See commentary by Popkin p1517

Antibiotic Exposure and the Risk for Depression, Anxiety, or Psychosis:
A Nested Case-Control Study

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ABSTRACT

Objective: Changes in the microbiota (dysbiosis) were suggested to increase the risk of several psychiatric conditions through neurologic, metabolic, and immunologic pathways. Our aim was to assess whether exposure to specific antibiotic groups increases the risk for depression, anxiety, or psychosis.

Method: We conducted 3 nested case-control studies during the years 1995–2013 using a large population-based medical record database from the United Kingdom. The study included 202,974 patients with depression, 14,570 with anxiety, and 2,690 with psychosis and 803,961, 57,862, and 10,644 matched controls, respectively. Cases were defined as individuals aged 15–65 years with any medical Read code for depression, anxiety, or psychosis. Subjects with diagnosis-specific psychotropic prescriptions > 90 days before index date were excluded. For every case, 4 controls were selected using incidence density sampling, matching on age, sex, practice site, calendar time, and duration of follow-up before index date. The primary exposure of interest was therapy with 1 of 7 antibiotic classes > 1 year before index date. Odds ratios (ORs) and 95% CIs were calculated for the association between each psychiatric disorder and exposure to individual classes of antibiotics using conditional logistic regression analysis. The risk was adjusted for obesity, smoking history, alcohol consumption, socioeconomic status, and number of infectious events before diagnosis.

Results: Treatment with a single antibiotic course was associated with higher risk for depression with all antibiotic groups, with an adjusted OR (AOR) of 1.23 for penicillins (95% CI, 1.18–1.29) and 1.25 (95% CI, 1.15–1.35) for quinolones. The risk increased with recurrent antibiotic exposures to 1.40 (95% CI, 1.35–1.46) and 1.56 (95% CI, 1.46–1.65) for 2–5 and > 5 courses of penicillin, respectively. Similar association was observed for anxiety and was most prominent with exposures to penicillins and sulfonamides, with an AOR of 1.17 (95% CI, 1.01–1.36) for a single course of penicillin and 1.44 (95% CI, 1.18–1.75) for > 5 courses. There was no change in risk for psychosis with any antibiotic group. There was a mild increase in the risk of depression and anxiety with a single course of antifungals; however, there was no increase in risk with repeated exposures.

Conclusion: Recurrent antibiotic exposure is associated with increased risk for depression and anxiety but not for psychosis.

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The human gastrointestinal tract contains a complex and diverse microbial community (microbiota) of over 1,000 different bacterial species.[1] Although the potential role of gut microbiota in fatigue, melancholia, and the neuroses was described as early as the 1900s, research in the field was neglected until recent years.[2] Contemporary studies, both in animal models and in humans, indicate that the microbiota and changes in its composition (dysbiosis) affect the central nervous system (CNS) through neuronal, metabolic, and immunologic pathways and may also alter behavior and induce psychiatric-like conditions.[3]

In animal models, the postnatal development of the hypothalamic-pituitary-adrenal (HPA) stress response was compared between germ-free and specific pathogen-free mice.[4] Plasma adrenocorticotropic hormone and corticosterone elevations in response to restraint stress (which involves cognitive processing) were substantially higher in germ-free mice than in specific pathogen-free mice. The exaggerated HPA stress response by germ-free mice was reversed by reconstitution with specific bacteria (eg, *Bifidobacterium infantis*). Moreover, there were region-specific changes in the brains of germ-free compared to specific pathogen-free mice, including reduced brain-derived neurotrophic factor (BDNF) expression levels in the cortex and hippocampus[4,5] and changes in the expression of 5-hydroxytryptamine receptor 1 (5-HT_1) in the hippocampus. Furthermore, increased turnover of anxiety-related neurotransmitters such as norepinephrine, dopamine, and 5-HT, was seen in germ-free mice, as well as changes in the levels of proteins that regulate the development and function of neural synapses (eg, synaptophysin and postsynaptic density protein 95).[5] Additionally, compared to conventionally colonized control animals, male germ-free animals have a significant elevation in the hippocampal concentration of 5-HT and 5-hydroxyindoleacetic acid, as well as increased plasma levels of tryptophan, suggesting a humoral route through which the microbiota can influence CNS serotonergic neurotransmission.[6]

In accordance with these observations, germ-free mice exhibit more exploratory and risk-taking

Clinical Points

- Animal models show a central role for the gut-brain axis in behavior and psychiatric pathology.
- The current large population-based study showed that recurrent antibiotic exposure is associated with increased risk for depression and anxiety, but not psychosis.
- This reported risk emphasizes the need to decrease unnecessary antibiotic treatments.
- Future human studies should assess the microbiota composition in psychiatric disorders.

behaviors and reduced anxiety than specific pathogen-free mice.[5,7] Infection with *Citrobacter rodentium* and chronic gut inflammation induced anxiety-like behavior[8,9] and decreased hippocampal BDNF messenger RNA (mRNA) levels.[9] Compared to controls, healthy mice that were fed probiotics exhibited decreased anxiety-like and depressive-like behaviors[10–13] and region-dependent alterations in $GABA_{B1b}$ and $GABA_{Aα2}$ mRNA in the brain.[12] Mice exposed to antibiotics for a single week showed increased exploratory behavior and hippocampal expression of BDNF.[14] Two weeks following termination of antibiotic treatment, both bacterial profiles and behaviors returned to normal. These observations were linked to changes in the bacterial composition.[5]

Limited studies in humans support the possible role for microbiota in anxiety and depression. Most studies focus on probiotics administration with resultant antidepressant and anxiety-reducing effects.[11,15,16] A 4-week intake of a fermented milk product with probiotic by healthy women affected activity of brain regions that control central processing of emotion and sensation, as assessed by functional magnetic resonance imaging before and after the intervention.[17]

External factors can alter the human microbiota. It has been shown that antibiotic therapy reduces the overall bacterial diversity, affecting up to 33% of the microbial population[18] with substantial consequences for the resultant functional stability of the microbiota. This impact might last for extended periods of time, as exemplified by the change in intestinal microbiota (specifically the *Bacteroides* group) lasting sometimes up to 4 years after treatment for *Helicobacter pylori* infection with clarithromycin, and metronidazole.[19–22]

Despite the high rate (up to 15%) of treatment with at least 1 antibiotic prescription during any given year in western countries[23,24] and the high prevalence of psychiatric illness (with a lifetime prevalence of 29% for anxiety disorders and 21% for mood disorders),[25] the possible association between antibiotic effect on microbiota and the risk of specific psychiatric diagnoses has not been evaluated to date.

The current study aimed to evaluate the association between prior antibiotic exposure and the risk of psychiatric diagnoses of depression, anxiety, or psychosis.

METHOD

Study Design

We conducted 3 nested case-control studies for depression, anxiety, and psychosis, with incidence density sampling using The Health Improvement Network (THIN) database. This design is computationally more efficient than a cohort study and produces odds ratios (ORs) that are unbiased estimates of incidence-rate ratios.[26] The study was approved by the institutional review board at the University of Pennsylvania and by the scientific review committee of THIN.

Data Source

THIN includes information regarding more than 10 million patients and is representative of the broader UK population. THIN is designed to serve research purposes. All practices contributing data to THIN follow a standardized protocol of entering information and transmitting information to the central database. Data available in THIN include demographic information, medical diagnoses, prescriptions, laboratory results, and lifestyle characteristics. Data quality is monitored through routine analysis of the entered data.[27,28] The suitability of THIN data as a resource for research into psychiatric diagnosis was previously validated.[29]

Study Cohort

THIN records of all individuals who received medical care during the years 1995–2013 from a THIN practitioner were eligible for inclusion. Unacceptable medical records (ie, records with incomplete documentation or out-of-sequence date of birth, registration date, date of death, or date of exit from the database) were excluded. Follow-up started at the latter of either the date when the THIN practice started using the electronic medical record software or 183 days after the date at which the patient registered with the general practitioner, and it ended on the date of psychiatric diagnosis for cases and, for controls, on the earliest of the following: date of death, date of transfer out of the database, or date at which the end date of the database was reached.[30]

Selection of Cases

The group of cases included all records of individuals from 15 to 65 years of age who were diagnosed with at least 1 Read code (the standard clinical terminology system used in general practices in the United Kingdom; see eAppendix 1 at PSYCHIATRIST.COM) of depression, anxiety, or psychosis that was not substance induced during follow-up in the THIN database. Individuals with psychiatric comorbidities (eg, mixed anxiety and depression) were excluded from the analysis. We excluded records of individuals who were diagnosed with depression, anxiety, or psychosis within the first 183 days after initiation of follow-up in order to avoid prevalent cases.[30] For consideration of a case for a specific psychiatric diagnosis, we excluded individuals that received pharmacologic treatment for the specific psychiatric diagnosis more than 90 days before the diagnosis was first

Table 1. Characteristics of Cases and Controls

Characteristic	Cases	Controls	*P* Value
Depressive disorder	(n = 202,974)	(n = 803,961)	
Age, mean ± SD, y	37.4 ± 12.7	37.4 ± 12.8	NA
Male sex, n (%)	79,418 (39.1)	314,734 (39.1)	NA
Follow-up duration, mean ± SD, y	4.0 ± 3.6	4.0 ± 3.6	NA
Obesity (BMI [kg/m^2] > 30), n (%)	29,454 (14.5)	87,066 (10.8)	< .0001
Smoking (ever), n (%)	82,723 (40.8)	227,362 (28.3)	< .0001
Alcohol use, n (%)	85,987 (42.4)	299,813 (37.3)	< .0001
Alcoholism, n (%)	2,199 (1.0)	2,686 (0.3)	< .0001
Townsend quintiles, mean ± SD[a]	2.9 ± 1.5	2.7 ± 1.5	< .0001
Pneumonia, mean ± SD	1.2 ± 0.5	1.2 ± 0.6	.18
Upper respiratory tract infections, mean ± SD	1.7 ± 1.4	1.6 ± 1.3	< .0001
Urinary tract infections, mean ± SD	2.1 ± 2.5	2.0 ± 2.3	< .0001
Anxiety disorder	(n = 14,570)	(n = 57,862)	Unadjusted OR (95% CI, *P* value)
Age, mean ± SD, y	38.6 ± 13.1	38.6 ± 13.1	NA
Male sex, n (%)	5,648 (38.8)	22,404 (38.7)	NA
Follow-up duration, mean ± SD, y	4.7 ± 3.9	4.7 ± 3.9	NA
Obesity (BMI [kg/m^2] > 30), n (%)	1,937 (13.3)	7,362 (12.7)	.07
Smoking (ever), n (%)	5,838 (40.1)	17,966 (31.1)	< .0001
Alcohol use, n (%)	6,658 (45.7)	23,401 (40.4)	< .0001
Alcoholism, n (%)	174 (1.2)	307 (0.5)	< .0001
Townsend quintiles, mean ± SD[a]	2.8 ± 1.5	2.6 ± 1.5	< .0001
Pneumonia, mean ± SD	1.2 ± 0.6	1.3 ± 0.9	.74
Upper respiratory tract infections, mean ± SD	1.8 ± 1.5	1.6 ± 1.3	< .0001
Urinary tract infections, mean ± SD	2.4 ± 2.9	2.1 ± 2.7	.01
Psychotic disorder	(n = 2,690)	(n = 10,644)	Unadjusted OR (95% CI, *P* value)
Age, mean ± SD, y	36.2 ± 12.8	36.1 ± 12.8	NA
Male sex, n (%)	1,611 (59.9)	6,370 (59.9)	NA
Follow-up duration, mean ± SD, y	4.1 ± 3.8	4.1 ± 3.9	NA
Obesity (BMI [kg/m^2] > 30), n (%)	248 (9.2)	1,090 (10.2)	.08
Smoking (ever), n (%)	1,125 (41.8)	3,172 (29.8)	< .0001
Alcohol use, n (%)	926 (34.4)	3,768 (35.4)	.96
Alcoholism, n (%)	89 (3.3)	71 (0.7)	< .0001
Townsend quintiles, mean ± SD[a]	3.3 ± 1.5	2.9 ± 1.5	< .0001
Pneumonia, mean ± SD	1.1 ± 0.4	1.2 ± 0.6	1.0
Upper respiratory tract infections, mean ± SD	1.7 ± 2.2	1.7 ± 1.6	.41
Urinary tract infections, mean ± SD	2.0 ± 3.0	2.0 ± 2.5	.59

[a]Townsend quintiles is a measure of socioeconomic status. Higher score implies a lower status.
Abbreviations: BMI = body mass index, NA = not applicable, OR = odds ratio.

recorded. This exclusion was made since in those cases the date of diagnosis of the psychiatric disorder could not be determined.

Selection of Controls

Selection of the control group was based on incidence density sampling.[26] The eligible control pool for each case with the respective psychiatric diagnosis consisted of all individuals from the THIN database who remained at risk for this specific psychiatric disorder on the calendar date when the case was first diagnosed. For each case, we matched up to 4 controls with regard to age, sex, practice site, and both duration and calendar time. Controls were assigned the same index date as their matched cases.

Exposures and Covariates

The primary exposure of interest was any antibiotic therapy, more than 1 year prior to index date (to avoid protopathic bias[31]) of the specific psychiatric diagnosis, with 1 of 7 antibiotic groups commonly used in the outpatient setting: penicillins, cephalosporins, macrolides, tetracyclines, sulfonamides, quinolones, and imidazole. Analysis was performed for each antibiotic class separately. We examined the effect of the type of antibiotic used based on number of courses (0, 1, 2–5, and > 5 courses) and duration of time from last antibiotic prescription (1–5, 5–10, and > 10 years). We also assessed antiviral and antifungal medications as possible negative controls.

As potential confounders, we examined a comprehensive list of variables including obesity (BMI [kg/m^2] > 30), smoking history (ever/never), alcohol consumption, socioeconomic status according to Townsend score quintiles,[32] and number of previous urinary tract and upper and lower respiratory infections.

Statistical Analysis

The baseline characteristics of cases and controls were compared using χ^2 test for categorical variables and *t* test for continuous variables. The primary analysis was a conditional logistic regression to estimate ORs and 95% confidence intervals (CIs) for the association between number of antibiotic courses for each antibiotic class and risk of depression, anxiety, and psychosis. The reference exposure group consisted of individuals without documented therapy with the specific antibiotic. The analysis was adjusted for all potential confounders. Bonferroni correction was performed to account for multiple comparisons due to assessment of 9 treatment groups (7 antimicrobial groups as well as antiviral and antifungal). The cutoff *P* value for statistical significance after applying the correction was .006. All analyses were performed using STATA 13 (Stata Corp; College Station, Texas).

RESULTS

The study populations included 202,974 cases with depression, 14,570 with anxiety, and 2,690 with psychosis and 803,961, 57,862, and 10,644 matched controls, respectively (Table 1). As expected, patients with psychiatric diagnoses had elevated risk for smoking, alcohol use, and lower socioeconomic status. The most commonly prescribed antibiotic among the study population was penicillin, with 84,265 (38.3%) among cases and 278,497 (31.9%) among controls.

Treatment with a single antibiotic course was associated with increased risk of depression for all antibiotic groups, with adjusted ORs (AORs) of 1.23 for penicillins (95% CI, 1.18–1.29) and cephalosporins (95% CI, 1.16–1.31) and 1.25 (95% CI, 1.15–1.35) for quinolones (Table 2). Treatment with 2–5 antibiotic courses was associated with increased risk of

Table 2. Risk for Depressive Disorder as a Function of the Number of Specific Antibiotic Courses

No. of Antibiotic Courses	Cases, n (%)	Controls, n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a,b]
Penicillins				
0	125,654 (61.91)	550,056 (68.42)	Reference	Reference
1	32,200 (15.86)	115,248 (14.34)	1.36 (1.33–1.39)	1.23 (1.18–1.29)
2–5	36,303 (17.89)	113,969 (14.18)	1.65 (1.61–1.68)	1.40 (1.35–1.46)
>5	8,817 (4.34)	24,688 (3.07)	2.00 (1.92–2.08)	1.56 (1.46–1.65)
Cephalosporins				
0	186,925 (92.09)	755,390 (93.96)	Reference	Reference
1	10,812 (5.33)	33,511 (4.17)	1.35 (1.31–1.40)	1.23 (1.16–1.31)
2–5	4,741 (2.34)	13,619 (1.69)	1.48 (1.41–1.56)	1.30 (1.20–1.42)
>5	496 (0.24)	1,441 (0.18)	1.49 (1.29–1.72)	1.24 (1.00–1.55)
Macrolides				
0	177,485 (87.44)	725,383 (90.23)	Reference	Reference
1	15,784 (7.78)	49,917 (6.21)	1.33 (1.30–1.37)	1.22 (1.16–1.28)
2–5	8,418 (4.15)	24,810 (3.09)	1.44 (1.39–1.50)	1.27 (1.20–1.35)
>5	1,287 (0.63)	3,851 (0.48)	1.44 (1.32–1.58)	1.28 (1.12–1.45)
Quinolones				
0	196,297 (96.71)	784,315 (97.56)	Reference	Reference
1	5,066 (2.50)	15,111 (1.88)	1.35 (1.29–1.42)	1.25 (1.15–1.35)
2–5	1,467 (0.72)	4,137 (0.51)	1.43 (1.32–1.56)	1.18 (1.03–1.35)
>5	144 (0.07)	398 (0.05)	1.48 (1.13–1.93)	1.25 (0.83–1.87)
Sulfonamides				
0	183,752 (90.53)	744,652 (92.62)	Reference	Reference
1	13,150 (6.48)	40,986 (5.10)	1.34 (1.30–1.38)	1.24 (1.17–1.30)
2–5	5,589 (2.75)	16,711 (2.08)	1.42 (1.36–1.48)	1.31 (1.22–1.41)
>5	483 (0.24)	1,612 (0.20)	1.28 (1.10–1.47)	1.17 (0.95–1.44)
Tetracyclines				
0	186,184 (91.73)	750,775 (93.38)	Reference	Reference
1	10,037 (4.94)	31,240 (3.89)	1.32 (1.27–1.36)	1.21 (1.14–1.28)
2–5	5,007 (2.47)	15,891 (1.98)	1.29 (1.24–1.35)	1.18 (1.09–1.27)
>5	1,746 (0.86)	6,055 (0.75)	1.18 (1.10–1.28)	1.19 (1.06–1.34)
Imidazole				
0	193,497 (95.33)	777,161 (96.67)	Reference	Reference
1	7,201 (3.55)	20,854 (2.59)	1.42 (1.36–1.48)	1.26 (1.18–1.35)
2–5	2,185 (1.08)	5,701 (0.71)	1.59 (1.49–1.71)	1.32 (1.17–1.48)
>5	91 (0.04)	245 (0.03)	1.57 (1.12–2.20)	1.14 (0.70–1.87)
Antifungals				
0	193,341 (95.25)	773,078 (96.16)	Reference	Reference
1	6,002 (2.96)	18,935 (2.36)	1.28 (1.23–1.33)	1.17 (1.08–1.25)
2–5	3,159 (1.56)	10,329 (1.28)	1.24 (1.17–1.31)	1.12 (1.02–1.23)
>5	472 (0.23)	1,619 (0.20)	1.18 (1.02–1.36)	1.01 (0.81–1.27)
Antivirals				
0	200,136 (98.60)	794,854 (98.87)	Reference	Reference
1	2,274 (1.12)	7,324 (0.91)	1.23 (1.15–1.32)	1.12 (1.01–1.24)
2–5	419 (0.21)	1,366 (0.17)	1.22 (1.04–1.42)	1.15 (0.91–1.44)
>5	145 (0.07)	417 (0.05)	1.38 (1.06–1.80)	1.22 (0.81–1.82)

[a]Adjusted for obesity (body mass index > 30), smoking (ever/never), alcohol consumption, Townsend quintiles, number of urinary tract infections, and upper and lower respiratory infections before index date.
[b]After the Bonferroni correction, the *P* value needed to show statistical significance was .006.
Abbreviation: OR = odds ratio.

depression for all antibiotic groups, with AORs ranging from 1.18 (95% CI, 1.09–1.27) for tetracyclines to 1.40 (95% CI, 1.35–1.46) for penicillins (Table 2). The risk increased with the number of antibiotic courses for penicillins and macrolides and reached 1.56 (95% CI, 1.46–1.65) for more than 5 courses of penicillins.

The risk of anxiety was significantly increased with treatment of penicillins and sulfonamides (Table 3). For a single course with these antibiotics, the AOR ranged from 1.17 (95% CI, 1.01–1.36) for penicillins to 1.35 (95% CI, 1.14–1.60) for sulfonamides. For 2–5 courses, the AOR ranged from 1.33 (95% CI, 1.15–1.53) for penicillins to 1.46 (95% CI, 1.17–1.82) for sulfonamides.

There was no increased risk for psychosis with antibiotics, antivirals, or antifungals, independent of number of treatment courses (Table 4). There was a mild increased risk for depression and anxiety with a single course of antifungal medication (AOR = 1.17; 95% CI, 1.08–1.25; and AOR = 1.35, 95% CI, 1.08–1.69, respectively). There was also a mild risk increase for depression with 2–5 courses of antifungal treatment (AOR = 1.12; 95% CI, 1.02–1.23). For antiviral, there was increased risk of depression with a single course of medication (AOR = 1.12; 95% CI, 1.01–1.24). This association was not seen with increased number of courses (Tables 2–4).

In an additional analysis, the higher risk for depression was maintained even when analyzing last prescriptions 5–10 years before index date (Supplementary eTable 1). Last antibiotic prescription with penicillins, cephalosporins, and macrolides 5–10 years before diagnosis of depression was associated with AOR of 1.15 (95% CI, 1.08–1.22), 1.19 (95% CI, 1.09–1.30), and 1.13 (95% CI, 1.05–1.22), respectively. Last sulfonamides prescription 5–10 years before the diagnosis of anxiety was associated with AOR of 1.30 (95% CI, 1.00–1.68) (Supplementary eTable 2). This effect was not seen in psychosis (Supplementary eTable 3).

DISCUSSION

The current large population-based study demonstrated an association between past exposure to specific antibiotic groups and a higher risk for depression and anxiety. The association for depression was demonstrated with all antibiotic groups and increased with recurrent exposures (2–5 and >5 antibiotic courses). For anxiety, a similar association was observed following exposures to penicillins and sulfonamides. There was no association between any antibiotic exposure and psychosis.

These results are in line with previous studies on the effect of microbiota and dysbiosis on the CNS. Animal model studies demonstrated exaggerated HPA stress response in germ-free compared to specific pathogen-free mice[4] as well as changes in several neurotransmitters and neurologic pathways, such as the serotonergic and noradrenergic pathways,[4–6] that are also known to be involved in the pathogenesis of depression and anxiety in humans.[33–38] As opposed to the studies on microbiota-associated mood and anxiety-like behavioral changes, literature regarding an association with psychosis is lacking. Only 2 previous works[39,40] suggested the involvement of gut microbiota in schizoid behavior and cognitive deficits in mice. These results were reported as indirect evidence of schizophrenia.[41]

Table 3. Risk for Anxiety Disorder as a Function of the Number of Specific Antibiotic Courses

No. of Antibiotic Courses	Cases, n (%)	Controls, n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a,b]
Penicillins				
0	8,487 (58.25)	36,598 (63.25)	Reference	Reference
1	2,365 (16.23)	8,805 (15.22)	1.25 (1.16–1.35)	1.17 (1.01–1.36)
2–5	2,905 (19.94)	9,863 (17.05)	1.43 (1.33–1.55)	1.33 (1.15–1.53)
>5	813 (5.58)	2,596 (4.49)	1.60 (1.41–1.83)	1.44 (1.18–1.75)
Cephalosporins				
0	13,127 (90.10)	53,215 (91.97)	Reference	Reference
1	921 (6.32)	3,035 (5.25)	1.27 (1.14–1.42)	1.21 (0.99–1.46)
2–5	464 (3.18)	1,426 (2.46)	1.39 (1.19–1.63)	1.33 (1.02–1.72)
>5	58 (0.40)	186 (0.32)	1.36 (0.90–2.07)	1.43 (0.76–2.66)
Macrolides				
0	12,390 (85.04)	50,693 (87.61)	Reference	Reference
1	1,307 (8.97)	4,355 (7.53)	1.26 (1.14–1.38)	1.17 (1.00–1.37)
2–5	733 (5.08)	2,360 (4.08)	1.31 (1.16–1.49)	1.11 (0.91–1.37)
>5	140 (0.96)	454 (0.78)	1.33 (1.01–1.74)	1.20 (0.81–1.77)
Quinolones				
0	13,935 (95.64)	55,982 (96.75)	Reference	Reference
1	469 (3.22)	1,405 (2.43)	1.36 (1.17–1.58)	1.43 (1.12–1.82)
2–5	153 (1.05)	432 (0.75)	1.45 (1.12–1.89)	1.33 (0.86–2.05)
>5	13 (0.09)	43 (0.07)	1.23 (0.52–2.95)	1.44 (0.28–7.27)
Sulfonamides				
0	12,771 (87.65)	52,247 (90.30)	Reference	Reference
1	1,126 (7.73)	3,715 (6.42)	1.29 (1.17–1.43)	1.35 (1.14–1.60)
2–5	596 (4.09)	1,714 (2.96)	1.50 (1.30–1.72)	1.46 (1.17–1.82)
>5	77 (0.53)	186 (0.32)	1.81 (1.25–2.64)	1.58 (0.90–2.78)
Tetracyclines				
0	12,991 (89.16)	53,025 (91.64)	Reference	Reference
1	905 (6.21)	2,801 (4.84)	1.35 (1.21–1.51)	1.44 (1.18–1.74)
2–5	500 (3.43)	1,498 (2.59)	1.40 (1.21–1.62)	1.26 (0.99–1.60)
>5	174 (1.19)	538 (0.93)	1.36 (1.06–1.73)	1.39 (0.96–2.00)
Imidazole				
0	13,660 (93.75)	55,108 (95.24)	Reference	Reference
1	675 (4.63)	2,071 (3.58)	1.35 (1.19–1.54)	1.40 (1.13–1.74)
2–5	225 (1.54)	651 (1.13)	1.46 (1.17–1.82)	1.42 (1.01–2.01)
>5	10 (0.07)	32 (0.06)	1.37 (0.51–3.72)	1.81 (0.53–6.20)
Antifungals				
0	13,689 (93.95)	54,972 (95.01)	Reference	Reference
1	523 (3.59)	1,708 (2.95)	1.25 (1.08–1.44)	1.35 (1.08–1.69)
2–5	297 (2.04)	1,007 (1.74)	1.20 (1.00–1.45)	1.33 (0.99–1.80)
>5	61 (0.42)	175 (0.30)	1.43 (0.95–2.15)	1.17 (0.60–2.26)
Antivirals				
0	14,317 (98.26)	56,999 (98.51)	Reference	Reference
1	198 (1.36)	691 (1.19)	1.13 (0.91–1.42)	1.20 (0.88–1.63)
2–5	40 (0.27)	117 (0.20)	1.37 (0.82–2.26)	1.08 (0.50–2.30)
>5	15 (0.10)	55 (0.10)	1.09 (0.49–2.44)	1.31 (0.47–3.65)

[a]Adjusted for obesity (body mass index > 30), smoking (ever/never), alcohol consumption, Townsend quintiles, number of urinary tract infections, and upper and lower respiratory infections before index date.
[b]After the Bonferroni correction, the *P* value needed to show statistical significance was .006.
Abbreviation: OR = odds ratio.

The risk for depression and anxiety following antibiotic exposure did not change in the current study, even after adjustment for the number of past infectious events. These findings together with the association between number of antibiotic courses and disease risk support the hypothesis that antibiotic exposure and not infection alone[42] might be a potential cause for the elevated risk, possibly through effect on the microbiota. Of note, previous case reports described mood changes (eg, mania) induced by antibiotic therapy.[43]

The fact that the association was demonstrated even for last antibiotic prescriptions more than 5 years before diagnosis points against the possibility of reverse causality in which an undiagnosed psychiatric disorder increased the use of medical services or exposed the individual to higher risk for infection events (and hence antibiotic prescriptions).

Our study has several important strengths, including a large population-based sample with over 1 million subjects, comprising 202,974 cases with depression, 14,570 with anxiety, and 2,690 with psychosis; long follow-up of up to 18 years (median = 6.2 years); and detailed information regarding epidemiologic and socioeconomic parameters, past medical history, and medication prescriptions (allowing us to evaluate specific antibiotic groups). Only individuals that were diagnosed more than 6 months after initiation of follow-up were considered as cases to avoid prevalent cases. By matching cases and controls on duration and calendar period of follow-up as well as practice site, we avoided time-window bias and minimized confounding secondary to different clinical judgment regarding antibiotic prescription and type of antibiotic used. To avoid protopathic bias, we analyzed only antibiotic prescriptions given more than 1 year before diagnosis date. Adjustment to the number of previous infections that might be associated with both antibiotic prescriptions and severe mental illness[44] limited the possibility of confounding by indication.

Despite the advantages, the current study had several limitations. Cases were defined according to Read codes. There was no information indicating whether the psychiatric diagnosis was made by mental health experts. If case individuals were misclassified with a psychiatric disorder, there is no reason to assume a differential misclassification and the association would have changed toward the null hypothesis. We also assumed that the patients initiated antibiotic therapy.[45] We expect that if compliance was actually lower it would have decreased the association observed.

The gut microbiota varies among populations and within individuals during life. The epidemiologic data available in THIN do not include information regarding the microbiota composition of individuals. Thus, the current work could not determine causality or demonstrate dysbiosis as the biological explanation for the observed association.

Socioeconomic status is an important confounder in psychiatric studies and might serve as a common risk factor for both psychiatric disorders and infectious events (and secondary antibiotic use). However, by using the directed acyclic graph approach, socioeconomic status can also be part of a causal pathway between psychiatric disorders and antibiotic use and thus might decrease the observed association. In the current work, we presented the data with adjustment for socioeconomic status; however, there was no change in association when socioeconomic status was not included in the adjustment (data not shown).

Table 4. Risk for Psychotic Disorder as a Function of the Number of Specific Antibiotic Courses

No. of Antibiotic Courses	Cases, n (%)	Controls, n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)[a,b]
Penicillins				
0	1,828 (67.96)	7,316 (68.73)	Reference	Reference
1	375 (13.94)	1,479 (13.90)	1.02 (0.85–1.23)	0.9 (0.63–1.28)
2–5	387 (14.39)	1,462 (13.74)	1.08 (0.88–1.32)	1.01 (0.71–1.43)
>5	100 (3.72)	387 (3.64)	1.06 (0.74–1.52)	0.94 (0.56–1.59)
Cephalosporins				
0	2,540 (94.42)	10,046 (94.38)	Reference	Reference
1	103 (3.83)	389 (3.65)	1.05 (0.76–1.45)	1.09 (0.65–1.83)
2–5	38 (1.41)	192 (1.80)	0.78 (0.47–1.30)	0.60 (0.27–1.36)
>5	9 (0.33)	17 (0.16)	2.13 (0.67–6.76)	1.49 (0.19–11.51)
Macrolides				
0	2,405 (89.41)	9,543 (89.66)	Reference	Reference
1	167 (6.21)	642 (6.03)	1.03 (0.80–1.33)	1.04 (0.68–1.59)
2–5	98 (3.64)	384 (3.61)	1.02 (0.73–1.41)	0.7 (0.40–1.24)
>5	20 (0.74)	75 (0.70)	1.06 (0.52–2.16)	0.81 (0.29–2.24)
Quinolones				
0	2,621 (97.43)	10,362 (97.35)	Reference	Reference
1	47 (1.75)	205 (1.93)	0.91 (0.58–1.43)	1.06 (0.53–2.15)
2–5	21 (0.78)	69 (0.65)	1.22 (0.61–2.45)	1.00 (0.33–3.00)
>5	1 (0.04)	8 (0.08)	0.50 (0.03–9.23)	1.08 (0.04–27.19)
Sulfonamides				
0	2,515 (93.49)	9,933 (93.32)	Reference	Reference
1	120 (4.46)	496 (4.66)	0.96 (0.71–1.29)	0.76 (0.46–1.26)
2–5	46 (1.71)	196 (1.84)	0.93 (0.58–1.49)	0.59 (0.27–1.26)
>5	9 (0.33)	19 (0.18)	1.80 (0.59–5.50)	0.63 (0.07–5.54)
Tetracyclines				
0	2,508 (93.23)	9,916 (93.16)	Reference	Reference
1	104 (3.87)	434 (4.08)	0.94 (0.69–1.29)	0.94 (0.56–1.59)
2–5	51 (1.90)	212 (1.99)	0.94 (0.61–1.47)	1.03 (0.52–2.03)
>5	27 (1.00)	82 (0.77)	1.30 (0.70–2.43)	1.83 (0.75–4.51)
Imidazole				
0	2,596 (96.51)	10,329 (97.04)	Reference	Reference
1	73 (2.71)	245 (2.30)	1.20 (0.82–1.76)	1.30 (0.73–2.32)
2–5	20 (0.74)	68 (0.64)	1.19 (0.58–2.44)	1.08 (0.40–2.92)
>5	1 (0.04)	2 (0.02)	2.06 (0.71–59.79)	NA
Antifungals				
0	2,582 (95.99)	10,259 (96.38)	Reference	Reference
1	52 (1.93)	202 (1.90)	1.01 (0.65–1.57)	0.79 (0.37–1.71)
2–5	49 (1.82)	152 (1.43)	1.3 (0.81–2.08)	1.08 (0.53–2.17)
>5	7 (0.26)	31 (0.29)	0.91 (0.28–2.92)	1.20 (0.23–6.14)
Antivirals				
0	2,658 (98.81)	10,517 (98.81)	Reference	Reference
1	26 (0.97)	96 (0.90)	1.08 (0.58–2.00)	0.75 (0.29–1.94)
2–5	4 (0.15)	24 (0.23)	0.66 (0.15–2.92)	0.97 (0.19–4.94)
>5	2 (0.07)	7 (0.07)	1.11 (0.12–10.04)	NA

[a]Adjusted for obesity (body mass index > 30), smoking (ever/never), alcohol consumption, Townsend quintiles, number of urinary tract infections, and upper and lower respiratory infections before index date.
[b]After the Bonferroni correction, the *P* value needed to show statistical significance was .006.
Abbreviations: NA = not applicable, OR = odds ratio.

There was a mild increase of depression and anxiety risk with a single course of antifungal medications. There was no tendency of increased risk with increased number of courses of antifungals. Similarly, there was a mild increased risk for depression with a single course of antiviral medications that was not replicated for anxiety or with increased number of courses. These associations might suggest residual confounding as an explanation to our results. However, since no association was observed for cases with psychosis with any antibiotic, antiviral, or antifungal medication or with any number of courses, this possibility is less likely. Although the number of individuals with antiviral and antifungal medications was low compared to antibiotics, our study did not lack statistical power.

Finally, since we performed multiple comparisons for exposure to various predefined antibiotic groups, we increased the likelihood of rejecting the null hypotheses when significant (type I error). We used the conservative Bonferroni correction in the final statistical analysis to address this issue.

In summary, this is the first population-based study that demonstrated an association between exposure to specific antibiotic groups and risk for both depression and anxiety, but not psychosis. The risk increased with the number of antibiotic exposures and reached approximately 50% for more than 5 courses of penicillin. Although we cannot rule out residual bias, those results are in line with recent animal models that show a central role for the gut-brain axis in neurologic pathways, behavior, and psychiatric pathology. Future human studies should assess the microbiota composition in psychiatric disorders, specifically depression and anxiety, and evaluate possible association between antibiotic administration, dysbiosis, and disease exacerbations. Additional studies may focus on the effect of probiotic administration in symptomatic patients with depression and anxiety.

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Supplementary material: Available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Antibiotic Exposure and the Risk for Depression, Anxiety, or Psychosis: A Nested Case-Control Study

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List of Supplementary Material for the article

1. **eTable 1** Risk for depressive disorders as a function of time from last prescription of specific antibiotic courses
2. **eTable 2** Risk for anxiety disorder as a function of time from last prescription of specific antibiotic courses
3. **eTable 3** Risk for psychotic disorder as a function of time from last prescription of specific antibiotic courses
4. **eAppendix 1** List of Read codes according to three psychiatric diagnoses (depression, anxiety, and psychosis)

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary eTable 1. Risk for Depressive Disorders as a Function of Time from Last Prescription of Specific Antibiotic Courses

Antibiotic type	Time from last antibiotic prescription (years)	Cases	Controls	Crude OR	Adjusted OR [a,b]
Penicillins	0	125,654 (61.91%)	550,056 (68.42%)	Reference	Reference
	1-5	67,960 (33.48%)	215,007 (26.74%)	1.54 (1.51-1.57)	1.38 (1.33-1.43)
	5-10	8,502 (4.19%)	34,913 (4.34%)	1.23 (1.19-1.28)	1.15 (1.08-1.22)
	>10	858 (0.42%)	3,985 (0.50%)	1.11 (0.99-1.23)	1.04 (0.92-1.18)
Cephalosporines	0	186,925 (92.09%)	755,390 (93.96%)	Reference	Reference
	1-5	12,460 (6.14%)	36,289 (4.51%)	1.44 (1.39-1.48)	1.31 (1.23-1.39)
	5-10	3,081 (1.52%)	10,311 (1.28%)	1.26 (1.19-1.34)	1.19 (1.09-1.30)
	>10	508 (0.25%)	1,971 (0.25%)	1.09 (0.94-1.26)	1.09 (0.93-1.28)
Macrolides	0	177,485 (87.44%)	725,383 (90.23%)	Reference	Reference
	1-5	20,352 (10.03%)	60,247 (7.49%)	1.42 (1.38-1.45)	1.29 (1.24-1.35)
	5-10	4,401 (2.17%)	15,598 (1.94%)	1.2 (1.14-1.26)	1.13 (1.05-1.22)
	>10	736 (0.36%)	2,733 (0.34%)	1.16 (1.03-1.31)	1.13 (0.99-1.30)
Quinolones	0	196,297 (96.71%)	784,315 (97.56%)	Reference	Reference
	1-5	5,320 (2.62%)	15,028 (1.87%)	1.42 (1.36-1.49)	1.31 (1.21-1.42)
	5-10	1,204 (0.59%)	4,135 (0.51%)	1.18 (1.07-1.29)	1.06 (0.94-1.21)
	>10	153 (0.08%)	483 (0.06%)	1.29 (1.00-1.67)	1.18 (0.87-1.61)
Sulfonamides	0	183,752 (90.53%)	744,652 (92.62%)	Reference	Reference
	1-5	15,662 (7.72%)	46,394 (5.77%)	1.41 (1.37-1.45)	1.33 (1.26-1.40)
	5-10	3,088 (1.52%)	11,356 (1.41%)	1.15 (1.08-1.21)	1.07 (0.98-1.16)
	>10	472 (0.23%)	1,559 (0.19%)	1.28 (1.10-1.49)	1.22 (1.03-1.45)
Tetracyclines	0	186,184 (91.73%)	750,775 (93.38%)	Reference	Reference
	1-5	13,457 (6.63%)	41,243 (5.13%)	1.33 (1.30-1.37)	1.24 (1.17-1.30)
	5-10	2,947 (1.45%)	10,576 (1.32%)	1.15 (1.08-1.22)	1.09 (1.00-1.19)
	>10	386 (0.19%)	1,367 (0.17%)	1.18 (1.00-1.39)	1.19 (0.99-1.43)
Imidazole	0	193,497 (95.33%)	777,161 (96.67%)	Reference	Reference
	1-5	7,569 (3.73%)	20,518 (2.55%)	1.51 (1.45-1.57)	1.34 (1.25-1.44)
	5-10	1,680 (0.83%)	5,522 (0.69%)	1.26	1.12

				(1.17-1.37)	(0.99-1.25)
	>10	228 (0.11%)	760 (0.1%)	1.26	1.17
				(1.02-1.55)	(0.92-1.49)
Antifungals	0	193,341 (95.25%)	773,078 (96.16%)	Reference	Reference
	1-5	7,808 (3.85%)	24,261 (3.02%)	1.3	1.18
				(1.25-1.35)	(1.10-1.26)
	5-10	1,625 (0.80%)	5,912 (0.74%)	1.11	1.04
				(1.03-1.20)	(0.93-1.17)
	>10	200 (0.10%)	710 (0.09%)	1.15	1.12
				(0.92-1.44)	(0.87-1.44)
Antivirals	0	200,136 (98.60%)	794,854 (98.87%)	Reference	Reference
	1-5	2,307 (1.14%)	7,233 (0.90%)	1.27	1.12
				(1.18-1.35)	(1.04-1.27)
	5-10	481 (0.24%)	1,684 (0.21%)	1.14	1.09
				(0.99-1.31)	(0.90-1.32)
	>10	50 (0.02%)	190 (0.02%)	1.05	1.00
				(0.68-1.63)	(0.60-1.65)

[a] Adjusted for obesity (body mass index > 30), smoking (ever/never), alcohol consumption, Townsend quantiles, number of urinary tract, and upper and lower respiratory infections before index date.
[b] After the Bonferroni correction, the *P* value needed to show statistical significance was .006.
Abbreviation: OR = odds ratio.

Supplementary eTable 2. Risk for Anxiety Disorder as a Function of Time from Last Prescription of Specific Antibiotic Courses

Antibiotic type	Time from last antibiotic prescription (years)	Cases	Controls	Crude OR	Adjusted OR [a,b]
Penicillins	0	8,487 (58.25%)	36,598 (63.25%)	Reference	Reference
	1-5	5,160 (35.42%)	17,581 (30.38%)	1.37 (1.29-1.47)	1.3 (1.15-1.47)
	5-10	818 (5.61%)	3,215 (5.56%)	1.23 (1.08-1.39)	1.18 (0.98-1.43)
	>10	105 (0.72%)	468 (0.81%)	1.09 (0.79-1.49)	1.09 (0.76-1.57)
Cephalosporines	0	13,127 (90.10%)	53,215 (91.97%)	Reference	Reference
	1-5	1,048 (7.19%)	3,260 (5.63%)	1.35 (1.21-1.50)	1.33 (1.09-1.62)
	5-10	329 (2.26%)	1,140 (1.97%)	1.22 (1.02-1.47)	1.13 (0.87-1.47)
	>10	66 (0.45%)	247 (0.43%)	1.13 (0.75-1.70)	1.18 (0.75-1.87)
Macrolides	0	12,390 (85.04%)	50,693 (87.61%)	Reference	Reference
	1-5	1,613 (11.07%)	5,168 (8.93%)	1.30 (1.20-1.42)	1.18 (1.01-1.38)
	5-10	487 (3.34%)	1,659 (2.87%)	1.24 (1.07-1.45)	1.14 (0.91-1.43)
	>10	80 (0.55%)	342 (0.59%)	1.00 (0.70-1.42)	0.99 (0.67-1.48)
Quinolones	0	13,935 (95.64%)	55,982 (96.75%)	Reference	Reference
	1-5	461 (3.16%)	1,362 (2.35%)	1.37 (1.18-1.60)	1.50 (1.16-1.94)
	5-10	146 (1.00%)	459 (0.79%)	1.31 (1.00-1.71)	1.13 (0.76-1.68)
	>10	28 (0.19%)	28 (0.19%)	1.99 (1.03-3.85)	1.90 (0.88-4.10)
Sulfonamides	0	12,771 (87.65%)	52,247 (90.30%)	Reference	Reference
	1-5	1,356 (9.31%)	4,148 (7.17%)	1.39 (1.26-1.53)	1.46 (1.24-1.73)
	5-10	373 (2.56%)	1,205 (2.08%)	1.33 (1.12-1.59)	1.30 (1.00-1.68)
	>10	70 (0.48%)	262 (0.45%)	1.16 (0.79-1.70)	1.16 (0.75-1.80)
Tetracyclines	0	12,991 (89.16%)	53,025 (91.64%)	Reference	Reference
	1-5	1,185 (8.13%)	3,521 (6.09%)	1.40 (1.27-1.55)	1.39 (1.17-1.66)
	5-10	343 (2.35%)	1,125 (1.94%)	1.28 (1.07-1.53)	1.32 (1.01-1.73)
	>10	51 (0.35%)	191 (0.33%)	1.12 (0.71-1.75)	1.33 (0.80-2.21)
Imidazole	0	13,660 (93.75%)	55,108 (95.24%)	Reference	Reference
	1-5	631 (4.33%)	1,918 (3.31%)	1.37 (1.20-1.56)	1.50 (1.19-1.89)
	5-10	244 (1.67%)	719 (1.24%)	1.43	1.30

				(1.16-1.78)	(0.95-1.80)
	>10	35 (0.24%)	117 (0.2%)	1.25	1.21
				(0.73-2.16)	(0.64-2.27)
Antifungals	0	13,689 (93.95%)	54,972 (95.01%)	Reference	Reference
	1-5	639 (4.39%)	2,182 (3.77%)	1.19	1.24
				(1.05-1.36)	(0.99-1.55)
	5-10	216 (1.48%)	605 (1.05%)	1.47	1.57
				(1.18-1.85)	(1.15-2.16)
	>10	26 (0.18%)	103 (0.18%)	1.04	1.24
				(0.56-1.93)	(0.64-2.40)
Antivirals	0	14,317 (98.26%)	56,999 (98.51%)	Reference	Reference
	1-5	191 (1.31%)	676 (1.17%)	1.12	1.13
				(0.89-1.40)	(0.82-1.55)
	5-10	53 (0.36%)	166 (0.29%)	1.28	1.36
				(0.82-1.97)	(0.76-2.41)
	>10	9 (0.06%)	21 (0.04%)	1.71	1.53
				(0.57-5.10)	(0.44-5.29)

[a] Adjusted for obesity (body mass index > 30), smoking (ever/never), alcohol consumption, Townsend quantiles, number of urinary tract, and upper and lower respiratory infections before index date.
[b] After the Bonferroni correction, the *P* value needed to show statistical significance was .006.
Abbreviation: OR = odds ratio.

Supplementary eTable 3. Risk for Psychotic Disorder as a Function of Time from Last Prescription of Specific Antibiotic Courses

Antibiotic type	Time from last antibiotic prescription (years)	Cases	Controls	Crude OR	Adjusted OR [a,b]
Penicillins	0	1,828 (67.96%)	7,316 (68.73%)	Reference	Reference
	1-5	723 (26.88%)	2,780 (26.12%)	1.05 (0.90-1.23)	0.95 (0.71-1.28)
	5-10	134 (4.98%)	483 (4.54%)	1.11 (0.81-1.51)	1.05 (0.67-1.65)
	>10	5 (0.19%)	65 (0.61%)	0.30 (0.08-1.10)	0.22 (0.04-1.17)
Cephalosporines	0	2,540 (94.42%)	10,046 (94.38%)	Reference	Reference
	1-5	99 (3.68%)	412 (3.87%)	0.96 (0.69-1.32)	0.87 (0.49-1.55)
	5-10	40 (1.49%)	155 (1.46%)	1.04 (0.62-1.74)	0.99 (0.48-2.05)
	>10	11 (0.41%)	31 (0.29%)	1.47 (0.53-4.07)	1.09 (0.33-3.60)
Macrolides	0	2,405 (89.41%)	9,543 (89.66%)	Reference	Reference
	1-5	214 (7.96%)	804 (7.55%)	1.06 (0.84-1.33)	0.89 (0.59-1.36)
	5-10	63 (2.34%)	237 (2.23%)	1.05 (0.69-1.60)	0.98 (0.54-1.80)
	>10	8 (0.30%)	60 (0.6%)	0.51 (0.17-1.48)	0.61 (0.18-2.05)
Quinolones	0	2,621 (97.43%)	10,362 (96.59%)	Reference	Reference
	1-5	50 (1.86%)	207 (1.94%)	0.96 (0.62-1.49)	0.96 (0.45-2.08)
	5-10	17 (0.63%)	63 (0.59%)	1.06 (0.50-2.28)	1.25 (0.48-3.21)
	>10	2 (0.07%)	12 (0.11%)	0.66 (0.08-5.54)	0.71 (0.04-14.10)
Sulfonamides	0	2,515 (93.49%)	9,933 (93.32%)	Reference	Reference
	1-5	134 (4.98%)	522 (4.90%)	1.01 (0.76-1.35)	0.76 (0.46-1.28)
	5-10	35 (1.30%)	161 (1.51%)	0.85 (0.50-1.46)	0.58 (0.26-1.31)
	>10	6 (0.22%)	28 (0.26%)	0.82 (0.21-3.14)	0.64 (0.13-3.10)
Tetracyclines	0	2,508 (93.23%)	9,916 (93.16%)	Reference	Reference
	1-5	132 (4.91%)	554 (5.20%)	0.94 (0.71-1.25)	1.18 (0.74-1.86)
	5-10	45 (1.67%)	142 (1.33%)	1.25 (0.76-2.04)	0.97 (0.46-2.05)
	>10	5 (0.19%)	32 (0.30%)	0.60 (0.16-2.32)	0.56 (0.12-2.57)
Imidazole	0	2,596 (96.51%)	10,329 (97.04%)	Reference	Reference
	1-5	72 (2.68%)	235 (2.21%)	1.24 (0.84-1.82)	1.25 (0.67-2.33)
	5-10	17 (0.63%)	61 (0.57%)	1.13	1.47

				(0.53-2.43)	(0.57-3.75)
	>10	5 (0.19%)	19 (0.18%)	1.04	0.96
				(0.26-4.20)	(0.19-4.83)
Antifungals	0	2,582 (95.99%)	10,259 (96.38%)	Reference	Reference
	1-5	82 (3.05%)	298 (2.80%)	1.10	0.97
				(0.77-1.57)	(0.53-1.75)
	5-10	26 (0.97%)	75 (0.70%)	1.36	1.15
				(0.71-2.59)	(0.45-2.96)
	>10	-	12 (0.11%)	NA	NA
Antivirals	0	2,658 (98.81%)	10,517 (98.81%)	Reference	Reference
	1-5	27 (1.00%)	86 (0.81%)	1.24	1.03
				(0.67-2.28)	(0.40-2.64)
	5-10	5 (0.19%)	36 (0.34%)	0.55	0.43
				(0.14-2.07)	(0.08-2.35)
	>10	-	5 (0.05%)	NA	NA

[a] Adjusted for obesity (body mass index > 30), smoking (ever/never), alcohol consumption, Townsend quantiles, number of urinary tract, and upper and lower respiratory infections before index date.
[b] After the Bonferroni correction, the *P* value needed to show statistical significance was .006.
Abbreviations: NA = not applicable, OR = odds ratio.

Supplementary eAppendix: List of Read codes according to the three psychiatric diagnoses (depression, anxiety, and psychosis)

Depression

1465; 212S.00; E112.00; E112.11; E112.12 ; E112.13; E112.14; E112000 ; E112100;

E112200; E112300; E112400; E112500; E112600; E112z00; E113.00; E113.11;

E113000; E113100; E113200; E113300; E113400; E113500; E113600; E113700;

E113z00; E11y200; E130.11; E135.00; E204.00; E290.00; E290z00; E291.00;

E2B..00; E2B0.00; E2B1.00; Eu32.00; Eu32.11; Eu32.12; Eu32.13; Eu32000;

Eu32100; Eu32200; Eu32211; Eu32212; Eu32213; Eu32300; Eu32311; Eu32312;

Eu32313; Eu32314; Eu32400 ; Eu32500; Eu32600; Eu32700; Eu32800; Eu32y00;

Eu32y11; Eu32y12; Eu32z00; Eu32z11; Eu32z12; Eu32z13; Eu32z14; Eu33.00;

Eu33.11; Eu33.12; Eu33.13; Eu33.14; Eu33000; Eu33100; Eu33211; Eu33212;

Eu33214; Eu33311; Eu33313; Eu33314; Eu33315; Eu33316; Eu33400; Eu33y00

Eu33z00; Eu33z11; Eu34113; Eu3y111.

Anxiety

1465; E200400; E200500; E202.12; Eu05400; Eu40.00; Eu40y00; Eu40z00; Eu41.00;

Eu41000; Eu41100; Eu41y00 ; Eu41z00; Eu41z11; Eu05400.

Psychosis

212 ;1464W.00; E100.00; E100.11; E100000; E100100; E100300; E100400;

E100500; E100z00; E101.00; E101000; E101100; E101200; E101300; E101400;

E101500; E101z00; E102.00; E102000; E102100; E102200 ; E102300; E102400;

E102500; E102z00; E103.00; E103000; E103100; E103200 ; E103300; E103400;

E103500; E103z00; E105.00; E105000; E105100; E105200 ; E105300; E105400;

E105500; E105z00; E106.00; E107.00; E107.11; E107000; E107100; E107200;

E107300; E107400; E107500; E107z00; E10y.00; E10y.11; E10y000; E10y100; E10yz00; E10z.00; E13z.11; Eu20.00; Eu20000; Eu20011; Eu20100; Eu20111; Eu20200; Eu20300; Eu20311; Eu20500; Eu20511; Eu20600; Eu20y00; Eu20y11; Eu20z00; Eu21.13; Eu23.00; Eu23111; Eu23112; Eu23200; Eu23300; Eu23y00; Eu23z00; Eu24.13; Eu25100; Eu25111; Eu25112: Eu25211; Eu2y.00; Eu2y.00; ZV11000; Eu05200.