitive impairment, and BMI

[c] Odds ratio (95% confidence interval)

in Table 4, except for β-lactams (OR = 0.42, 95% *CI*: 0.19–0.95), these classes of phenicols (OR = 1.99, 95% *CI*: 1.03–3.82), VAs (OR = 1.80, 95% *CI*: 1.06–3.04), PVAs (OR = 1.82, 95% *CI*: 1.02–3.26) and all antibiotics (OR = 2.64, 95% *CI*: 1.03–6.79) were positively related to with the increased risk of depression in the elderly aged ≤ 70 years, respectively. Furthermore, individual antibiotics, such as oxytetracycline (*OR* = 2. 49, 95% *CI*: 1. 18–5.27), ciprofloxacin (*OR* = 2.16, 95% *CI*: 1.07–4.37) and florfenicol (*OR* = 2.18, 95% *CI*: 1.11–4.29) were separately positively associated with depression (Fig. S2).

Discussion

Our results suggest that the participants' bodies incurred a heavy antibiotic burden from widespread exposure to multiple antibiotics (VAs and PVAs). In China, although biomonitoring data indicate widespread antibiotic exposure among different populations, most studies have focused on children, pregnant women or younger adults rather than older adults (Wang et al. 2018b). Notably, the overall antibiotic detection rate (93%) in the present study was much higher than that in 536 pregnant women from eastern China (41.6%) (Wang et al.

Table 3 Associations of creatinine-adjusted urinary antibiotics with depression by multinomial logistic regression in males and female (less than LODs was used as the control) ($n = 990$)

Antibiotics	Model A[a]		Model B[b]	
	Low	High	Low	High
Males				
Groups by antibacterial mechanism				
Macrolides	0.96 (0.52, 1.77)[c]	0.95 (0.48, 1.91)	1.31 (0.66, 2.61)	1.10 (0.50, 2.40)
β-Lactams	0.71 (0.34, 1.48)	0.90 (0.45, 1.78)	0.88 (0.39, 1.98)	0.61 (0.28, 1.32)
Sulfonamides	0.71 (0.41, 1.24)	1.36 (0.82, 2.27)	0.70 (0.38, 1.29)	1.35 (0.77, 2.38)
Tetracyclines	1.66 (0.99, 2.78)	1.10 (0.63, 1.92)	1.60 (0.88, 2.90)	1.05 (0.56, 1.96)
Fluoroquinolones	1.34 (0.81, 2.23)	0.96 (0.55, 1.67)	1.43 (0.81, 2.53)	0.96 (0.51, 1.80)
Phenicols	1.74 (0.97, 3.12)	1.51 (0.87, 2.64)	1.85 (0.95, 3.61)	1.51 (0.29, 1.74)
Groups by usage				
HAs	0.66 (0.35, 1.22)	0.64 (0.36, 1.15)	0.89 (0.44, 1.78)	0.53 (0.28, 1.02)
VAs	1.26 (0.73, 2.16)	**1.73 (1.01, 2.97)***	1.26 (0.69, 2.31)	**2.04 (1.13, 3.71)***
PHAs	0.61 (0.30, 1.22)	0.93 (0.50, 1.76)	0.70 (0.32, 1.51)	0.80 (0.40, 1.64)
PVAs	1.15 (0.65, 2.04)	1.12 (0.63, 1.98)	1.27 (0.67, 2.42)	1.10 (0.58, 2.07)
All antibiotics	0.59 (0.25, 1.39)	0.76 (0.33, 1.77)	0.77 (0.30, 1.94)	0.97 (0.39, 2.42)
Females				
Groups by antibacterial mechanism				
Macrolides	0.67 (0.38, 1.18)	0.83 (0.50, 1.37)	1.10 (0.58, 2.10)	0.97 (0.56, 1.69)
β-Lactams	0.63 (0.35, 1.13)	1.13 (0.67, 1.91)	0.77 (0.40, 1.45)	0.98 (0.56, 1.73)
Sulfonamides	0.94 (0.60, 1.48)	1.23 (0.80, 1.89)	0.97 (0.59, 1.60)	1.15 (0.72, 1.83)
Tetracyclines	0.80 (0.50, 1.30)	**1.56 (1.00, 2.42)***	0.80 (0.47, 1.34)	**1.74 (1.07, 2.85)***
Fluoroquinolones	1.25 (0.79, 1.96)	**1.60 (1.04, 2.47)***	1.12 (0.68, 1.84)	1.34 (0.84, 2.14)
Phenicols	1.51 (0.87, 2.64)	1.17 (0.70, 1.96)	1.24 (0.68, 2.27)	1.16 (0.66, 2.04)
Groups by usage				
HAs	**0.48 (0.28. 0.83)****	0.90 (0.58, 1.39)	0.72 (0.40, 1.30)	0.96 (0.60, 1.55)
VAs	1.27 (0.81, 2.00)	1.34 (0.87, 2.07)	1.19 (0.73, 1.95)	1.30 (0.81, 2.08)
PHAs	0.78 (0.47, 1.31)	0.99 (0.61, 1.63)	0.99 (0.56, 1.76)	0.85 (0.50, 1.76)
PVAs	1.06 (0.67, 1.70)	**1.64 (1.04, 2.58)***	1.11 (0.67, 1.84)	1.53 (0.94, 2.51)
All antibiotics	1.73 (0.82, 3.64)	**2.28 (1.09, 4.76)***	1.73 (0.78, 3.85)	**2.24 (1.01, 4.94)***

The bold, $p < 0.05$, indicates that the difference was statistically significant

LODs, less than limits of detection; *HAs*, human antibiotics; *VAs*, veterinary antibiotics; *PHAs*, antibiotics preferred as HAs; *PVAs*, antibiotics preferred as VAs

*$0.001 \leq p < 0.05$; **$p < 0.001$

[a] Model A was the crude model

[b] Model B was adjusted for gender, age, marital status, educational level, previous occupation, living alone, drinking, physical activity, dietary structure, ADL, cognitive impairment, and BMI

[c] Odds ratio (95% confidence interval)

2017); 582 students in Shanghai (79.6%) (Wang et al. 2016); 31 preschool children in Hong Kong (77.4%) (Li et al. 2017); and 107 healthy adults in Dalian (26.2%) (Liu et al. 2017). The higher concentrations of antibiotic residues in the present study may be related to older adults' lower metabolic level, bacterial susceptibility, and dietary structure, as past studies have noted (An et al. 2018; Fraser et al. 2000; Zhang et al. 2020).

Urinary analysis indicated a positive association between depression and exposure to sulfaclozine, oxytetracycline, or florfenicol. After the antibiotics were classified according to their mechanism, a significant association was observed between phenicols and depression; after they were classified according to usage, a significant association was observed between depression and HAs. However, exposure to β-lactams was negatively associated with depression. Regarding depression-related risk factors, we found significant positive associations of depression with exposure to azithromycin, sulfaclozine, tetracyclines, and VAs. In general, exposure to antibiotics such as VAs and PVAs was associated with an increased risk of depression.

Table 4 Associations of creatinine-adjusted urinary antibiotics with depression by multinomial logistic regression in ages (less than LODs was used as the control) (n = 990)

Antibiotics	Model A[a]		Model B[b]	
	Low	High	Low	High
60–70 years				
Groups by antibacterial mechanism				
Macrolides	0.98 (0.53, 1.83)[c]	1.27 (0.72, 2.22)	1.50 (0.75, 2.99)	1.49 (0.81, 2.76)
β-Lactams	**0.45 (0.21, 0.95)***	0.92 (0.50, 1.69)	**0.42 (0.19, 0.95)***	0.85 (0.45, 1.62)
Sulfonamides	**0.59 (0.35, 0.99)***	1.14 (0.71, 1.82)	0.66 (0.37, 1.16)	1.27 (0.76, 2.13)
Tetracyclines	1.07 (0.65, 1.76)	1.45 (0.86, 2.43)	1.17 (0.68, 2.03)	1.74 (0.99, 3.07)
Fluoroquinolones	1.35 (0.82, 2.23)	1.53 (0.94, 2.49)	1.28 (0.75, 2.20)	1.48 (0.88, 2.49)
Phenicols	**2.08 (1.15, 3.74)***	0.96 (0.50, 1.83)	**1.99 (1.03, 3.82)***	0.96 (0.48, 1.93)
Groups by usage				
HAs	0.72 (0.41, 1.28)	**0.55 (0.32,0.95)***	1.05 (0.56, 1.97)	0.61 (0.34, 1.10)
VAs	0.97 (0.59, 1.61)	1.52 (0.93, 2.46)	1.00 (0.58, 1.74)	**1.80 (1.06, 3.04)***
PHAs	0.54 (0.28, 1.04)	0.96 (0.55, 1.66)	0.52 (0.25, 1.05)	0.86 (0.48, 1.56)
PVAs	1.30 (0.76, 2.20)	**1.71 (1.00, 2.93)***	1.41 (0.79, 2.51)	**1.82 (1.02, 3.26)***
All antibiotic	1.49 (0.62, 3.58)	2.04 (0.85, 4.87)	1.72 (0.67, 4.44)	**2.64 (1.03, 6.79)***
> 70 years				
Groups by antibacterial mechanism				
Macrolides	0.65 (0.37, 1.14)	0.64 (0.35, 1.17)	0.95 (0.50, 1.81)	0.70 (0.37, 1.35)
β-lactams	0.91 (0.51, 1.62)	1.20 (0.68, 2.10)	1.31 (0.68, 2.56)	0.86 (0.46, 1.62)
Sulfonamides	1.03 (0.65, 1.65)	1.37 (0.87, 2.16)	1.21 (0.71, 2.07)	1.21 (0.73, 2.02)
Tetracyclines	1.14 (0.70, 1.87)	1.28 (0.81, 2.01)	1.13 (0.65, 1.96)	1.27 (0.76, 2.12)
Fluoroquinolones	1.22 (0.77, 1.93)	1.17 (0.73, 1.87)	1.13 (0.68, 1.90)	1.03 (0.60, 1.74)
Phenicols	1.27 (0.73, 2.21)	1.11 (0.63, 1.95)	1.18 (0.64, 2.19)	1.06 (0.56, 2.02)
Groups by usage				
HAs	**0.44 (0.24, 0.79)****	1.08 (0.69, 1.69)	0.58 (0.30, 1.10)	1.03 (0.62, 1.71)
VAs	1.50 (0.94, 2.41)	1.45 (0.91, 2.32)	1.50 (0.88, 2.55)	1.40 (0.83, 2.36)
PHAs	0.91 (0.53, 1.55)	1.02 (0.59, 1.76)	1.40 (0.76, 2.59)	0.83 (0.45, 1.54)
PVAs	0.92 (0.56, 1.52)	1.13 (0.71, 1.81)	1.11 (0.63, 1.94)	1.13 (0.67, 1.92)
All antibiotic	0.88 (0.42, 1.82)	1.12 (0.54, 2.29)	0.91 (0.40, 2.06)	1.07 (0.50, 2.39)

The bold, $p < 0.05$, indicates that the difference was statistically significant

LODs, less than limits of detection; *HAs*, human antibiotics; *VAs*, veterinary antibiotics; *PHAs*, antibiotics preferred as HAs; *PVAs*, antibiotics preferred as VAs

*$0.001 \leq p < 0.05$; ** $p < 0.001$

[a] Model A was the crude model

[b] Model B was adjusted for gender, age, marital status, educational level, previous occupation, living alone, drinking, physical activity, dietary structure, ADL, cognitive impairment, and BMI

[c] Odds ratio (95% confidence interval)

Exposure to individual antibiotics such as sulfaclozine and azithromycin was associated with a slight increase in the risk of depression. Compared with the control group, individuals with a high level of exposure to sulfaclozine and azithromycin had a 1.81- and 1.54-times greater likelihood of developing depression, respectively. In one of our previous studies, we discussed several pathways or routes by which older adults may be exposed to antibiotics: clinical use, contaminated animal–derived food and drinking water (Zhu et al. 2020). Sulfaclozine, a sulfonamide, is generally used as a feed additive in veterinary clinics and poultry farming or in the treatment of poultry diseases. One study detected sulfonamides, including sulfaclozine, in urban sewage, vegetables and animal-derived food. Some of these sulfonamides exceeded standard limits in several foods (Tang et al. 2015). Therefore, contaminated food or the environment may be the main routes of exposure to sulfaclozine (a VA) in older adults. In addition, Lurie et al. identified sulfonamide exposure as a risk factor for depression (Lurie et al. 2015). Notably, our previous animal study indicated that exposure to

sulfamonomethoxine during pregnancy increased anxiety-related and depression-like behavior in mice offspring (Zhang et al. 2017). These findings indirectly support our results. Notably, as an HA, azithromycin may primarily accumulate in the body through medical use, and has a relatively higher detection rate in macrolides (1.3 to 27.9%) (Wang et al. 2018a; Wang et al. 2016; Wang et al. 2018b). A study reported that azithromycin was the most commonly used in macrolides in the primary, secondary and tertiary care hospitals of 28 provinces in China (Liu et al. 2020). However, cephalosporins, rather than azithromycin, are the most frequently used in China, which was similar to observations in Romania (Zaha et al. 2019; Zaha et al. 2020). As a derivative of erythromycin, azithromycin is a second-generation macrolide, which is widely used in medical prescriptions because of its characteristics such as easy absorption, long half-life, few side effects and broad spectrum of bacteriostatic (Firth and Prathapan 2020). In the USA, azithromycin was prescribed more than 12 million times in 2017 alone (Firth and Prathapan 2020). A recent study reported that the use of azithromycin as a prescription drug was inappropriate in New York City emergency departments at 37.8% and primary care departments at 49.0% (Kiel et al. 2020). In addition, azithromycin was found to account for the highest proportion of antibiotic prescriptions during the 2013–2014 and 2014–2015 influenza seasons, and was more easily prescribed in the middle-aged and elderly population (Havers et al. 2018) (we have summarized the use of antibiotics in different countries in Table S3). Thus, as a prescription drug, azithromycin widely used in clinical practice and unreasonable use may lead to antibiotic residues in human bodies. Azithromycin can also affect gut microbiota composition, reduce gut microbiota biodiversity and even alter gut homeostasis (Sylvia et al. 2017; Wei et al. 2018). In a randomized controlled trial, azithromycin reduced gut microbiota richness by 23% and Shannon diversity by 13% over a short duration. Abundance of the probiotic *Bifidobacterium* was particularly substantially reduced (Wei et al. 2018). In addition, azithromycin-related neurological adverse events have been reported in clinical trials of both children and older adults, although these incidences were low (Cone et al. 2003; Schiff et al. 2010). Thus, we speculated that azithromycin may affect brain function through the gut–brain axis, leading to depression-like behavior.

In the present study, higher concentrations of VAs and tetracyclines were respectively associated with a 53% and 48% greater risk of depression. VAs are used extensively as therapeutic drugs or feed additives in modern agriculture. In recent years, VAs have been detected in meat (Muaz et al. 2018), milk (Kurjogi et al. 2019) and environmental water samples (Li et al. 2011). Given that the exposure pathways of antibiotics generally depend on their use, humans, who are at the top of the food chain, are primarily exposed to VAs through contaminated food or water. Two 2019 studies showed that even subtherapeutic concentrations (in the range of ng/mL) of antibiotics can alter gut bacteria in zebrafish (Almeida et al. 2019; Schlomann et al. 2019). In addition, altered gut bacteria composition and function may affect signaling pathways, including neural, endocrine, and immune pathways, related to the pathogenesis of stress-related diseases such as depression and potentially contribute to their development (Hao et al. 2020; Huang et al. 2019; Wang et al. 2020). As such, we speculate that a long-time ingestion of VAs from food chains or drinking water may have an adverse impact on the pathogenesis of depressive disorder by inducing dysbiosis of human gut microbiota. The more researches in human are necessary to test this hypothesis.

Tetracyclines, which are available over the counter in most countries, are commonly used as an additive in livestock feed or in veterinary medicine to prevent bacterial infections or diseases. Tetracycline consumption in China is on the rise, having been found in surface water (Wei et al. 2011), drinking water (Liu and Wong 2013), soil, vegetables (Li et al. 2011), meat, milk, and egg products (Li et al. 2017). Thus, older adults can be easily exposed to tetracyclines through the food chain. Experimental studies in mice have revealed that subchronic ingestion of low or therapeutic dosages of doxycycline, a widely used tetracycline, reduces gut microbiota diversity and alters gut microbiota composition and function (Hou et al. 2019). A nested case–control study demonstrated a link between tetracycline therapy and elevated risk of depression (Lurie et al. 2015). This conclusion is consistent with our present findings. However, other studies have presented contradictory findings for some antibiotics. For example, a substantial increase in aggressiveness rather than depressive behavior was observed in newborn BALB/c mice exposed to penicillin for 6 weeks (Leclercq et al. 2017). Such inconsistent findings may be attributed to the timing of the interventions and the type of antibiotics administered. Although that experiment did not reveal depression-like behavior, the ability of antibiotic exposure to induce abnormal behavior is possible and indicates a potential association between antibiotic exposure and mental disorders.

Disruption of the gut microbiota is a mechanism by which antibiotics can increase the risk of depression. Evidence from neuroscience studies supports the premise that the human gut microbiota modulates brain function or behavior, particularly in relation to depression, primarily through a two-way communication pathway known as the gut–brain axis (Dinan and Cryan 2017). Antibiotics have a substantial effect on the composition and function of the human gut microbiota (Becattini et al. 2016; Jahansouz et al. 2019; Reese et al. 2018). Moreover, our previous animal study revealed that apart from substantially altering the composition and function of the gut microbiota, antibiotic exposure induced mental disorders such as depression and cognitive disorders (Zhang et al. 2017).

This evidence suggests that low concentrations of antibiotic residues may alter the gut microbiota of older adults, consequently affecting their mood and increasing their risk of depression. Infancy is a crucial stage for the development of gut microbiota (Yatsunenko et al. 2012), but at the other extreme of life, old age is correlated with reduced microbial diversity (Dinan and Cryan 2017). Evidence has suggested that the core microbiota in the human gut can change dynamically with age, particularly in older adults (Claesson et al. 2011; Dinan and Cryan 2017). Notably, the number of *Bifidobacterium* strains decreases with age (Biagi et al. 2016). This may cause dysbiosis of the gut microbiota in older adults, leading to increased susceptibility to antibiotic treatment compared with younger adults and contributing to adverse mental health outcomes. This indirectly supports our finding that antibiotic exposure increases the risk of depression among older adults. We speculate that antibiotics induce depression by altering gut microbiota composition and interfering with the physiological function of the gut–brain axis. However, the exact mechanism requires further research.

In the present study, we also observed a sex-specific association between antibiotic exposure and depression. In men, exposure to sulfaclozine or higher concentrations of VAs was associated with an increased risk of depression. In women, associations were observed between higher levels of exposure to all antibiotics (including azithromycin, norfloxacin, and tetracyclines) and depression. Moreover, more significant associations between antibiotic exposure and depression were noted in women than in men. This finding is consistent with that of a study of sex-specific differences in associations between antibiotic exposure and risk of obesity in school children (Wang et al. 2016). Another study reported a strong sex-specific difference in social behaviors of individuals under the same antibiotic treatment: the social behaviors of women were more affected than were those of men (Sylvia et al. 2017). A 2020 study suggested that prenatal exposure to a low dose of penicillin causes long-term sex-specific changes in murine behavior, immune regulation, and gut microbiota (Champagne-Jorgensen et al. 2020). Although the mechanisms underlying these sex-specific differences are not well understood, the gut microbiota is believed to be involved (Jašarević et al. 2016). Furthermore, antibiotic exposure has sex-specific effects on the gut microbiota and metabolism of host mice (Gao et al. 2019).

An age-specific difference was observed in the association between antibiotic exposure and depression in the study population. The most significant associations were noted in the participants aged 60–70 years. Specifically, in this group, positive correlations between depression and phenicols, VAs, PVAs, and all antibiotics were identified, whereas exposure to β-lactams (HAs) was negatively correlated with depression risk. In the participants aged > 70 years, no significant association between antibiotic exposure and depression was observed. Older elderly adults may pay more attention to food quality and safety or medication use than younger elderly adults, which may explain the lower intake of food contaminated by antibiotic residues or more prudent antibiotic use among younger elderly adults. Moreover, younger elderly adults may have a higher intake of animal-derived food containing residues of VAs and PVAs.

In general, our study reveals that VAs and PVAs from the environment and diet, as well as clinically used HAs, may have some connections with the development of psychiatric disorders in the elderly. However, excessive consumption of antibiotics leads to antibiotic selection pressure in the environment and the production of multi-drug resistance in the population, which is also a problem that we cannot ignore and worry about (Bungau et al. 2021). Long-term low-dose cumulative exposure and a high-dose antibiotic administration may be the reasons for the emergence of drug resistance (Bungau et al. 2021; Dinleyici et al. 2018), but these situations are more common in rural areas of China. It is worth noting that since our country rarely conducts laboratory culture and sensitivity testing in medical treatment, this will greatly reduce the accuracy of antibiotic treatment programs, resulting in prolonged disease treatment time and unnecessary use of antibiotics. Moreover, there is a big gap in the public awareness of rational drug use, lack of publicity and education about the safety of antibiotics and patients' non-compliance with medical advice and self-medication occurs from time to time (Chatterjee et al. 2018; Grigoryan et al. 2019). These have further promoted the development of antibiotic resistance. Therefore, multi-drug-resistant bacteria pose a danger to public health and require the government to take measures to regulate, reform the medical system and strengthen the public's knowledge of drug use in order to create a healthy environmental ecology and human ecosystem.

Limitations

This study had some limitations. First, because of its cross-sectional design, causal relationships between antibiotic exposure and depression could not be determined. Second, antibiotic use and residues differ widely by geographical area (Zhang et al. 2015), but the study population was from one city in one province of China. Thus, it may not represent China's general elderly population. However, the large sample size we used may support the generalizability of the findings. Finally, the majority of the detected antibiotics were characterized by relatively short biological half-lives. Thus, the antibiotic concentrations in spot urine samples may have varied greatly among participants.

Conclusion

Exposure to some antibiotics, such as sulfaclozine, azithromycin, tetracyclines and VAs, may increase the risk of depression in older adults. Sex- and age-specific associations were noted

between antibiotic exposure and depression, and most of the significant associations were found in women and participants aged 60–70 years. Given the cross-sectional design of this study, further epidemiological and experimental studies are warranted to explore these associations and their mechanisms, those both related and unrelated to gut microbiota. Considering that the incidence of depression is increasing yearly, recognizing the relationship between antibiotics and depression based on the standard use of antibiotics and identifying effective treatments for depression are essential tasks.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11356-021-12560-2.

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Author contribution Xinji Liu: formal analysis, data curation, writing—Original Draft. Jingjing Zhang: data curation, writing—review and editing. Kaiyong Liu: investigation, conceptualization, methodology, supervision. Yanru Sang: investigation, resources. Yitian Zhu: investigation, resources. Linsheng Yang: investigation, resources. Sufang Wang: investigation, resources. Jie Sheng: investigation, resources. Qunan Wang: investigation, resources. Dongmei Zhang: investigation, resources. Hongjuan Cao: investigation, resources. Fangbiao Tao: validation, conceptualization, supervision.

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Data availability The datasets generated during and analyzed during the current study are not publicly available due to the privacy of the research group, but are available from the corresponding author on reasonable request.

Compliance with ethical standards

Ethics approval and consent to participate All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Anhui Medical University (No. 20170284). Informed consent was obtained from all individual participants included in the study.

Consent for publication Patients signed informed consent regarding publishing their data and photographs

Competing interests The authors declare no competing interests.

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