Typical antibiotic exposure and dysglycemia risk in an elderly Chinese population

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Abstract
Studies examined the connection between antibiotic exposure in urine and dysglycemia risk (including prediabetes and diabetes) in the elderly were limited. Multiple linear regression, binary logistic regression, restricted cubic splines (RCS), and stratified analysis were applied to analyze the relationship between antibiotic exposure and dysglycemia risk. We observed that sulfaclozine exposure 0.07 (95% confidence interval [CI]: 0.01–0.23) significantly increased fasting blood glucose (FBG) level. By mechanism, usage, and antimicrobial action, sulfonamides 0.08 (95% CI: 0.06–0.36), veterinary antibiotics (VA) 0.07 (95% CI: 0.01–0.30), or bacteriostatic antibiotics 0.07 (95% CI: 0.02–0.29) significantly increased FBG level. Additionally, sulfaclozine exposure 1.54 (95% CI: 1.02–2.33) resulted in a higher dysglycemia risk, while doxycycline exposure 0.53 (95% CI: 0.30–0.95) resulted in a lower dysglycemia risk. By mechanism, usage, and antimicrobial action, sulfonamides 1.44 (95% CI: 1.02–2.04), VA 1.68 (95% CI: 1.21–2.35), or bacteriostatic antibiotics 1.40 (95% CI: 1.02–1.93) exposure had a higher dysglycemia risk. Taken together, exposure to sulfonamides, VA, especially sulfaclozine, was correlated with a higher dysglycemia risk in the elderly. Exposure to bacteriostatic antibiotics was associated with a higher dysglycemia risk in the female.

Keywords Biomonitoring · Urine · Antibiotics · Diabetes · Prediabetes · Elderly · Dysglycemia

Introduction
Diabetes is a metabolic disorder marked by an elevated blood glucose level as a result of decreased insulin sensitivity or insulin deficiency, which has become one of the prime causes of mortality and disability in the world (Vos et al. 2017). Prediabetes, characterized by a higher blood glucose level than normal that has not yet reached the diabetic level, is a precursor for the development of diabetes mellitus and approximately half of patients with prediabetes develop diabetes within 5 years (Mutie et al. 2020). Prediabetes can independently predict a patient’s progression from being normoglycemic to having diabetes (Wang et al. 2010). The prevalence of diabetes and prediabetes also has increased prominently in recent years, especially in developing countries (Mancini et al. 2018). It is estimated that the number of the diabetes was 537 million globally in 2021, and 80% of them were living in low-income and middle-income countries (Zhou et al. 2022; Maria et al. 2021; Teufel et al. 2021). In the mainland of China, a national cross-sectional study revealed the weighted prevalence of diabetes increased from
9.7 to 11.2% within a decade according to the WHO (World Health Organization) criteria and the prevalence of prediabetes also has risen from 12.8% in 2015 to 35.2% in 2017 according to the American Diabetes Association (ADA) criteria (Zhu et al. 2020).

In general, the etiology of diabetes encompasses genetic, behavioral, and environmental factors (Chin et al. 2018; International Diabetes Federation 2021). However, recent researches have suggested that composition and function of gut microbiota may also play a vital role in the development of diabetes (Clemmensen et al. 2017; Muller et al. 2020). Increasing evidence on experimental studies shows that the relationship between gut microbiota and diabetes is not just correlated, but causal (Blaser 2016). Furthermore, based on next-generation sequencing techniques, a growing body of studies has demonstrated that existing disparities of the gut microbiome between the normal and the diabetes (Alvarez-Silva et al. 2021; Doumatay et al. 2020; Zhang et al. 2020) and gut microbiota composition was strongly correlated with glucose metabolism, insulin secretion (Zhang et al. 2021), and insulin sensitivity (Shi et al. 2021). Mechanically, entero-endocrine cells (EEC), the vagus nerve (VN), and enteric neurons can recognize some vital gut microbiota metabolites, such as short chain fatty acids (SCFAs) and secondary biliary acids, which play vital roles in maintaining glucose homeostasis (Grasset and Burcelin 2019; Muller et al. 2020).

Antibiotics can disrupt gut microbiota and have multiple effects on host physiology, including effects on glucose homeostasis. An epidemiology study indicated the abundance of five Bifidobacterium members decreased in the stool samples of infants after antibiotic use and individuals with islet autoimmunity had higher abundance of Bifidobacterium species and higher serum glucose levels compared with the control group (Vatanen et al. 2018). In animals, mice treated with specific antibiotics in early life had higher incidence of type 1 diabetes by disrupting the gut microbiome than the control group (Livanos et al. 2016). Another experimental study revealed that chronically treating non-obese diabetic (NOD) mice with macrolides accelerated the development of type 1 diabetes early in life, and after transplanting the cecal contents from NOD mice to germ-free mice, similar effects were observed in the recipient mice (Zhang et al. 2018). Similar to hyperglycemia, hypoglycemia is known to be an infrequent serious adverse effect imposed by antibiotic exposure. An animal study showed that healthy mice exhibited a reduced fasting glucose concentration without weight change after treatment with individual (ampicillin, metronidazole, neomycin, vancomycin) or antibiotic cocktails (Rodrigues et al. 2017).

These diverse results indicated antibiotic exposure may be closely correlated to the risk of dysglycemia by altering gut microbiota composition. Mechanically, not only did some broad-spectrum antibiotics destroy harmful bacteria but also commensal bacteria and ultimately altered normal composition of gut microbiota. Therefore, increasing research attention has been paid to the profiles of altered gut microbiota caused by antibiotics and the subsequent health effects.

Aging has been demonstrated to be an inducing factor of abnormal glucose metabolism and regulation (Yu et al. 2019). Usually, gut microbiota of the elderly have decreased diversity and degenerative stability compared with younger adults (Cryan et al. 2019), which have been demonstrated to be one of the reasons of metabolic syndrome. In an experimental study on the transplantation of the microbes of young and old mice into germ-free mice, the result revealed that the mice who received the microbes from the older mice exhibited a distinct inflammatory response (Thevaranjan et al. 2017). Our previous study noted that the presence of trimethoprim, thiamphenicol, and lincomycin in urine indicated a microbiological-related health risk to 6.7% of older adults (Zhu et al. 2020). Further analysis confirmed that obesity in the elderly individuals was influenced by exposure to tetracyclines and fluoroquinolones, possibly through food (Sang et al. 2021). As such, further examination of the connection between antibiotic exposure and the risk of dysglycemia in the elderly population is necessary.

Given the aforementioned considerations, we quantified the levels of urinary antibiotics in approximately 1000 elderly in Lu’an, China, and further examined the association between antibiotics and the risk of dysglycemia. This is the first study to examine the dysglycemia risk of antibiotic exposure in elderly by means of a biomonitoring method.

Materials and methods

Study population

During the period of June to September 2016, in collaboration with the Lu’an Centers for Disease Control and Prevention, the Cohort of Elderly Health and Environment Controllable Factors was carried out in Lu’an Municipality, West Anhui, China. In this research, the data were from the baseline survey of the cohort. Two counties were selected randomly from West Anhui, China, by a stratified cluster sampling method. Subsequently, all subjects from two counties were randomly divided into a rural community and an urban community according to the administration partition. The participants were selected in accordance with the following inclusion criteria: (1) aged ≥ 60 years, (2) had lived at the study site for at least 6 months before the survey, (3) had no mental illness affecting normal communication, (4) signed an informed consent and voluntarily participated.
In the day before the field survey, 1217 individuals participated in a telephone appointment. Then, in the field investigation, 1080 participants completed a questionnaire and a relevant health examination approximately 2 to 3 h at the local hospital. Due to 59 urinary samples were not provided and 31 urinary creatinine data were lacking, 990 participants with complete data participated ultimately in the current analysis. Of them, 539 were females, 486 aged 60–70 years and 543 were from urban areas.

**Questionnaire survey and the assessment of covariates**

The questionnaire was self-designed and included questions on basic demographic characteristics (e.g., age, sex, residence), lifestyles (e.g., alcohol drinking status and eating habits) and the history of chronic diseases (e.g., hypertension, diabetes).

Each participant’s height and weight were measured using a mechanical height gage and lever scale, respectively. Drinking was ascertained as ≥ 1 drink in the past 30 days. Smoking was ascertained as continuous smoking or having a cumulative smoking history of ≥ 6 months. Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters. Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters. 

Deemed overweight; an individual with a BMI of 24.0 to 28.0 kg/m² was deemed normal; an individual with a BMI of 18.5 to 23.9 kg/m² was deemed underweight; an individual with a BMI of 18.5 to 23.9 kg/m² was deemed normal; an individual with a BMI of 24.0 to 28.0 kg/m² was deemed overweight; an individual with a BMI > 28.0 kg/m² was deemed obese (Sang et al. 2021). Waist circumference (WC) was determined by measuring the length of the highest point of the iliac crest (to the nearest 1 mm) at minimal respiration. WC ≥ 85 cm in men and ≥ 80 cm in women were defined as abnormal (Zhai et al. 2017). Hypertension was defined as SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg based on the 2010 Chinese guidelines for the management of hypertension (Liu 2011).

**Ascertainment of dysglycemia**

Given the close association of prediabetes and diabetes, the individuals with prediabetes or diabetes were combined to form the dysglycemia group for analyzing the association between antibiotic exposure and the risk of dysglycemia. According to WHO criteria, diabetes was ascertained as a FBG concentration ≥ 7 mmol/L, self-reported history, or active treatment with any hypoglycemic drug. Prediabetes was ascertained as a FBG concentration between 6.1 and 6.9 mmol/L (Huang et al. 2016; World Health Organization 2006).

**Collection of urine samples**

On the day of the health examination, morning urine samples of at least 30 mL were collected by participants and were provided to researchers at the local hospital. Details were described in our previous publications (Liu et al. 2021; Sang et al. 2021; Zhu et al. 2020).

**Antibiotic exposure assessment**

According to the detection frequency of antibiotics in animal-origin foods and in human urines (Du et al. 2019; Wang et al. 2017; Zhao et al. 2019), forty-five antibiotics and two antibiotics metabolites were measured. Urinary antibiotic concentrations were measured using the HPLC–MS/MS method, which had been developed and reported in our previous work (Zhu et al. 2020). Thirty-four antibiotics and two metabolites were detected, which included eight categories according to antimicrobial mechanism, namely macrolides, β-lactams, tetracyclines, fluoroquinolones, sulfonamides, phenicols, lincosamide, and quinoxaline, according to the usage, which were grouped into four categories, namely human antibiotics (HA), veterinary antibiotics (VA), preferred as human antibiotics (PHA) and preferred as veterinary antibiotics (PVA), according to the antibacterial type, which were classified into two categories, namely broad-spectrum and narrow-spectrum, according to the antimicrobial action, which were classified into two categories, namely bactericidal and bacteriostatic. The antibiotic concentrations were corrected by urinary creatinine concentration.

**Statistical analysis**

The distribution of FBG in individuals with varied demographic characteristics and dysglycemia-related risk factors was analyzed by Student’s t-test and F-test. The median, quartile, and maximum concentrations of antibiotics were separately provided to describe the exposure status of antibiotic in the elderly. The detection frequency and the distribution of antibiotics concentrations were provided to analyze the disparity of exposure level between the normoglycemic and the dysglycemia by Kruskal–Wallis test. The multiple linear regression analysis was used to determine whether a dose–response relationship exists between the logarithmically transformed antibiotic concentrations and FBG levels. A binary logistic regression model was fitted to characterize the association of antibiotic concentrations and the risk of dysglycemia, and the urinary antibiotic concentrations below the limits of detection (LODs) were replaced with LODs/2 (Geng et al. 2020). The antibiotic concentrations were divided into three groups: tertile 1 (a concentration less than the 33rd percentile) as the reference group, tertile
2 (a concentration between the 33rd and the 66th percentile) with a low exposure level, tertile 3 (a concentration more than the 66th percentile) with a high exposure level. Model A was adjusted for age and sex and model B was adjusted for age, sex, education, BMI, WC, alcohol drinking status, smoking, consumption of sugar, family history of diabetes, hypertension, low-density lipoprotein cholesterol (LDL-C) levels, and triglyceride (TG) levels. Of these variables, age, BMI, WC, hypertension, LDL-C levels, and TG levels were adjusted as continuous variables, and the others were adjusted as categorical variables. Furthermore, a stratified analysis by sex was performed. In addition, in order to characterize the dose–response curve of the association of antibiotic concentrations and the risk of dysglycemia, the restricted cubic splines were applied by modeling the antibiotic concentrations with 4 knots. All statistical analyses were conducted by SPSS software (version 23.0, Chicago, IL, USA), and dose–response curves and forest plots were visualized using R software (version 4.1.0). P < 0.05 was considered to reveal a significance in statistics.

### Results

#### Characteristics of the study population

The general demographic characteristics in relation to FBG level are presented in Table 1. Compared to the males, the female participants had higher FBG levels and the participants whose education level did not extend beyond high school had higher average FBG levels than those with more extensive education. Those with higher BMI, higher WC, certain chronic illnesses such as hypertension and dyslipidemia, and the people with family history of diabetes also had higher FBG levels. The participants who drank alcohol had higher FBG levels than those who did not.

#### Detection frequencies and concentrations of antibiotics

In this study, the total detection frequency reached up to 93% and among 34 individual antibiotics, detection frequencies varied between 0.2% (thiamphenicol) and 35.5% (sulfaclozine), and 12 antibiotics detection frequency was > 10% (Table S1). By mechanism and usage, sulfonamides and PVA had the highest detection frequencies. By antibacterial type and antimicrobial action, broad-spectrum and bacteriostatic antibiotics had higher detection frequencies. Detection frequencies and concentration distribution of the 34 antibiotics in the subjects with normoglycemic and with dysglycemia are presented in Fig. 1. As could be seen from the results, the antibiotic exposure levels in most subjects with normoglycemic ranged from 5 to 10 µg/g, and the detection frequency was 19.7%. However, among the subjects with dysglycemia, the antibiotic exposure level was between 10 and 20 µg/g, and the detection frequency was 19.2%. And frequencies and concentration distribution of 34 antibiotics in the subjects with normoglycemic, prediabetes, or diabetes are presented in Fig. S1. And the detection

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**Table 1** Fasting blood glucose (FBG) in relation to demographic variables and dysglycemia-related risk factors

| Variables                        | N  | FBG (mmol/L)± | P-value
|----------------------------------|----|--------------|---------
| Age (years)                      |    |              |         |
| 60–70                            | 486| 6.27±1.74    | 0.400   |
| >70                              | 504| 6.17±1.71    |         |
| Gender                           |    |              |         |
| Male                             | 451| 6.09±1.76    | 0.028   |
| Female                           | 539| 6.33±1.69    |         |
| Education                        |    |              |         |
| High school and below            | 956| 6.23±5.82    | 0.009   |
| College and above                | 34 | 5.84±5.78    |         |
| BMI                              |    |              |         |
| Underweight                      | 54 | 5.62±1.14    | <0.001  |
| Normal                           | 432| 6.11±1.70    |         |
| Overweight                       | 357| 6.17±1.52    |         |
| Obesity                          | 147| 6.89±2.20    |         |
| Waist circumstance               |    |              |         |
| Normal                           | 316| 5.87±1.53    | <0.001  |
| Abnormal                         | 674| 6.38±1.79    |         |
| Alcohol drinking status          |    |              |         |
| No                               | 619| 6.29±1.83    | 0.080   |
| Yes                              | 371| 6.10±1.54    |         |
| Smoking                          |    |              |         |
| No                               | 800| 6.26±1.68    | 0.717   |
| Yes                              | 114| 6.20±1.88    |         |
| Consumption of sugar             |    |              |         |
| Low                              | 620| 6.44±1.89    | <0.001  |
| General                          | 259| 5.87±1.37    |         |
| High                             | 111| 5.83±1.25    |         |
| Family history of diabetes       |    |              |         |
| No                               | 919| 6.18±1.72    | 0.005   |
| Yes                              | 71 | 6.77±1.78    |         |
| Hypertension                     |    |              |         |
| No                               | 488| 6.03±1.55    | <0.001  |
| Yes                              | 502| 6.40±1.86    |         |
| LDL-C (mmol/L)                   |    |              |         |
| LDL-C ≤4.1                       | 839| 6.15±1.64    | 0.020   |
| LDL-C >4.1                       | 151| 6.58±2.11    |         |
| TG (mmol/L)                      |    |              |         |
| TG <2.3                          | 793| 6.07±1.54    | <0.001  |
| TG ≥2.3                          | 197| 6.82±2.24    |         |

*Mean±standard deviation. *P-value by Student’s t-test or F test. BMI, body mass index; LDL-C, low density lipoprotein cholesterol; TG, triglyceride
frequencies of the 12 antibiotics with a > 10% detection frequency in the elderly with normoglycemic, prediabetes or diabetes is displayed in Fig. S2. In addition, concentration distributions of 34 antibiotics and their detection frequencies in the participants with dysglycemia are displayed in Table S1. Notably, among the 12 antibiotics with a detection frequency of > 10%, the median concentration of ciprofloxacin was higher in the participants with dysglycemia than in those with normoglycemic (P = 0.049), as revealed by Kruskal–Wallis test analysis. Although no significant disparity for other antibiotics existed, the median of antibiotic concentrations of participants with normoglycemic was lower than those with dysglycemia for most antibiotics. By mechanism, the participants with normoglycemic had a lower concentration of sulfonamides than those with dysglycemia. Subsequently, the concentration distributions of the 34 antibiotics among the elderly with normoglycemic, prediabetes, or diabetes are displayed in Table S2, where the median concentration of trimethoprim was higher in the diabetes than in those with the normoglycemic. Likewise, the disparity was nonsignificant in statistics, but among the 12 antibiotics with a > 10% detection frequency, 8 antibiotics had higher median concentrations in the prediabetes or the diabetes than that in the participants with normoglycemic. Furthermore, the detection frequencies and concentration distributions of antibiotics by usage are presented in Tables S3 and S4, respectively, and the disparity of the concentration distributions of VA was significant between the normoglycemic and the prediabetes (P = 0.012). A nonsignificant disparity was noted between the detection frequency and concentration distributions of antibiotics by antibacterial type and antimicrobial action, as presented in Tables S5 and S6, respectively, and broad-spectrum, narrow-spectrum, and bacteriostatic antibiotics had higher median concentrations in the prediabetes or the diabetes than that in the participants with normoglycemic.

**Association of exposure to antibiotics with dysglycemia risk**

Table 2 shows the relationships between antibiotic concentrations and FBG levels. Multiple linear regression analysis indicated sulfaclozine had a positive linear correlation with FBG levels after all the confounding factors were adjusted (β = 0.07, 95% CI: 0.01–0.23). Furthermore, by mechanism, usage, and antimicrobial action, sulfonamides (β = 0.08, 95% CI: 0.06–0.36), VA (β = 0.07, 95% CI: 0.01–0.30), and bacteriostatic antibiotics (β = 0.07, 95% CI: 0.02–0.29) presented positive linear correlations with FBG levels.

As presented in Table 3, binary logistic regression analysis indicated that the elderly with high levels of sulfaclozine, compared to the reference, had a higher risk of dysglycemia (tertile 3: 1.54 [95% CI: 1.02–2.33]) in model B, and those with exposure to low levels of doxycycline had a lower risk of dysglycemia (tertile 2: 0.52 [95% CI: 0.30–0.92]). Notably, the effect still existed after adjusting for other confounding factors in model B (tertile 2: 0.53 [95% CI: 0.30–0.95]). By mechanism and usage, binary logistic regression analysis unfolded that the elderly exposed to higher levels of sulfonamides had a higher risk of dysglycemia compared with the reference group (tertile 3: 1.44 [95% CI: 1.02–2.04]). Additionally, exposure to high concentration of VA also increased the risk of dysglycemia compared with the reference group (tertile 3: 1.68 [95% CI: 1.21–2.35]). By antimicrobial action, exposure to high concentration of bacteriostatic also increased the risk of dysglycemia compared with the reference group (tertile 3: 1.40 [95% CI: 1.02–1.93]). These effects did not disappear after adjustment for more confounding factors. As illustrated in Fig. S3, the RCS indicated that no nonlinear associations existed between the antibiotic exposure level and the odds ratio (OR) of dysglycemia, and we could observe an increased tendency of OR.
Table 2  Multiple linear analysis of antibiotic exposure levels and FBG

| Antibiotics        | Model A       | Model B       |
|--------------------|---------------|---------------|
| **Individual**     |               |               |
| Azithromycin       | 0.06(0.01, 0.44)* | 0.05(−0.04, 0.38)* |
| Sulfaclozine       | 0.05(−0.30, 0.20) | 0.07(0.01, 0.23)* |
| Trimethoprim       | 0.15(0.01, 0.56)* | 0.02(−0.12, 0.20) |
| Oxytetracycline    | −0.03(−0.26, 0.08) | −0.03(−0.24, 0.09) |
| Tetracycline       | −0.05(−0.37, 0.05) | −0.04(−0.33, 0.08) |
| Doxycycline        | 0.00(−0.26, 0.22) | 0.01(−0.27, 0.19) |
| Ofloxacin          | −0.02(−0.17, 0.10) | −0.02(−0.16, 0.10) |
| Enrofloxacin       | 0.06(−0.02, 0.40) | 0.03(−0.09, 0.32) |
| Ciprofloxacin      | 0.03(−0.08, 0.21) | 0.01(−0.12, 0.16) |
| Norfloxacin        | −0.04(−0.21, 0.04) | −0.06(−0.24, 0.00) |
| Penicillin V       | −0.06(−0.05, −0.00)* | −0.05(−0.41, 0.03) |
| Florfenicol        | −0.03(−0.21, 0.08) | −0.03(−0.21, 0.07) |
| **Category**       |               |               |
| Sulfonamides       | 0.07(0.02, 0.33)* | 0.08(0.06, 0.36)* |
| Macrolides         | 0.02(−0.14, 0.25)* | 0.02(−0.15, 0.24) |
| β-Lactams          | −0.01(−0.26, 0.17) | 0.00(0.20, 0.21) |
| Tetracyclines      | 0.02(−0.22, 0.13) | −0.01(−0.21, 0.14) |
| Fluoroquinolones   | −0.01(−0.14, 0.10) | −0.03(−0.17, 0.06) |
| Chloramphenicol    | 0.05(−0.06, 0.60) | 0.06(0.02, 0.60) |
| **Usage**          |               |               |
| VA                 | 0.06(0.00, 0.29)* | 0.07(0.01, 0.30)* |
| PVA                | −0.02(−0.18, 0.08) | −0.03(−0.19, 0.07) |
| HA                 | 0.04(−0.06, 0.24) | 0.06(0.01, 0.28) |
| PHA                | −0.04(−0.25, 0.07) | 0.03(−0.24, 0.08) |
| **Antibacterial type** |           |               |
| Broad-spectrum     | 0.03(−0.07, 0.17) | 0.03(−0.06, 0.18) |
| Narrow-spectrum    | −0.06(−0.45, −0.00)* | −0.05(−0.41, 0.03) |
| **Antimicrobial action** |         |               |
| Bactericidal       | −0.02(−0.17, 0.08) | −0.03(−0.19, 0.06) |
| Bacteriostatic     | 0.05(−0.02, 0.26)* | 0.07(0.02, 0.29)* |

The association between 1-unit increase in logarithmic transformation of 12 individual antibiotics that detection frequency > 10% and fasting blood glucose was elaborated in the table; antibiotics were divided into different classes based on the mechanism, usage, antibacterial type and antimicrobial action, the association between 1-unit increase in logarithmic transformation of antibiotic exposure levels and fasting blood glucose was also shown in this table. Of 8 categories, because of the low detection frequency of lincosamides and quinolamines, the result of multiple linear regression analysis may inaccurate, the results were not shown in the table. Model A: adjusted for age, gender. Model B: adjusted for age, gender, education, BMI, WC, alcohol drinking status, smoking, consumption of sugar, family history of diabetes, hypertension, LDL-C, TG, FBG, fasting blood glucose; HA, human antibiotic; VA, veterinary antibiotic; PHA, antibiotic preferred as HA; PVA, antibiotic preferred as VA. β coefficients (95% confidence interval). *P-value <0.05

for sulfaclozine and also a decreased tendency of OR for doxycycline with the increasing of corresponding antibiotic concentration.

Discussion

The participants in our study had a diabetes prevalence of 20.8%, similar to that (18.8%) in the report of the International Diabetes Federation (IDF) (Sinclair A et al. 2020) and that (19.7% for 60–69-year-old people, 21.4% for 70-year-old people) in a national cross-sectional study (Zhu et al. 2020). In addition, the detection frequency of antibiotics, 93% in our study, is higher than that in school children (79.6%) in Shanghai (Wang H et al. 2016), in adults in Shanghai (45.9%) (Wang et al. 2018), and in children and pregnant women (38.6%) in Jiangsu (Zhou et al. 2021). This is the first study to investigate the association of antibiotic exposure levels of the elderly and the risk of dysglycemia by biomonitoring.

In our study, a total of 34 antibiotics were detected among the elderly. We determined that exposure to sulfaclozine was positively related to an increased risk of dysglycemia. By mechanism, usage and antimicrobial action, exposure to sulfonamides, VA, or bacteriostatic antibiotics was positively related to the elevated risk of dysglycemia, too. Notably, these associations still existed after adjustment for demographic factors, family history of diabetes, lifestyle factors, and other confounding factors. Sulfaclozine, as one of the sulfonamides, was widely applied for antibacterial and anticoccidial feed additives in animal husbandry (Sentepe and Eraslan 2010; Yamaguchi et al. 2015). Therefore, sulfaclozine residues were frequently detected in animal foods as well. A study from Vietnam detected high levels of sulfonamides residues, and the detection concentration ranged from 2 500 to 2 700 µg/kg in chicken and pork samples (Yamaguchi et al. 2015). Sheridan et al. demonstrated that sulfaclozine was often detected in chicken jerky dog treats (Sheridan et al. 2014). Generally, through the food chain, sulfaclozine was finally consumed by humans. A case–control study indicated that sulfonamides exposure was related to the risk of diabetes (OR = 1.15, 95% CI: 1.13–1.17) (Mikkelsen et al. 2015). A cohort study revealed that a 100-mg

Association of antibiotic exposure with dysglycemia risk by gender

The participants were stratified by sex, and subsequently, the association of exposure to antibiotics with dysglycemia risk was analyzed by binary logistic regression. The results showed that a lower risk of dysglycemia for lower exposure level of doxycycline in men (tertile 2: 0.24 [95% CI: 0.08–0.74]), but not in women. By the antimicrobial action, exposure to high concentration of bacteriostatic led to a higher risk of dysglycemia in women, but not in men and an association was noted between a high exposure level of VA and a risk of dysglycemia, regardless of sex (Figs. S4–S6).
An increase in the mean daily dose of sulfonamides antibiotic, the risk of diabetes increased by 1.05 \( (HR = 1.05, \ 95\% CI: 1.02–1.08) \) among veterans (Davis et al. 2019). These results demonstrated a positive relationship between sulfonamides exposure and the risk of diabetes. Mechanically, a study demonstrated that *Drosophila melanogaster* exposed to sulfamethoxazole (a sulfonamides antibiotic) disturbed glucolipid metabolism, altered profile of intestinal microbiota, and increased proportion of *Firmicutes*. (Yu et al. 2020). And in humans, more than 90% of gut microbiota are composed of *Firmicutes* and *Bacteroidetes* (Qin et al. 2010), and the *Firmicutes/Bacteroidetes* (F/B) ratio is associated with low-grade inflammation and many metabolic diseases, particularly obesity and diabetes (Pascale et al. 2019). However,

| Antibiotics         | Dysglycemia vs normoglycemic | Model A | Model B |
|---------------------|-----------------------------|---------|---------|
|                     | Tertile1 | Tertile2 | Tertile3 | Tertile1 | Tertile2 | Tertile3 |
| Individual          |          |          |          |          |          |          |
| Azithromycin        | Ref      | 1.90(1.13, 3.20)\(^a\) | 1.48(0.87, 2.51)\(^a\) | Ref      | 1.58(0.91, 2.72) | 1.45(0.83, 2.53) |
| Sulfadiazine        | Ref      | 1.19(0.80, 1.77) | 1.41(0.95, 2.09) | Ref      | 1.20(0.79, 1.82) | 1.54(1.02, 2.33) |
| Trimethoprim        | Ref      | 1.09(0.65, 1.81) | 1.37(0.83, 2.27) | Ref      | 1.04(0.61, 1.77) | 1.30(0.77, 2.19) |
| Oxytetracycline     | Ref      | 0.77(0.45, 1.32) | 1.05(0.62, 1.78) | Ref      | 0.78(0.45, 1.36) | 1.03(0.60, 1.77) |
| Tetracycline        | Ref      | 1.08(0.64, 1.89) | 0.86(0.51, 1.45) | Ref      | 1.04(0.61, 1.78) | 0.95(0.55, 1.65) |
| Doxycycline         | Ref      | 0.52(0.30, 0.92)\(^a\) | 0.91(0.53, 1.56) | Ref      | 0.53(0.30, 0.95)\(^a\) | 0.84(0.48, 1.47) |
| Ofloxacin           | Ref      | 1.03(0.64, 1.63) | 0.86(0.53, 1.39) | Ref      | 1.01(0.63, 1.63) | 0.85(0.51, 1.41) |
| Enrofloxacin        | Ref      | 1.26(0.63, 2.52) | 1.88(0.93, 3.79) | Ref      | 1.22(0.59, 2.51) | 1.64(0.79, 3.40) |
| Cefpodoxime         | Ref      | 1.03(0.59, 1.81) | 1.40(0.80, 2.44) | Ref      | 1.05(0.58, 1.89) | 1.19(0.67, 2.11) |
| Norfloxacine        | Ref      | 0.71(0.36, 1.40) | 0.67(0.34, 1.33) | Ref      | 0.60(0.29, 1.22) | 0.65(0.32, 1.33) |
| Penicillin V         | Ref      | 0.93(0.54, 1.59) | 1.02(0.60, 1.76) | Ref      | 0.97(0.55, 1.70) | 1.02(0.58, 1.80) |
| Florfenicol          | Ref      | 0.69(0.42, 1.13) | 1.07(0.67, 1.70) | Ref      | 0.67(0.40, 1.12) | 1.15(0.69, 1.90) |
| Category             |          |          |          |          |          |          |
| Sulfonamides        | Ref      | 1.06(0.75, 1.48)\(^a\) | 1.42(1.02, 1.97)\(^a\) | Ref      | 1.10(0.77, 1.56) | 1.44(1.02, 2.04) |
| Macrolides          | Ref      | 0.79(0.52, 1.22) | 0.74(0.41, 1.31) | Ref      | 0.92(0.59, 1.44) | 0.83(0.46, 1.52) |
| β-Lactams           | Ref      | 1.24(0.76, 1.95) | 0.88(0.56, 1.40) | Ref      | 1.36(0.84, 2.19) | 0.97(0.60, 1.57) |
| Tetracyclines       | Ref      | 1.05(0.73, 1.50) | 0.92(0.64, 1.32) | Ref      | 1.02(0.70, 1.50) | 0.91(0.63, 1.32) |
| Fluoroquinolones    | Ref      | 0.81(0.57, 1.16) | 1.20(0.85, 1.69) | Ref      | 0.74(0.51, 1.07) | 1.06(0.74, 1.52) |
| Chloramphenicol     | Ref      | 0.67(0.41, 1.08) | 1.12(0.71, 1.76) | Ref      | 0.68(0.41, 1.12) | 1.22(0.76, 1.97) |
| Usage               |          |          |          |          |          |          |
| VA                  | Ref      | 0.91(0.65, 1.26) | 1.67(1.21, 2.30)\(^a\) | Ref      | 0.92(0.65, 1.29) | 1.68(1.21, 2.35) |
| PVA                 | Ref      | 0.95(0.70, 1.30) | 0.90(0.62, 1.29) | Ref      | 0.97(0.70, 1.35) | 0.86(0.59, 1.26) |
| HA                  | Ref      | 0.91(0.58, 1.42) | 0.97(0.54, 1.76) | Ref      | 1.03(0.64, 1.64) | 1.22(0.66, 2.28) |
| PHA                 | Ref      | 1.06(0.70, 1.61) | 0.98(0.64, 1.48) | Ref      | 1.09(0.70, 1.69) | 0.99(0.64, 1.53) |
| Antibacterial type  |          |          |          |          |          |          |
| Broad-spectrum      | Ref      | 0.75(0.55, 1.03) | 1.23(0.91, 1.66) | Ref      | 0.72(0.52, 1.00)\(^a\) | 1.19(0.87, 1.64) |
| Narrow-spectrum     | Ref      | 0.93(0.54, 1.59) | 1.02(0.60, 1.76) | Ref      | 0.97(0.55, 1.70) | 1.02(0.58, 1.80) |
| Antimicrobial action|          |          |          |          |          |          |
| Bactericidal       | Ref      | 1.04(0.74, 1.45) | 1.15(0.83, 1.59) | Ref      | 0.98(0.70, 1.39) | 1.01(0.72, 1.43) |
| Bacteriostatic      | Ref      | 0.75(0.55, 1.03) | 1.33(0.98, 1.80) | Ref      | 0.75(0.54, 1.04) | 1.40(1.02, 1.93) |

The association between 12 individual antibiotics (detection frequency >10%) concentration and dysglycemia risk was shown in this table; antibiotics were divided into different classes based on the mechanism, usage, antibacterial type and antimicrobial action, the relationship between antibiotics exposure levels and dysglycemia risk was analyzed. Of 8 categories, because of the low detection frequency of lincosamides and quinoxalines, the result of logistic regression analysis may inaccurate; the results were not shown in the table. And antibiotics concentration was divided into three groups based on its concentration. Tertile 1: antibiotics concentration \( \leq P_{33} \); tertile 2: antibiotics concentration ranged from \( P_{33}-P_{66} \); tertile 3: antibiotics concentration \( >P_{66} \). Model A: adjusted for age, gender. Model B: adjusted for age, gender, education, BMI, WC, alcohol drinking status, smoking, consumption of sugar, family history of diabetes, hypertension, LDL-C, TG. HA, human antibiotic; VA, veterinary antibiotic; PHA, antibiotic preferred as HA; PVA, antibiotic preferred as VA. \(^a\)Odds ratio (95% confidence interval). \(^*\)P-value <0.05.
a variety of researches have revealed that the effect of lower blood glucose of sulfonamides (Demir and Koksal 2020),
and our previous study found that in the maternal mice exposed to high-dose sulfamonomethoxine, their female offspring mice had a lower concentration of blood glucose and their male offspring mice had a higher serum insulin level on postnatal day (PND) 22 (Zhang et al. 2017). Clinically, some sulfonamide drugs are employed to treat diabetes and its complications (National Institute of Diabetes and Digestive and Kidney Diseases 2012). But it is worth noting that recent researches have indicated that more sulfonamide use may result in the chronic hyperglycemia, damage to the pancreas and hyperinsulinemia (Frederico et al. 2017), and the hyperinsulinemia has been demonstrated to induce diabetes by disturbing the balance of the insulin-GH-IGF axis (Janssen 2021) (growth hormone [GH], insulin-like growth factor-I [IGF-1]). Therefore, we speculated these inconsistent results might be attributed to greater stimuli to pancreas by sulfonamide antibiotics, which further induced damage of pancreas and subsequent chronic hyperglycemia.

However, a negative correlation between exposure to doxycycline within a certain concentration range and the risk of dysglycemia was observed in this study. Research has discovered the serum matrix metalloproteinase-8 (MMP-8) levels increased in obese individuals, and MMP-8 could degrade human insulin receptor (INSR), while doxycycline could inhibit the cleavage of INSR by MMP-8 (Lauhio et al. 2016). An animal study has revealed that treated mice with doxycycline in sub-antimicrobial concentrations had a decrease in FBG level and an improvement in glucose tolerance (Chen et al. 2021). Mechanically, a low-dose of tetracyclines could generate an anti-inflammatory effect, but the composition of gut microbiota was not affected (Schaller 2017), wherein the negative correlation of doxycycline (one of tetracyclines) and the risk of dysglycemia might be partly explained by the its anti-inflammatory effect.

In very recent years, increasing evidence has indicated the relationship between antibiotics and the risk of diabetes could be explained by the effect of antibiotics on gut microbiota. Some antibiotics could increase the abundance of gram-negative bacteria (Hiippala et al. 2018). As well-known, the lipopolysaccharide (LPS) from gram-negative bacteria has been demonstrated to induce intestinal inflammation and followed by systematic low-grade inflammation, finally resulting in diabetes (Henschel et al. 2018; Wen and Duffy 2017). The levels of microbiome-derived metabolites, which are of great significance to the host, might be altered because of the altered gut microbiota profile after the use of antibiotics (Bejaoui and Poulsen 2020). For example, SCFAs, which are produced by the fermentation of dietary fibers by gut microbiota, play crucial roles in regulating the host immunity function, anti-inflammation, energy balance, and glucose metabolism (Yao et al. 2020). Another research revealed that after pregnant non-obese diabetic mice were treated with vancomycin, their gut microbiota profile was changed, and immune homeostasis was disrupted, and the diabetes type 1 offspring model was established. In addition, this research revealed that the degree of insulitis or the incidence of diabetes was lower in the offspring from the dams treated with vancomycin and butyrate than that in their mothers treated with only vancomycin (Jia et al. 2020). The result indicated some SCFAs could ameliorate diabetes symptoms driven by antibiotics. In our study, a positive association of sulflofoxazole exposure and the risk of dysglycemia observed; we speculated that sulflofoxazole exposure might decrease the number of certain beneficial gut microbiota and induce an altered gut microbiota profile, consequently cause diabetes. However, some antibiotics could decrease the diversity of diabetic bacteria and improve the situation of the diabetes. Lv et al. indicated that after treating diabetic mice with metronidazole, neomycin, and vancomycin, the abundance of Bifidobacterium increased, and the effects of Mesenchymal stem cell (MSC) transplantation to treat type 1 diabetes mellitus improved (Lv et al. 2020).

Also, we found that exposure to low-dose doxycycline decreased the risk of dysglycemia in men, but not in women. Probably, exposure to sub-inhibitory concentration of doxycycline primarily plays an anti-inflammatory effect rather than an anti-bactericidal effect (Chen et al. 2021; Schaller 2017). We also found that with exposure to high concentration of bacteriostatic, the dysglycemia risk increased in women, but not in men. A study had revealed that exposure to bacteriostatic might increase the risk of diabetes type 2 (Mikkelsen et al. 2015). In addition, some animal and human studies have noted disparities in gut microbiota composition between men and women by antibiotics. An animal study revealed that the different abundance of gut microbiota between male and female was observed (Org et al. 2016). Furthermore, another research indicated that the effect of antibiotics on gut microbiota composition was associated with sex (Gao et al. 2019). Therefore, we speculated that the disparity in the association of bacteriostatic exposure with the risk of dysglycemia by sex might result from the various effects of antibiotics on gut microbiota. In addition, we revealed that a positive association of exposure to VA with the risk of diabetes regardless of sex. Qian et al. revealed that exposure to some VA (doxycycline, oxytetracycline, and florfenicol) could change the gut microbiota profiles of zebrafish and could induce the glycolipid metabolism disorder (Qian et al. 2021).

One of the strengths in our study is the first study examined the effects of urinary antibiotics in an elderly population and uncovered the association between antibiotics exposure and dysglycemia risk. In addition, 34 antibiotics were measured in our study, covering the antibiotics used widely in humans and animals. What’s more, we focused on
the prediabetes and we combined the prediabetes and the diabetes into one study group to access, which contributed to assess the risk of dysglycemia effectively and benefited to promote the advance of the prevention gate. However, some inevitable limitations existed in our study. First, as a cross-sectional study, the causal relationship of antibiotic exposure levels with the risk of diabetes could not be confirmed, but we provided an evidence that antibiotics were a factor of dysglycemia. Second, some potential confounding factors were not included in our study, but traditional diabetes risk factors were included in our study. Third, diet can affect the antibiotics exposure level, but diet factors included in our study were limited.

**Conclusion**

We firstly investigated the associations of antibiotic exposure and the risk of dysglycemia among an elderly population by biomonitoring. A positive association between exposure to sulfaclozine and the risk of dysglycemia and a negative association between exposure to doxycycline and the risk of dysglycemia were observed in this study. By mechanism, usage, and antimicrobial action, we found the association between exposure to sulfonamides, VA, or bacteriostatic antibiotics and a higher risk of dysglycemia. To determine the causal relationships and elucidate the potential mechanisms between antibiotics exposure and the risk of dysglycemia, further researches were required.

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**Author contribution** SY contributed to formal analysis, data curation, and writing. KL, LG, YZ, XL, YS, QW, SW, DZ, and HC contributed to investigation and resources. KL contributed to investigation, conceptualization, methodology, and supervision. FT contributed to validation, conceptualization, and supervision.

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

**Code availability** The software has been licensed.

**Declarations**

**Ethics approval** 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.

**Consent to participate** 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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