Supporting Information

Typical antibiotic exposure and dysglycemia risk in an elderly Chinese population

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Table S1 Detection frequency and concentration (μg/g) of antibiotics in the elderly with normoglycemic or dysglycemia.

Antibiotics	Usage	All (N=990)	Normoglycemic (n=574)			Dysglycemia (n=416)			*P*-value [e]
		N (%) [a]	n (%) [a]	$P_{50}(P_{25}, P_{75})$	Maximum	n (%) [a]	$P_{50}(P_{25}, P_{75})$	Maximum	
Sulfonamides [b]		552(55.8)	314(54.7)	3.98(1.50, 9.10)	51770.05	238(57.2)	5.21(1.79, 11.94)	14301.41	0.043
Sulfamethoxazole	PVA	26(2.6)	13(2.3)	2.21(0.61, 35.09)	21964.17	13(3.1)	6.35(1.79, 71.99)	8612.11	0.204
Sulfaclozine	VA	351(35.5)	197(34.3)	5.77(3.48, 12.75)	680.56	154(37.0)	6.96(3.89, 13.53)	190.06	0.115
Trimethoprim [d]	PVA	201(20.3)	115(20.0)	0.37(0.20, 1.59)	29803.34	86(20.7)	0.51(0.28, 1.68)	10572.11	0.159
Sulfamethazine	VA	6(0.6)	2(0.3)	0.76(0.62, -)	0.91	4(1.0)	3.45(1.98, 5.46)	5.91	0.133
Sulfadiazine	PVA	28(2.8)	19(3.3)	1.32(0.95, 3.63)	5.30	9(2.2)	0.77(0.39, 2.24)	120.19	0.530
Sulfachloropyridazine	VA	45(4.5)	29(5.1)	0.74(0.39, 1.45)	4.66	16(3.8)	1.30(0.37, 6.09)	28.71	0.162
Sulfamonomethoxine [c]	VA	65(6.6)	39(6.8)	1.33(0.77, 2.91)	68.61	26(6.3)	1.51(0.58, 3.65)	39.46	0.851
Macrolides [b]		282(28.5)	153(26.7)	0.24(0.07, 1.40)	4966.18	129(31.0)	0.22(0.08, 1.34)	1682.54	0.847
Erythromycin	PHA	85(8.6)	53(9.2)	1.43(0.58, 3.34)	4965.25	32(7.7)	2.75(0.95, 9.58)	25.43	0.080
Clarithromycin	HA	27(2.7)	14(2.4)	0.14(0.08, 0.42)	1.67	13(3.1)	0.20(0.11, 0.36)	4.26	0.650
Azithromycin	HA	180(18.2)	89(15.5)	0.10(0.05, 0.28)	33.34	91(21.9)	0.12(0.07, 0.31)	981.49	0.225
Roxithromycin	HA	27(2.7)	18(3.1)	0.19(0.06, 0.68)	1413.46	9(2.2)	0.14(0.09, 152.62)	1661.98	0.820
β-Lactams [b]		253(25.6)	146(25.4)	1.64(0.65, 4.93)	13520.02	107(25.7)	1.56(0.66, 3.18)	10876.13	0.836
Cefaclor	HA	3(0.3)	1(0.2)	1.67 [f]	1.67	2(0.5)	5.71(1.82, -)	9.60	1.000
Cefotaxime	HA	8(0.8)	5(0.9)	12.88(5.79, 23.61)	24.00	3(0.7)	1.60(0.64, -)	9.75	0.143
Penicillin V	PHA	176(17.8)	104(18.1)	1.11(0.62, 2.55)	163.63	72(17.3)	1.35(0.61, 2.46)	36.40	0.971
Amoxicillin	PHA	77(7.8)	42(7.3)	2.46(0.71, 25.55)	13520.02	35(8.4)	2.01(0.58, 31.26)	10876.13	0.751
Tetracyclines [b]		440(44.4)	263(45.8)	1.25(0.58, 2.98)	30574.33	177(42.5)	1.45(0.58, 2.80)	18666.88	0.757
Oxytetracycline	PVA	187(18.9)	111(19.3)	0.65(0.38, 1.86)	30168.85	76(18.3)	0.76(0.36, 2.03)	18221.93	0.974
Chlortetracycline	PVA	77(7.8)	47(8.2)	1.21(0.62, 4.41)	906.36	30(7.2)	1.35(0.85, 4.54)	28.71	0.715
Tetracycline	PVA	193(19.5)	123(21.4)	0.82(0.45, 2.30)	1042.67	70(16.8)	1.00(0.58, 1.99)	364.61	0.344
Doxycycline	PVA	182(18.4)	109(19.0)	0.98(0.57, 2.07)	29.26	73(17.5)	0.74(0.41, 1.63)	80.34	0.097
Fluoroquinolones [b]		495(50.0)	281(49.0)	2.97(0.77, 13.64)	179829.84	214(51.4)	3.15(0.57, 13.15)	21865.36	0.557
Pefloxacin	PVA	40(4.0)	18(3.1)	4.73(2.51, 8.81)	342.50	22(5.3)	1.49(0.78, 2.09)	26.21	<0.001
Lomefloxacin	PVA	14(1.4)	8(1.4)	0.85(0.19, 1.34)	3656.44	6(1.4)	2.89(0.47, 44.15)	108.36	0.414
Danofloxacin	VA	40(4.0)	16(2.8)	10.45(2.72, 45.00)	158397.90	24(5.8)	8.03(3.43, 16.36)	33.79	0.557
Sarafloxacin	VA	16(1.6)	13(2.3)	0.35(0.16, 0.62)	2.30	3(0.7)	0.15(0.05, -)	214.82	0.704

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Table S1. Continued

Ofloxacin	PVA	235(23.7)	135(23.5)	0.84(0.33, 3.37)	113.95	100(24.0)	0.55(0.26, 2.86)	86.95	0.330
Levofloxacin	HA	33(3.3)	20(3.5)	68.32(22.06, 624.05)	179826.37	13(3.1)	47.99(25.92, 121.22)	263.47	0.392
Difloxacin	VA	7(0.7)	4(0.7)	3.71(0.43, 11.35)	13.00	3(0.7)	6.37(0.89, -)	7.32	1.000
Enrofloxacin	VA	103(10.4)	53(9.2)	0.48(0.18, 1.50)	17.11	50(12.0)	0.83(0.33, 2.41)	22.43	0.126
Ciprofloxacin	PVA	163(16.5)	95(16.6)	1.84(0.82, 4.39)	122.53	68(16.3)	3.28(1.06, 9.17)	83.71	0.049
Norfloxacin	PVA	117(11.8)	76(13.2)	3.83(1.54, 19.81)	62670.01	41(9.9)	2.38(1.00, 19.92)	21862.55	0.385
Chloramphenicols [b]		247(24.9)	153(26.7)	2.43(1.38, 4.34)	1811.49	94(22.6)	2.96(1.57, 6.99)	425.53	0.089
Thiamphenicol	PVA	2(0.2)	1(0.2)	57.74	57.74	1(0.2)	203.85	203.85	1.000
Chloramphenicol	HA	27(2.7)	16(2.8)	13.66(4.78, 56.68)	1811.49	11(2.6)	83.88(12.10, 149.45)	425.53	0.121
Florfenicol [c]	VA	228(22.3)	142(24.7)	2.12(1.30, 3.64)	111.93	86(20.7)	2.40(1.54, 5.27)	79.55	0.098
Lincosamides [b]		36(3.6)	27(4.7)	6.89(1.52, 117.64)	122849.52	9(2.2)	25.63(6.25, 1000.57)	194642.29	0.218
Lincomycin	PVA	36(3.6)	27(4.7)	6.89(1.52, 117.64)	122849.52	9(2.2)	25.63(6.25, 1000.57)	194642.29	0.218
Quinoxalines [b]		29(2.9)	10(1.7)	9.76(4.51, 19.85)	58.02	19(4.7)	8.60(6.19, 19.10)	79.30	0.910
Cyadox	VA	29(2.9)	10(1.7)	9.76(4.51, 19.85)	58.02	19(4.7)	8.60(6.19, 19.10)	79.30	0.910
All antibiotics		921(93.0)	527(91.8)	8.74(3.60, 25.02)	186556.63	394(94.7)	10.47(2.95, 27.89)	194972.47	0.835

Notes:

Based on the FBG (fasting blood glucose), the subjects were divided into two groups, including normoglycemic group and dysglycemia group. The distribution of antibiotics concentration and detection frequency in two groups were shown in this table.

HA: Human antibiotic; VA: Veterinary antibiotic; PHA: Antibiotic preferred as HA; PVA: Antibiotic preferred as VA.

-: No value.

[a]: Positive detection number (detection frequency, %).

[b]: Sum of mass concentration of antibiotics in corresponding category.

[c]: The urinary levels of sulfamonomethoxine and florfenicol were separately considered to be the sum of their prototypes and metabolites (sulfamonomethoxine-N_4-acetyl and florfenicol amine).

[d]: Due to the similar antibacterial mechanisms, trimethoprim was included in the sulfonamides.

[e]: *P*-value refers to the significant difference of antibiotic concentration distribution between groups of normoglycemic and dysglycemia by *Mann-Whitney* test.

[f]: Only one value in this group.

Table S2 Detection concentration (μg/g) of antibiotics in the elderly with normoglycemic, prediabetes or diabetes.

Antibiotics	Normoglycemic (n=574)	*P*-value [e]	Prediabetes (n=206)	*P*-value [f]	Diabetes (n=210)	*P*-value [g]
	$P_{50}(P_{25}, P_{75})$		$P_{50}(P_{25}, P_{75})$		$P_{50}(P_{25}, P_{75})$	
Sulfonamides [a]	3.98(1.50, 9.10)	0.066	4.98(1.37, 11.73)	0.359	5.90(1.96, 12.35)	0.019
Sulfamethoxazole	2.21(0.61, 35.09)	0.406	6.86(1.28, 22.05)	0.244	3.23(1.79, 1924.19)	0.393
Sulfaclozine	5.77(3.48, 12.75)	0.288	7.04(3.75, 13.65)	0.210	6.87(4.05, 13.25)	0.204
Trimethoprim [c]	0.37(0.20, 1.59)	0.035	0.35(0.28, 1.45)	0.887	0.90(0.33, 2.38)	0.014
Sulfamethazine	0.76(0.62, -)	0.102	2.24(1.72, -)	0.333	5.01(4.12, -)	0.333
Sulfadiazine	1.32(0.95, 3.63)	0.349	0.69(0.29, 1.72)	0.246	60.85(1.50, -)	0.651
Sulfachloropyridazine	0.74(0.39, 1.45)	0.200	1.96(0.61, 6.09)	0.056	0.71(0.22, 7.68)	0.814
Sulfamonomethoxine	1.33(0.77, 2.91)	0.119	0.92(0.53, 3.90)	0.150	1.97(1.08, 3.65)	0.145
Macrolides [a]	0.24(0.07, 1.40)	0.973	0.23(0.08, 1.44)	0.788	0.19(0.08, 1.13)	0.986
Erythromycin	1.43(0.58, 3.34)	0.199	2.40(0.58, 6.41)	0.199	3.30(0.95, 15.95)	0.136
Clarithromycin	0.14(0.08, 0.42)	0.743	0.19(0.12, 0.36)	0.781	0.24(0.08, -)	0.645
Azithromycin	0.10(0.05, 0.28)	0.477	0.12(0.07, 0.31)	0.297	0.13(0.07, 0.34)	0.351
Roxithromycin	0.19(0.06, 0.68)	0.825	0.12(0.08, 0.73)	0.974	152.37(0.22, -)	0.600
β-Lactams [a]	1.64(0.65, 4.93)	0.448	1.32(0.59, 3.07)	0.385	1.81(0.66, 4.14)	0.524
Cefaclor	1.67[d]	0.221	9.60	-	1.81	1.000
Cefotaxime	12.88(5.79, 23.61)	0.101	-	-	1.60(0.64, -)	0.143
Penicillin V	1.11(0.62, 2.55)	0.984	1.19(0.59, 2.62)	0.906	1.43(0.66, 2.33)	0.929
Amoxicillin	2.46(0.71, 25.55)	0.449	1.03(0.53, 14.32)	0.297	2.68(0.55, 49.20)	0.652
Tetracyclines [a]	1.25(0.58, 2.98)	0.934	1.46(0.50, 2.81)	0.909	1.34(0.72, 2.88)	0.700
Oxytetracycline	0.65(0.38, 1.86)	0.894	0.67(0.35, 2.06)	0.827	0.82(0.37, 2.03)	0.721
Chlortetracycline	1.21(0.62, 4.41)	0.323	1.77(0.96, 5.34)	0.215	1.19(0.71, 3.77)	0.697
Tetracycline	0.82(0.45, 2.30)	0.628	0.99(0.61, 1.97)	0.370	1.10(0.49, 2.08)	0.596
Doxycycline	0.98(0.57, 2.07)	0.093	0.54(0.38, 1.48)	0.027	1.02(0.44, 2.13)	0.607
Fluoroquinolones [a]	2.97(0.77, 13.64)	0.777	3.41(0.65, 13.99)	0.844	2.01(0.53, 12.87)	0.462
Pefloxacin	4.73(2.51, 8.81)	0.001	1.22(0.62, 1.96)	0.001	1.75(1.08, 2.44)	0.010
Lomefloxacin	0.85(0.19, 1.34)	0.099	22.74(5.01, -)	0.085	0.52(0.31, -)	0.776
Danofloxacin	10.45(2.72, 45.00)	0.782	5.78(2.90, 15.94)	0.520	8.15(3.46, 16.50)	0.803
Sarafloxacin	0.35(0.16, 0.62)	0.075	107.49(0.15, -)	0.143	0.05	0.114

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Table S2. Continued

Ofloxacin	0.84(0.33, 3.37)	0.064	0.65(0.33, 6.01)	0.596	0.51(0.22, 1.18)	0.040
Levofloxacin	68.32(22.06, 624.05)	0.675	45.03(32.99, 76.53)	0.498	66.03(19.60, 169.92)	0.533
Difloxacin	3.71(0.43, 11.35)	0.526	6.84(6.37, -)	1.000	0.89	0.800
Enrofloxacin	0.48(0.18, 1.50)	0.278	0.76(0.43, 2.24)	0.296	0.88(0.19, 3.05)	0.153
Ciprofloxacin	1.84(0.82, 4.39)	0.133	2.22(1.17, 8.96)	0.244	3.53(1.01, 9.65)	0.060
Norfloxacin	3.83(1.54, 19.81)	0.625	3.82(1.09, 21.10)	0.330	2.09(0.93, 15.99)	0.700
Chloramphenicols [a]	2.43(1.38, 4.34)	0.168	2.53(1.54, 6.18)	0.425	3.51(1.74, 9.88)	0.067
Thiamphenicol	57.74	0.317	-	-	203.85	1.000
Chloramphenicol	13.66(4.78, 56.68)	0.031	8.89(4.93, 65.93)	0.820	89.77(78.29, 168.47)	0.018
Florfenicol [b]	2.12(1.30, 3.64)	0.232	2.24(1.54, 5.24)	0.313	2.86(1.69, 5.33)	0.114
Lincosamides [a]	6.89(1.52, 117.64)	0.448	74.29(1.88, 643.88)	0.509	25.63(14.38, 97916.90)	0.281
Lincomycin	6.89(1.52, 117.64)	0.448	74.29(1.88, 643.88)	0.509	25.63(14.38, 97916.90)	0.281
Quinoxalines [a]	9.76(4.51, 19.85)	0.870	8.81(4.56, 13.59)	0.579	8.08(6.68, 30.17)	0.720
Cyadox	9.76(4.51, 19.85)	0.870	8.81(4.56, 13.59)	0.579	8.08(6.68, 30.17)	0.720
All antibiotics	8.74(3.60, 25.02)	0.866	9.99(3.09, 23.29)	0.926	12.18(2.72, 35.38)	0.669

Notes:

Based on the FBG (fasting blood glucose), the subjects were divided into three groups, including normoglycemic group, prediabetes group and diabetes group. The distribution of antibiotic concentration in three groups were shown in this table.

-: No value.

[a]: Sum of mass concentration of antibiotics in corresponding category.

[b]: 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).

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

[d]: Only one value in this group.

[e]: *P*-value refers to the significant difference of antibiotic concentration distribution among groups of normoglycemic, prediabetes and diabetes by *Kruskal-wallis* test.

[f]: *P*-value refers to the significant difference of antibiotic concentration distribution between groups of normoglycemic and prediabetes by *Mann-Whitney* test.

[g]: *P*-value refers to the significant difference of antibiotic concentration distribution between groups of normoglycemic and diabetes by *Mann-Whitney* test.

Table S3 Detection frequency and concentration (μg/g) of antibiotics by usage in the elderly with normoglycemic or dysglycemia.

Antibiotics	All(N=990)	Normoglycemic (n=574)			Dysglycemia (n=416)			*P*-value [b]
	N (%) [a]	n (%) [a]	$P_{50}(P_{25}, P_{75})$	Maximum	n (%) [a]	$P_{50}(P_{25}, P_{75})$	Maximum	
VA	623(62.9)	356(62.0)	4.69(2.21, 10.49)	158437.71	267(64.2)	6.08(2.79, 14.85)	243.73	0.004
PVA	720(72.7)	422(73.5)	2.92(0.98, 9.06)	122851.70	298(71.6)	2.41(0.83, 8.66)	194958.32	0.251
HA	271 (27.4)	145(25.3)	0.22(0.07, 10.88)	179826.41	126(30.3)	0.22(0.08, 9.53)	1666.43	0.829
PHA	306 (30.9)	180(31.4)	1.6(0.63, 4.45)	13520.02	126(30.3)	2.03(0.66, 4.37)	10876.13	0.450

Notes:

By usage, antibiotics were grouped into four categaries, the distributions of these antibiotics concentration and detection frequency in normoglycemic group and dysglycemia group were shown in this table.

HA: Human antibiotic; VA: Veterinary antibiotic; PHA: Antibiotic preferred as HA; PVA: Antibiotic preferred as VA.

[a]: Positive detection number (detection frequency, %).

[b]: *P*-value represent significant difference of antibiotic concentration distribution between groups of normoglycemic and dysglycemia by *Mann-Whitney* test.

Table S4 Detection concentration (μg/g) of antibiotics by usage in the elderly with normoglycemic, prediabetes or diabetes.

Antibiotics	Normoglycemic (n=574)	*P*-value [a]	Prediabetes(n=206)	*P*-value [b]	Diabetes(n=210)	*P*-value [c]
	$P_{50}(P_{25}, P_{75})$		$P_{50}(P_{25}, P_{75})$		$P_{50}(P_{25}, P_{75})$	
VA	4.69(2.21, 10.49)	0.015	6.08(2.84, 15.95)	0.012	6.11(2.77, 13.87)	0.037
PVA	2.92(0.98, 9.06)	0.517	2.57(0.78, 8.22)	0.379	2.33(0.93, 9.74)	0.347
HA	0.22(0.07, 10.88)	0.313	0.17(0.07, 4.38)	0.554	0.34(0.09, 57.53)	0.280
PHA	1.65(0.63, 4.45)	0.472	1.83(0.63, 3.93)	0.909	2.27(0.67, 8.58)	0.232

Notes:

By usage, antibiotics were grouped into four categaries, the distributions of these antibiotics concentration and detection frequency in normoglycemic group, prediabetes group and diabetes group were shown in this table.

HA: Human antibiotic; VA: Veterinary antibiotic; PHA: Antibiotic preferred as HA; PVA: Antibiotic preferred as VA.

[a]: *P*-value refers to the significant difference of antibiotic concentration distribution among groups of normoglycemic, prediabetes and diabetes by *Kruskal-wallis test.*

[b]: *P*-value refers to the significant difference of antibiotic concentration distribution between groups of normoglycemic and prediabetes by *Mann-Whitney test*.

[c]: *P*-value refers to the significant difference of antibiotic concentration distribution between groups of normoglycemic and diabetes by *Mann-Whitney test*.

Table S5 Detection frequency and concentration (μg/g) of antibiotics by antibacterial type and antimicrobial action in the elderly with normoglycemic or dysglycemia.

Antibiotics	All(N=990)	Normoglycemic (n=574)			Dysglycemia (n=416)			*P*-value [b]
	N (%) [a]	n (%) [a]	$P_{50}(P_{25}, P_{75})$	Maximum	n (%) [a]	$P_{50}(P_{25}, P_{75})$	Maximum	
Antibacterial type								
Broad-spectrum	907(91.6)	520(90.6)	7.65(3.15, 20.99)	179915.81	387(93.0)	8.78(2.64, 25.91)	21875.92	0.732
Narrow-spectrum	176(17.8)	104(18.1)	1.11(0.62, 2.55)	163.63	72(17.3)	1.35(0.61, 2.46)	36.40	0.971
Antimicrobial action								
Bactericidal	578(58.4)	325(56.6)	3.05(0.86, 12.28)	179829.84	253(60.8)	2.43(0.78, 11.50)	21865.36	0.391
Bacteriostatic	840(84.8)	479(83.4)	4.74(1.91, 10.93)	51772.40	361(86.8)	5.21(1.66, 16.06)	20352.32	0.430

Notes:

By antibacterial type and antimicrobial action, antibiotics were grouped two groups, respectively. The distributions of these antibiotics concentration and detection frequency in normoglycemic group and dysglycemia group were shown in this table.

[a]: Positive detection number (detection frequency, %).

[b]: *P*-value represent significant difference of antibiotic concentration distribution between groups of normoglycemic and dysglycemia by *Mann-Whitney* test.

Table S6 Detection concentration (μg/g) of antibiotics by antibacterial type and antimicrobial action in the elderly with normoglycemic, prediabetes or diabetes.

Antibiotics	Normoglycemic (n=574)	*P*-value [a]	Prediabetes(n=206)	*P*-value [b]	Diabetes(n=210)	*P*-value [c]
	$P_{50}(P_{25}, P_{75})$		$P_{50}(P_{25}, P_{75})$		$P_{50}(P_{25}, P_{75})$	
Antibacterial type						
Broad-spectrum	7.65(3.15, 20.99)	0.672	8.75(2.65, 22.28)	0.595	8.82(2.40, 31.28)	0.398
Narrow-spectrum	1.11(0.62, 2.55)	0.984	1.19(0.59, 2.62)	0.906	1.43(0.66, 2.33)	0.929
Antimicrobial action						
Bactericidal	3.05(0.86, 12.28)	0.539	2.56(0.80, 11.61)	0.858	2.27(0.71, 11.47)	0.272
Bacteriostatic	4.74(1.91, 10.93)	0.770	4.81(1.79, 13.33)	0.934	5.99(1.57, 18.17)	0.526

Notes:

By antibacterial type and antimicrobial action, antibiotics were grouped two groups, respectively. The distributions of these antibiotics concentration and detection frequency in normoglycemic group, prediabetes group and diabetes group were shown in this table.

[a]: *P*-value refers to the significant difference of antibiotic concentration distribution among groups of normoglycemic, prediabetes and diabetes by *Kruskal-wallis test.*

[b]: *P*-value refers to the significant difference of antibiotic concentration distribution between groups of normoglycemic and prediabetes by *Mann-Whitney test*.

[c]: *P*-value refers to the significant difference of antibiotic concentration distribution between groups of normoglycemic and diabetes by *Mann-Whitney test.*

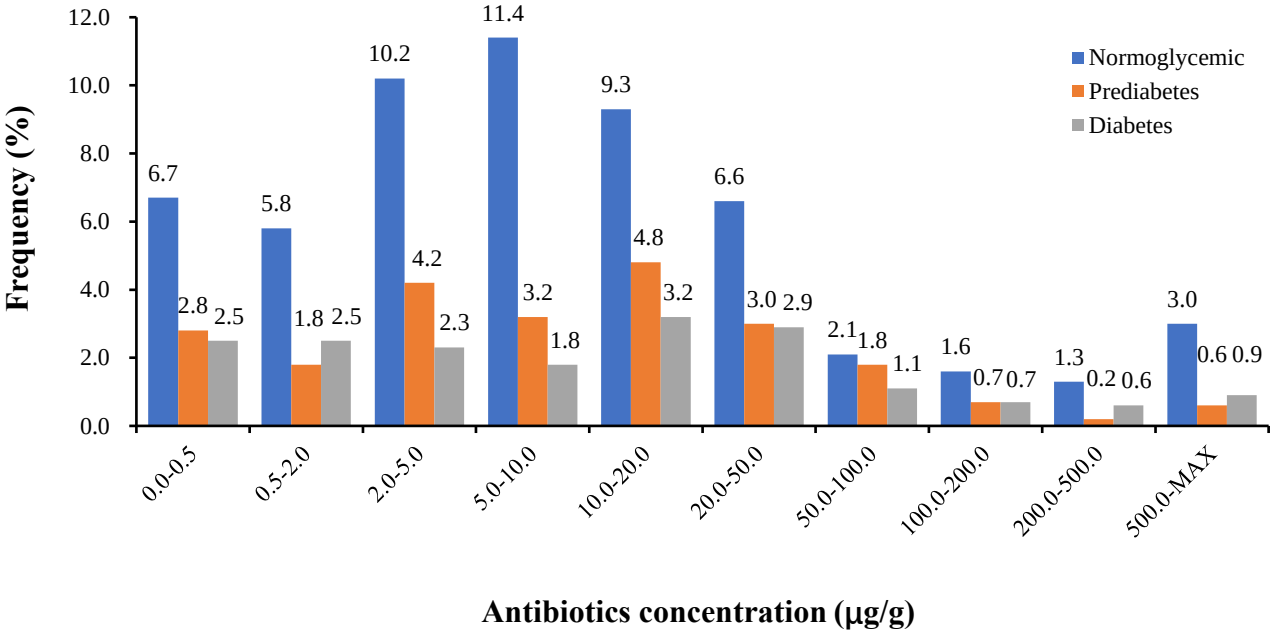

Fig S1 Frequency and concentration (μg/g) distribution of 34 antibiotics in the subjects with normoglycemic, prediabetes or diabetes.

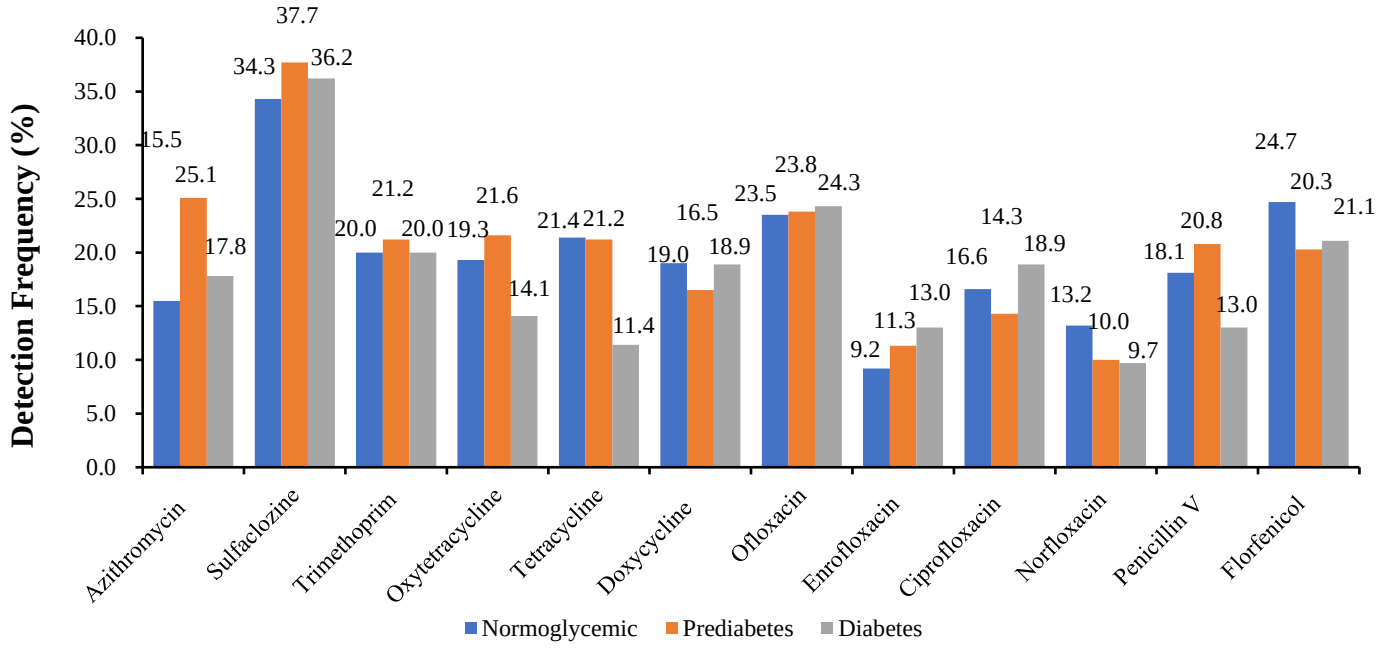

Fig S2 The detection frequency of 12 antibiotics (detection frequency >10%) in the subjects with normoglycemic, prediabetes or diabetes.

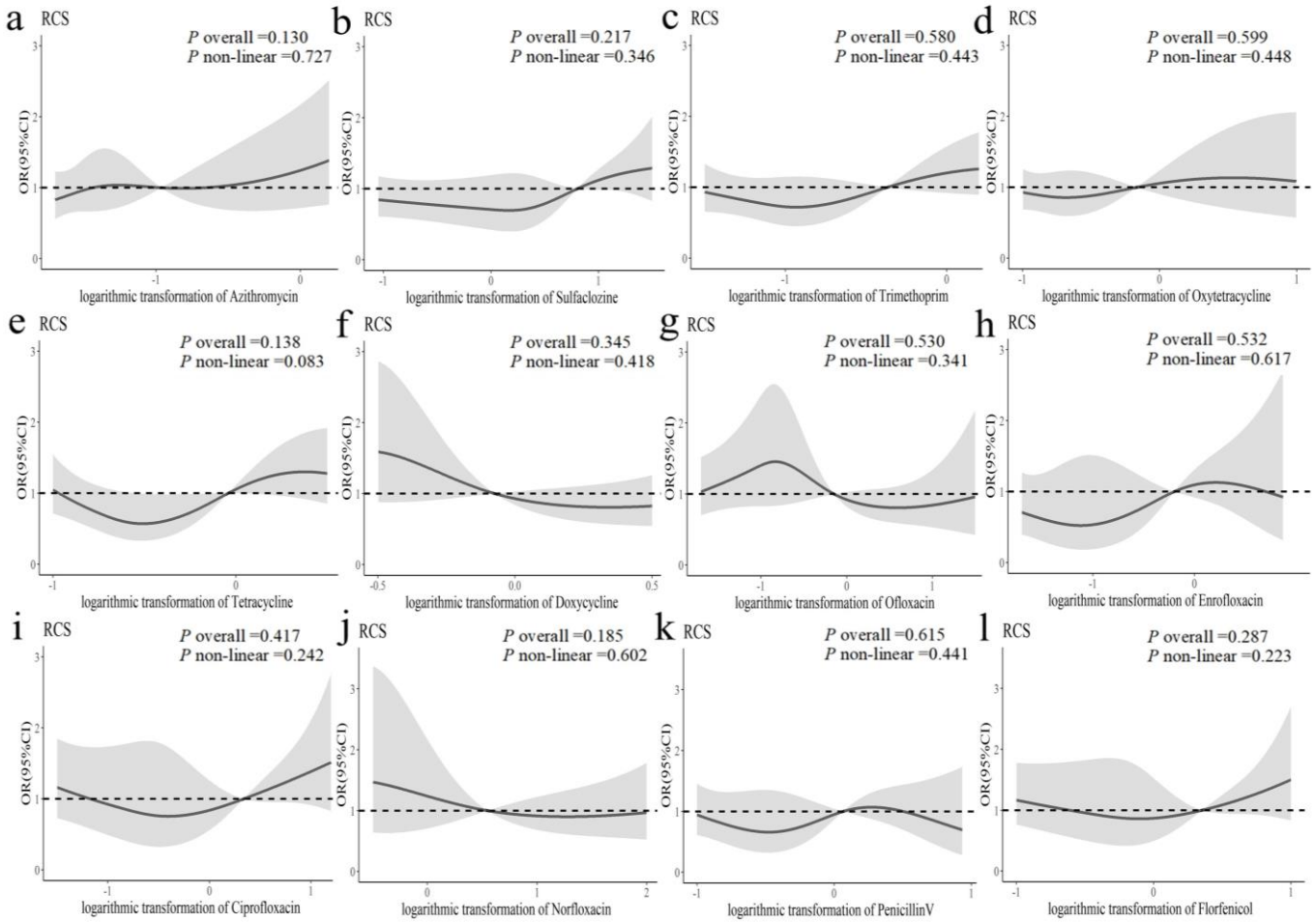

Fig S3 Restricted cubic splines were used to characterize the dose response curve of 12 antibiotic exposure that detection frequency >10% in all subjects and the odds ratio of dysglycemia.

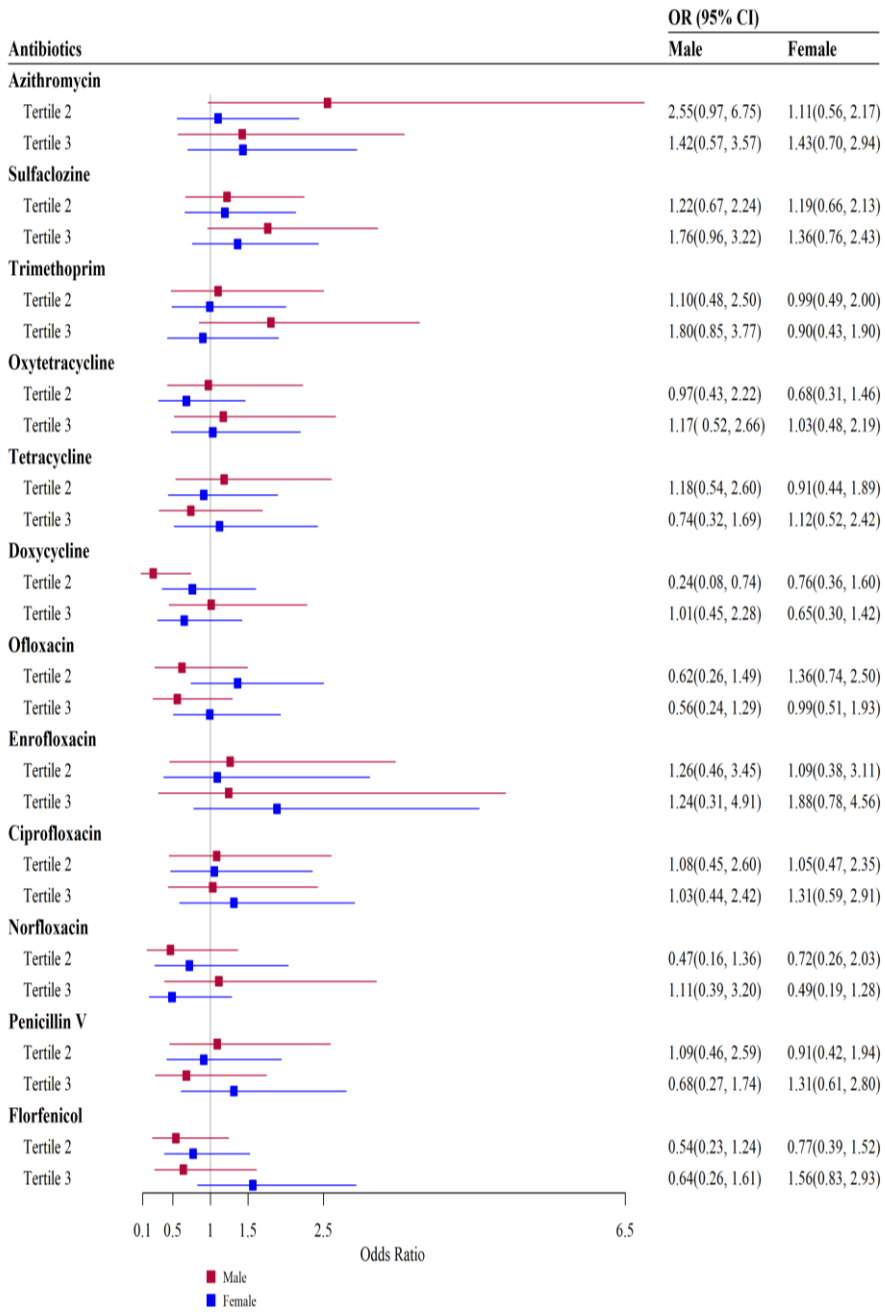

Fig S4 Association of antibiotics (detection frequency >10%) exposure concentration with dysglycemia risk by logistic regression in the elderly stratified by gender.

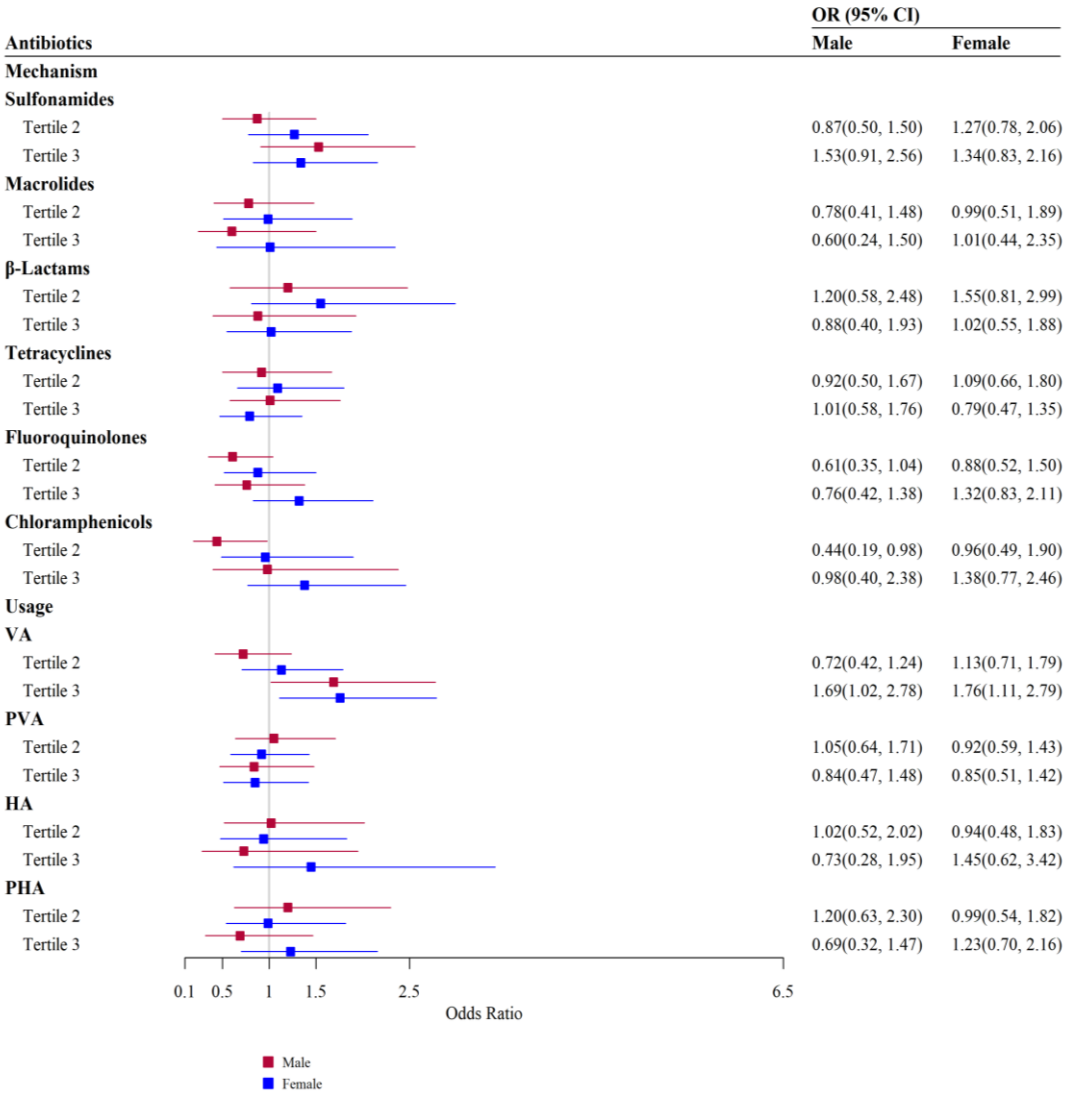

Fig S5 Association of antibiotics exposure concentration by mechanism and usage with dysglycemia risk by logistic regression in the elderly stratified by gender.

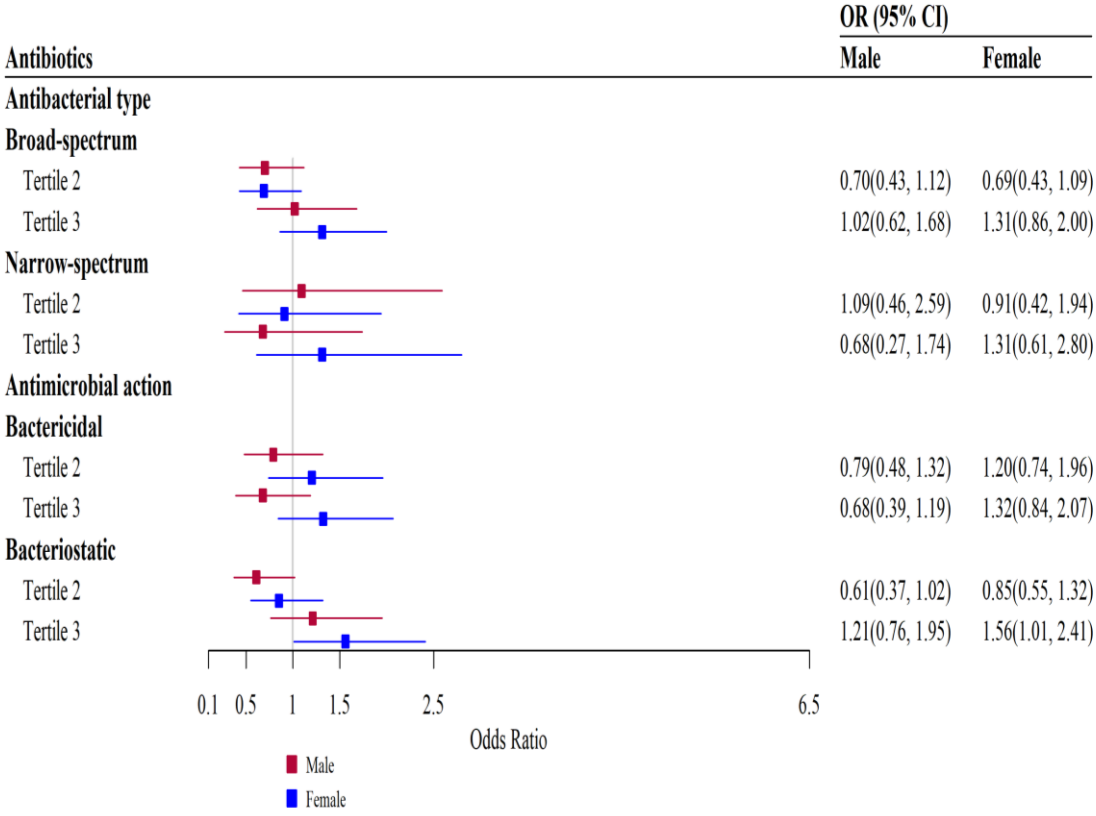

Fig S6 Association of antibiotics exposure concentration by antibacterial type and antimicrobial action with dysglycemia risk by logistic regression in the elderly stratified by gender.