MEDICINE OVER MIND: A COMPREHENSIVE LITERATURE REVIEW ON ANTIBIOTIC USE AND PSYCHIATRIC DISORDERS

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ABSTRACT

Background: Psychiatric disorders, especially depression and anxiety, are exponentially increasing in post-industrial society. Antibiotic exposure may partly be attributable to the development of such psychiatric disorders. This review study aimed to summarize and explore the associations between antibiotic exposure and human psychiatric disorders, scrutinize the research gaps, and contemplate future research perspectives. This study also identified the reasons for antibiotic misuse and possible prevention and management strategies. **Methods:** PubMed, Scopus databases, and Google Scholar search engines were searched for relevant articles using the exposure keywords "antibiotic exposure" and outcome keywords "psychiatric disorder" and associated medical subheading terms (MeSH). Human epidemiological studies were retrieved irrespective of age, race, country, and publication year up to August 2024. Finally, 15 articles that fulfilled our inclusion criteria were selected and summarized in the present review. **Results:** This review summarized all associations between antibiotic exposure and psychiatric disorders along with potent confounders. Most of the studies found a positive association between antibiotic exposure and psychiatric disorders, especially with depression and anxiety, even after adjustment for major lifestyle and demographic factors. The associations might depend on gender, age, antibiotic types, and type of bacterial infections. The magnitude of these associations was higher for higher doses, more frequent uses, and recent uses of antibiotics. **Conclusions:** Our summarized pieces of evidence indicate that antibiotic exposure might be associated with depression and anxiety in humans. However, a nationwide prospective cohort using human biomonitoring data of antibiotics is warranted to explore the overall scenario in the future.

KEYWORDS: Antibiotics; depression; anxiety; psychiatric disorder.

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Introduction

The psychiatric disorder, also known as mental illness, refers to a broad range of problems that disturb thoughts, feelings, behavior, or mood [Busfield, 2011; Kendler et al., 2011]. Most severely diagnosed forms of psychiatric disorders include depression, anxiety, personality disorders, and schizophrenia. However, in recent years, depression and anxiety have become common types of psychiatric disorders among all groups of populations worldwide [Henderson et al., 2011; Skoog, 2011]. The major determinants of depression include deficient pleasure in daily life matters, feeling sadness, sleeping difficulties, experiencing worthlessness, and suicidal ideation [Liao et al., 2015]. Approximately 280 million people in the world (5% adults and 5.7% elderly, >60 years) have been affected by depression [WHO, 2021]. It was reported that 17.8% of patients with depression increased from 2005 to 2015; thus, it is considered the leading cause of disability-adjusted life years in 2019 [Collaborators, 2019]. Likewise, anxiety is an emotional state of mind where one generally feels tension and worries about thoughts and physical changes [APA, 2023]. In the American subcontinent, more than 58 million people are estimated to be suffering from anxiety disorders in 2015, among them ~8% female and 4% male [APA, 2023; PAHO, 2023]. The key risk stage for the development of anxiety disorders, namely specific phobia, social phobia, agoraphobia, panic disorder, and so on, is the early childhood and adolescence period [Beesdo at al., 2009]. According to the report of the US CDC, nearly 4.4 million US children with 3 to 17 years of age have been diagnosed with anxiety [Ghandour et al., 2019]. Even the rate of anxiety and depression in young children (6 to 17 years old) is getting higher (from 5.4% in 2003 to 8.4% in 2011) with time [Bitsko et al., 2018]. Several biological and environmental risk factors, including antibiotic exposure in prenatal and postnatal stages, notably in early childhood have been reported to be associated with depression and anxiety [Braithaite et al., 2014; Johnson and Marlow, 2011].

On the other hand, antibiotics were most commonly prescribed for the treatment of bacterial infections, and considered as a prime treatment strategy against different types of infectious diseases, and disease severity [Lee et al., 2021]. The number and frequency of antibiotic use are rapidly increasing with the significant improvement of modern treatment facilities [Klein et al., 2018]. Previously, it was reported that antibiotic consumption increased to 21.1-34.8 billion defined daily doses between 2000 and 2015 globally [Klein et al., 2018; Klein et al., 2021]. The prescription rate rapidly increased in pregnant women from 37% to 65.8% [Mensah et al., 2017; Stokholme et al., 2013] and 58% in children [Di Martino et al., 2017]. The over-prescription of antibiotics during pregnancy and early childhood may cause immune dysregulation and bacterial resistance [Langdon et al., 2016]. Single or combined exposure to antibiotics in infections may alter the gut microbiome and its composition, called dysbiosis, defined in the microbiota-gut-brain axis cognitive theory, which ultimately affects the brain [Gareau, 2014; Ishii et al., 2016]. In support of the theory, several animal studies have also shown that antibiotic exposure was positively associated with depression and anxiety [Bercik et al., 2011; Farzi et al., 2018; Jang et al., 2018; Leclercq et al., 2017; Verdu et al., 2006]. However, human epidemiological research is limited. Even the existing literature review to summarize such a type of study is rare. Therefore, we aimed to summarize the human epidemiological studies and explore the associations between antibiotic exposure and psychiatric disorders in humans, scrutinize the research gaps, and contemplate future research. Finally, we discussed the possible reasons for frequent antibiotic use and how the misuse and/or overdose of antibiotics can be prevented or managed.

Methodology

PubMed & Scopus databases, and Google Scholar search engine were searched for relevant articles specifically that investigated the associations of antibiotic exposure with psychiatric disorders by the keyword "antibiotic exposure" and associated medical subject heading terms (MeSH), AND "psychiatric disorder" and associated MeSH especially "anxiety" and "depression" to identify original research articles of human epidemiological studies. Additional filtering was performed to customize the research based on article type (journal articles), study subjects (human), and language (English). We did not limit the publication year and considered all articles published up to August 2024. The references of the retrieved research articles were also searched for relevant publications.

The full-length original research work from all over the world, regardless of gender, age group, and race/ethnicity, was included in this review. Inclusion criteria were (1) observational studies that evaluated the relationships of antibiotic use with psychiatric disorders (cohort, cross-sectional, case-control study); (2) all ages and/or life stage of antibiotic exposure; (3) assessment of antibiotic exposure/uses made by medical history or questionnaire-based survey or human biomonitoring (4) outcome was psychiatric disorders; and, (5) article must be written in English and published up to August 2024. Information regarding the study design and study participants, antibiotic exposure assessment or usage, outcome ages, covariates or confounders, and psychiatric disorders was retrieved and summarized. All case reports, clinical trials, and treatment strategies or intervention studies were excluded. The articles that investigated the associations of antibiotic exposure with ADHD or ASD, and the association of anti-infective agents (did not mention antibiotic) with psychiatric disorders, were also excluded. Finally, a total of 15 articles that fulfill our inclusion criteria were selected (Figure 1) and summarized in this review (Table 1). The first author of the present study searched and retrieved the existing relevant research articles, and the second authors cross-checked to avoid selection bias. We did not select articles based on only positive association; rather, we considered all articles addressing positive, negative, and null associations.

Add Figure 1 here.

Results

In this review, we summarized a total of 15 original research articles, among them 11 were cohort studies, 2 were cross-sectional, and the remaining 2 were case-control studies (Table 1). They recruited vast population groups, including pregnant women, mother-child pairs, children, adolescents, adults, and elderly people, depending on their study design. Most of the studies evaluated antibiotic exposure through a questionnaire-based survey and retrieved information on the history of antibiotic use, types of antibiotics used, types of infections/diseases for which the antibiotic was used, the dose and frequency/course of antibiotic use, etc. We found only one study where antibiotic exposure was assessed through human urinary biomonitoring [Liu et al., 2021]. The most common outcomes were anxiety and depression. All of the studies evaluated the associations between exposure (antibiotics) and outcomes (mental disorder) after adjusting for potential confounders or covariates.

Table 1. Summary of studies highlighting the associations of antibiotic exposure with depression and anxiety (n=15)

Ref.	Study design, Country	Study subjects, Age (n)	Antibiotic exposure	Outcome age	Outcome (s)	Covariates	Key findings
Prichett et al., 2022	Retrospective cohort (USA)	Children, adolescents, and adults, 8-20y (5244)	Antibiotic use Types (Questionnaire)	8-20y	Anxiety and/or Depression	a, b, d, i	• Antibiotic prescription (any) was found to be associated with an increased risk of anxiety and/or depression [HRR=119 (1.00, 1.430]. • A broad-spectrum antibiotic prescription (first) had a higher risk than no prescription, narrow-spectrum prescription, or topical prescription [HRR=1.27 (1.04, 1.54)]. • In males, antibiotic prescription (any) showed a higher risk [HRR=1.45 (1.05, 1.99)], whereas in females there was no risk

							[HRR=1.08 (0.87, 1.34)]
Hu et al., 2022	Cohort (Sweden)	Adults, ≥30y (309,419 cancer patients, antibiotics used =116,290 and not used =193,129)	Antibiotic use Dose Frequency (Questionnaire/medical databases)	≥30y	Psychosis, depression, anxiety, or stress-related disorders	J, k, l, m	• Usage of any antibiotic over no antibiotic use had a higher risk for composite psychiatric disorders [HR= 1.23 (1.16, 1.30)], depression [HR= 1.21 (1.11, 1.31)], anxiety [HR=1.32 (1.22, 1.44)] and stress-related disorders [HR= 1.21 (1.05, 1.39)]. • The association was very strong for broad-spectrum antibiotics [HR=1.27 (1.18, 1.37)], higher doses [HR=1.32 (1.22, 1.44)], more frequent use [HR=1.33 (1.21, 1.46)], and recent use [HR=1.26 (1.17, 1.35)].
Lee et al., 2021	Retrospective cross-sectional (South Korea)	Adults ≥20y, (With MDD=16950, without MDD=67800)	Antibiotic use Dose Frequency (Questionnaire/medical database)	≥20y	Depression	A, b, n, k,	• Treatment with antibiotics in patients with MDD showed 1.31-fold higher risks (95% CI: 1.25, 1.36) for depression in comparison to those without MDD patients. • With increased age and prescription days, the association between antibiotic treatment and MDD was found to be increased.
Liang et al., 2021	Cohort (UK)	Early life-teenager or childhood (158444)	Antibiotic use Dose Frequency (Questionnaire)	40–69 y	Depression and anxiety	a, b, o,	• Long-term antibiotic use during early life was positively associated with anxiety (p <0.05, b = 0.12) and depression (p<0.05, b = 0.25).
Liu et al., 2021	Cross-sectional (China)	Elder people, ≥ 60y (990)	Human biomonitoring, 45 antibiotics by LC-MS	≥ 60y	Depression	a, b, c, e, p, g, h, q, r, s, t, u	• The elderly exposed to higher concentrations of azithromycin and sulfaclozine had increased risks of depression [OR = 1.81 (1.09, 3.00)] and [OR = 1.54 (1.05, 2.28)], respectively than that of the control group. • Tetracyclines [OR = 1.48 (1.02, 2.16)] and veterinary antibiotics (Vas) [OR = 1.53 (1.06, 2.20)] were positively correlated with increased risks of depression over other groups. • In males, high concentrations of VAs were associated with elevated risks of depression [OR = 2.04 1.13, 3.71)]. The high concentrations of tetracyclines [OR =1.74 (1.04, 2.85)] and all antibiotics [OR = 2.24 (1.01, 2.94)], were positively associated with depression in females, respectively. • After sex stratification, they found significant associations mainly in the subjects under the age of 70.
Delara et al., 2021	Retrospective cohort (Canada)	Mother-infant dyads, up to 3y, (221139)	Antibiotic use Dose Frequency (Questionnaire)	>3 to 19y	Mood and anxiety disorders (MADs)	a, b, d, w, y, z, aa, ab, ac, ad, ae.	• Prenatal exposure (during pregnancy) to one or more antibiotic courses showed significantly higher rates of MADs in children [aHR=1.08 (1.03, 1.13)] in comparison to non-exposed. • Antibiotic exposure during the first three years of life (overall) showed null associations with MADs [aHR=1.00 (0.94, 1.07)]. • Postnatal exposure to tetracyclines, aminoglycosides, quinolones (33%), or sulfonamides and trimethoprim (28%) was shown a significantly increased risk of MADs.
Fan et al., 2020	Cohort (UK)	Mother-children, Mother=14-50 y, children=birth-	Antibiotic use Dose Frequency (Questionnaire)	birth to 14 y	Cerebral palsy	af, ag	• Prenatal macrolide or penicillin antibiotic use (50-10 wk before pregnancy, 1st trimester, 2nd-3rd trimester, or any time) had no associations with children's cerebral palsy and epilepsy.

		14y (104605 children)					
Lavebratt et al., 2019	Cohort (Finland)	Mother-infant pair, up to 2 years (990098)	Antibiotic use Dose Frequency (Questionnaire)	>2y	Anxiety, mood, sleep, ASD, ADHD, and conduct disorder	a, ah	• First to third-trimester antibiotic exposure associated with increased risk (1-15%) for any psychiatric diagnosis in children from birth (1996-2012) to 2014 [T1, HR=1.15 (1.13, 1.18); T2, HR= 1.14 (1.12, 1.16); T3, HR = 1.14 (1.12, 1.17), respectively]. • In the second year, the strongest risk was seen in sleep disorders [HR1-2y=1.40 (1.24, 1.60)], followed by ADHD/conduct disorder [HR1-2y=1.26 (1.20, 1.33)], and other behavioral and emotional disorders [$HR_{1–2y}$= 1.24 (1.17, 1.31)].
Slykerman et al., 2019	Cohort (New Zealand)	Children, <2y (474)	Antibiotic use (Questionnaire)	11y	Anxiety, ADHD, impulsivity, hyperactivity, and so on.	y, ai, d, w	• Antibiotic exposure in the first 6 months of life was significantly associated with increased risk of executive function [OR=3.8 (1.2, 11.7)], anxiety [OR=5.4 (1.4, 20.7)], and emotional problems [OR= 9.2 (2.0, 43.0)].
Sun et al., 2019	Case-control (Sweden)	Adults and elder, mean 68.6y (ALS=2484, control=5×2484)	Antibiotic use Types Dose Frequency (Questionnaire)	mean 68.6y	ALS	a, b, r	• Antibiotic use was positively associated with a higher risk of ALS. The ORs were increasing with the number of prescriptions [for 1 prescription, OR=1.06 (0.94, 1.19), 2-3 prescriptions, OR=1.13 (1.00, 1.28), and ≥4 prescriptions, OR= 1.18 (1.03, 1.35)]. • More than two prescriptions of beta-lactamase-sensitive penicillin were associated with a higher risk of ALS [OR=1.28 (1.10, 1.50)] over other antibiotics.
Kohler-Forseberg et al., 2019	Cohort (Denmark)	At birth between 1995-2012 (1098 930)	Antibiotic use Types Dose Frequency (Questionnaire)	Mean age of 9.76 (4.91) y	Schizophrenia, OCD, personality & and behavior disorders, mental disorders, etc.	a, b, aj	• Any antibiotic use was found to be exhibited increased risk estimates of mental disorder [HRR=1.41 (1.35, 1.46)]. • Broad spectrum [HRR= 1.35 (1.27, 1.44)], moderate [HRR=1.24 (1.16, 1.32)], narrow spectrum [HRR=1.24 (1.16, 1.33)] and topical [HRR= 1.22 (1.14, 1.30)] antibiotic uses were also associated with the increased risk of mental disorder.
Murphy et al., 2018	Cohort (USA)	Pregnant women, 18–40 Y, intrapartum through the first 14 days postpartum (124)	Antibiotic use Dose (Questionnaire)	first 6-months postpartum	Depression	a, d, e, p, y, ak	• Antibiotic exposure was associated with postpartum depressive symptoms at 1 month [β = 0.43 (0.01, 0.86)] and 2- months (β = 0.51 (0.08, 0.94)] postpartum. • The null association was found for the relationship between antibiotic exposure and postpartum depressive symptoms at 3- or 6-month postpartum.
Kohler et al., 2017	Cohort (Denmark)	Danish people >10 y of age	Antibiotic use Dose Frequency (Medical databases)	>10y	Schizophrenia, bipolar disorder, depression	A, b, c,	• Antibiotic use (any) was associated with an increased risk of schizophrenia [HRR= 1.44 (1.25, 1.66)] and affective disorder (bipolar disorder and depression) [HRR=1.65 (1.49, 1.84)]. • The associations were similar for all types of antibiotics (broad spectrum, moderate spectrum, narrow spectrum, and topical antibiotic).
Slykerman et al., 2017	Cohort (New Zealand)	Mother-child pair, <1y and >1 to 3.5y (871)	Antibiotic use Dose Frequency (Medical databases)	3.5, 7, and 11 y	Depression ADHD, behavioral problems, etc.	v, b, am, y, w	• The study participants had more behavioral difficulties and more symptoms of depression at follow-up and reported antibiotic use. • Higher total behavioral difficulty score at the age of 3.5 and 11 years (in particular conduct problems), higher self-rated peer difficulties,

							lower self-rated prosocial behavior scores at age 11, higher parent-rated ADHD symptoms at age 11, higher teacher-reported symptoms of ADHD at age 11 and higher depression symptom scores at age 11 was significantly associated with antibiotic use at 1y of life. • The association between the ages of 1y and 3.5y was null.
Lurie et al., 2015	3 nested case-control (UK)	Adolescents and adults, 15-65y (Depression=202974& control=803961, Anxiety=14570 & control 57862 and Psycosis=2690& control=10644)	Antibiotic use Dose Frequency (Medical databases)	15-65y	Depression Anxiety Psychosis	f, an, h,	• A single antibiotic course was associated with a higher risk for depression with all antibiotic groups; penicillins, [AOR=1.23 (1.18, 1.29), and quinolones [AOR=1.25 (1.15, 1.35)]. • The risk was found to be increased recurrent antibiotic exposure for 2-5 [AOR=1.40(1.35-1.46)] and >5 courses of penicillin [AOR=1.56(1.46-1.65)], respectively. • A similar association was observed for anxiety [AOR=1.17 (1.01, 1.36) for a single course of penicillin and [AOR=1.44(1.18, 1.75)] for >5 courses. • Association was null for psychosis with any group of antibiotics.

[a]age/maternal age; [b]sex/gender/infant sex; [c]education; [d]race/ethnicity; [e]income; [f]obesity; [g]physical activity; [h]alcohol consumption/ drinking; [i]insurance status; [j]socio demographic factors; [k]medical comorbidity; [l]potential indications for antibiotics; [m]cancer stage and type; [n]the type of National Health Security program; [o]10 principal components of population structure; [p]marital status; [q]previous/present occupation; [r]living status; [s]dietary structure; [t] cognitive impairment; [u]ADL; [v]small for gestational age (SGA); [w] breastfeeding status; [x]age; [y]mode of delivery; [z]region of residence; [aa]number of births per pregnancy; [ab]number of children in the household; [ac]child medical comorbidity and antibiotic use; [ad]health care utilization; [ae]maternal history of MADs and medical conditions; [af]parity; [ag]multiple birth, chronic medical treatments, genitourinary tract infections and sexually transmitted infections during pregnancy; [ah]maternal smoking during pregnancy; mother unmarried, mother born elsewhere than Finland cesarean section mother's inpatient care due to mental health disorders, mother's purchase of psychotropic drugs (N05 or N06) during pregnancy, mother's diagnoses related to systemic inflammatory disorders, multiple birth, offspring sex, perinatal health problems; [ai]probiotic treatment group assignment; [aj]Charlson Comorbidity Index, highest parental educational level, any parental mental disorder since 1969, calendar period, and hospitalization for infection; [ak]hours in labor, perineal injury; [al]calendar-period, parental mental disorders, anti-infective prescriptions during childhood, and hospitalizations due to infections after 1995; [am]maternal school leaving age, maternal smoking in pregnancy; [an]smoking, town send quintiles, number of urinary tract infections and upper and lower respiratory tract infection.

Among the 11 cohort studies, 8 investigated the associations of prenatal or early childhood antibiotic exposure with mental disorders [Delara et al., 2021; Fan et al., 2020; Kohler-Forsberg et al., 2019; Lavebratt et al., 2019; Liang et al., 2021; Murphy et al., 2018; Slykerman et al., 2019; Slykerman et al., 2017], whereas the remaining 3 investigated the associations cross-sectionally, although the main study design was cohort [Hu et al., 2022; Kohler et al., 2017; Prichett et al., 2022]. Among the 8 cohorts, 5 recruited the mother-child pairs and investigated the associations between antibiotic exposure during pregnancy and psychiatric disorders in early childhood [Delara et al., 2021; Fan et al., 2020; Lavebratt et al., 2019; Murphy et al., 2018; Slykerman et al., 2017] whereas the other 3 recruited neonates, early child (<2y), and teenagers [Kohler-Forsberg et al., 2019; Liang et al., 2021; Slykerman et al., 2019]. Most studies found an increased risk of mental disorders in early childhood due to the use of antibiotics during early or late pregnancy [Delara et al., 2021; Lavebratt et al., 2019; Murphy et al., 2018; Slykerman et al., 2019], except one study that found null associations [Fan et al., 2020]. However, the associations between early life exposure to antibiotics with psychiatric disorders in the late childhood and adolescence period were contradictory [Delara et al., 2021; Kohler-Forsberg et al., 2019; Lavebratt et al., 2019; Liang et al., 2021; Murphy et al., 2020; Slykerman et al., 2017].

In a cross-sectional analysis of three cohorts, researchers found positive associations of any antibiotic use with the increased risk of depression, anxiety, psychosis, schizophrenia, bipolar disorder, and stress-related disorders in children, adolescents, and adults [Hu et al., 2022; Kohler et al., 2017; Prichett et al., 2022]. They also reported the increased risk of aforementioned mental disorders due to the use of broad-spectrum antibiotics in comparison to no prescription, narrow-spectrum, or tropical prescriptions [Hu et al., 2022; Prichett et al., 2022]. However, Kohler et al. found positive associations between all types of antibiotics (broad spectrum, narrow spectrum, and tropical) with psychiatric diseases [Kohler et al., 2017]. Both studies also found sex-specific relationships (positive in males and null in females) between antibiotic use and mental disorders. The magnitude of these associations was higher for higher doses, more frequent uses, and recent uses of antibiotics [Hu et al., 2022].

Among the two cross-sectional studies, one was a retrospective cross-sectional study that was conducted in South Korea by recruiting ≥ 30-year-old adult people [Lee et al., 2021]. They found a 1.31-fold higher risk of depression among MDD patients than that of patients without MDD after treatment with antibiotics, and the associations were age-dependent. They also reported that the number of antibiotic prescription days was positively associated with depression in MDD patients [Lee et al., 2021]. Another cross-sectional study was conducted in China, which recruited ≥ 60-year-old elderly people and assessed antibiotic exposure through urinary biomonitoring of 45 different antibiotics [Liu et al., 2021]. They found that higher concentrations of Azithromycin and sulfaconazine had increased the risk of depression. They also categorized the antibiotics and reported that tetracyclines and veterinary antibiotics were positively associated with depression. They also found sex-dependent associations between male and female study participants. Notably, after age stratifications, they found positive associations under 70 years only[Liu et al., 2021].

In a case-control study, researchers recruited ALS patients and 5 times control patients with a mean of 68.6 years and found that any antibiotic use had positive associations with a higher risk of ALS [Sun et al., 2019]. The OR for 1, 2-3, and >4 prescriptions of antibiotics was higher in comparison to the no-prescription groups of populations. Among the different groups of antibiotics, beta-lactamase-sensitive penicillin prescriptions for more than two have been reported to be associated with a higher risk of ALS [Sun et al., 2019]. Three nested case-control studies conducted in the United Kingdom found that treatment with a single antibiotic course was associated with a higher risk for depression and anxiety in all antibiotic groups, with the highest AORs for penicillins and quinolones at 15-65 years old study participants [Lurie et al., 2015]. The risk of depression and anxiety increased with the number of penicillin courses. However, they found null associations for psychosis [42].

Discussion

We summarized all the possible associations between antibiotic exposure and psychiatric disorders. This review found a positive relationship between both prenatal and postnatal antibiotic use with a few psychiatric disorders. The associations were very strong for high antibiotic doses, long duration of use or higher frequency, broad-spectrum antibiotics, and current antibiotic use status. A few studies found age and sex-specific associations, too. However, the insufficient numbers of studies (n=15) summarized in the current review might unable to conclude the evidence level.

Most of the studies found positive relationships between prenatal antibiotic exposures with early childhood psychiatric disorders. It is assumed that maternal antibiotic use may be a representative marker of her lifestyle or genetic susceptibility to infection that might be inherited by offspring. Accordingly, it may increase the vulnerability to developing different psychiatric disorders in offspring, often called the genetic transmission hypothesis [Blaser and Bello, 2014; Stokholm et al., 2014]. Thus, both the maternal and paternal lifetime history of psychiatric diagnoses need to be considered during the diagnosis of the offspring's mental health. Also, the possibility of gene-environmental interactions should not be overlooked [Delara et al., 2021]. Thus, collecting this paternal information and adjusting as a potential confounder could have certainly undermined the genetic transmission hypothesis.

The findings of the present study might be confounded by the number of antibiotic prescriptions and their related characteristics, including infection severity and type of bacteria, since antibiotic courses are usually altered based on infection patterns, numbers, and severity [Delara et al., 2021]. So, the patterns and number of infections that require more antibiotics should be considered, as infections stimulate the overproduction of some inflammatory cytokines that can cross the blood-brain barrier and affect brain function. Subsequently, by inducing pro-inflammatory responses at systemic and CNS levels, it may influence the mental health status [Ishii et al., 2016], leading to the development of psychiatric disorders [Pfau et al., 2018]. For example, some bacterial infections can affect microbiome composition and gut permeability which lead to the development of mood disorders [Gareau et al., 2014; Duke et al., 2015; Pan et al., 2015; Seminog and Goldacre,2013]. Even, pathogenic bacterial toxins might regulate signaling to the brain and modify its function through the aforementioned changes [Lyte, 2014]. So, the co-existence of diseases that may stimulate the infections should be adjusted to strengthen the findings in the future.

Finally, the careful and precise diagnosis of non-severe infections, and the sensible use of antibiotics, might help to determine whether the infections are responsible for the development of anxiety and depression [Prichett et al., 2022, John and Matthew, 2014]. This could ultimately assist in controlling behavioral and psychiatric disorders in all age groups of people.

The potential sex differences were found in the relationship between antibiotic exposure and mental health in our summarized studies. This could be explained by the susceptibility to the changes in the microbiome environment between male and female participants. Male children and adolescents might be more susceptible to changes in the microbiome that cause dysregulation of the gut-brain axis in comparison to females [Albert, 2015; Kozyrskyj et al., 2016; Kushak et al., 2020]. The infection types and patterns are somehow common in both males and females in early childhood, but different from each other. One of the studies reported that males were more frequently diagnosed with respiratory infections than females, whereas females were more frequently diagnosed with genitourinary infections [Prichett et al., 2022]. They concluded that different types of infection and/or antibiotics prescribed for these conditions could be behind the sex differences seen in the results [Prichett et al., 2022].

There are some racial differences also found in the current review. Racial bias in diagnosis, preferential access to mental health professionals, or race-related suspicion of mental health care services might be the possible reasons [Cook et al., 2019; Garb, 2021]. However, there is no substantial evidence of sex bias in the diagnosis of psychiatric disorders as reported in a previous study [Garb, 2021; Tsirgiotis et al., 2022].

Research gaps and prospects

Most of the studies evaluated the exposure-outcomes relationship cross-sectionally. The causal relationships between antibiotic exposure and psychiatric disorders might not be determined because of the cross-sectional design. Most of the studies recruited their study participants from one city or state of the respective country, warranting the generalizability, although the sample size was large. A nationwide cohort with significant numbers of participants is warranted. Most of the studies did not report the genetic history of psychiatric disorders. It is assumed that offspring from psychiatric parents are porn to develop psychiatric disorders based on the genetic transmission hypothesis [Blaser and Bello, 2014; Stokholm et al., 2014]. So, parents' life history should be considered in future studies.

Exposure misclassification might happen in case of some confounders including maternal nutrition, paternal history of mental health disorders, family stressors, exclusive breastfeeding, and indirect exposure to antibiotics at other parts of the healthcare system (e.g., hospital, emergency room, and nursing stations) or through food or the environment, consumption of filled prescriptions. On the contrary, there was no data on the microbiome and the factors that may alter its composition (e.g., diet, probiotics) to explore the underlying mechanisms that warranted further investigation. Finally, 14 out of 15 studies of the present review were questionnaire-based surveys that evaluated antibiotic use through the prescription history. We found only one human biomonitoring study that evaluated antibiotic exposure by measuring urinary concentrations of some antibiotics in participants, which limits the discussion. In the future, human biomonitoring studies should be developed following targeted and non-targeted analytical approaches to quantify the antibiotic exposure levels and evaluate the subsequent associations of single or cumulative antibiotic exposure with psychiatric disorders.

Lastly, post post-COVID era has already started, which might be influenced by human quality of life. Since poor life quality is associated with mental illness [Ljungqvist et al., 2016], a new epidemiological study that will consider a pandemic like COVID may strengthen the findings for sure.

Reasons for frequent use of antibiotics in low and middle-income countries

The sanitation and hygiene in middle-income countries are not well-maintained. As a result, they develop several types of infectious diseases so frequently and visit doctors at the last stage with severe infections. Physicians are forced to treat these groups of people with antibiotics for immediate recovery. Many people still have no formal education or have only completed primary-level education. The knowledge and perception regarding hygiene, sanitation, and safe use of antibiotics are inadequate. Most of the mothers who give birth child through cesarean section are treated with antibiotics too. Seasonal variations in climate, weather, humidity, and temperature changes may result the infectious diseases that need antibiotic treatments to cure. Although the antibiotic is a prescription drug, many people purchase the drug without a prescription to treat the general cough or fever in many third-world and developing countries, including Bangladesh. Many people become antibiotic-resistant due to the frequent use of self-purchased antibiotics. Consequently, they need a second or third line of antibiotics for the treatment of infectious diseases. Other possible reasons might include the use of antibiotics in agriculture, poor quality of antibiotics, surveillance insufficiency, factors associated with poor healthcare standards, malnutrition, chronic and recurring infection, and the inability to afford more effective and costly drugs.

Possible prevention and management

Government and non-government policymakers should work on improving the hygiene and sanitation of mass people as a first line of defense against infections to prevent or control the use of antibiotics. Most people should be aware of the adverse effects or consequences of frequent antibiotic use. Drug regulatory authorities should ensure the quality of drugs and regulate pharmacists not selling antibiotics without a physician's prescription. Policymakers and law enforcement agencies should improve market surveillance, ensure the nutritional status of the mass population, and improve healthcare facilities. Train the mass population regarding the basic knowledge about the safe use of antibiotics and the health consequences of misuse and/or overdoses of antibiotics, like depression and anxiety. A pregnant mother should discourage cesarean section rather than give a normal delivery to consider their health and their children.

Strengths and limitations

This study searched three databases to retrieve articles considering appropriate selection criteria, which may reduce selection bias. The current study represented the findings without considering the associations between exposure and outcome relationship, explained the possible role of confounders, identified significant research gaps, and drew future research perspectives. This study has a few limitations, too. The current study was not a systematic review and meta-analysis, so it did not provide the PRISMA flow chart. We did not assess the quality of the included articles using a quality assessment scale due to insufficient numbers (n=15). Finally the findings might not be generalizable globally since the studies were conducted in a specific region of a country.

Conclusion

Existing epidemiological data explicitly stated that there is an association between antibiotic exposure and psychiatric disorders. A nationwide, large prospective cohort study is warranted to explore the association. This finding will aware physicians, clinicians, and policymakers to ensure safe or judicious use of antibiotics and partially to prevent mental illness.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

RS: Writing-original draft, investigation, data curation, formal analysis, and writing-review editing; NS: investigation, data curation, and NCM: writing-original draft (in part), conceptualization, supervision.

References

1. Albert, P.R. (2015) ‘Why is depression more prevalent in women?’, *Journal of Psychiatry & Neuroscience*, 40(4), pp. 219–221.
2. American Psychological Association (APA) (n.d) Anxiety. Available at: https://www.apa.org/topics/anxiety (Accessed: 15 August 2023).
3. Beesdo, K., Knappe, S. and Pine, D.S. (2009) ‘Anxiety and anxiety disorders in children and adolescents: developmental issues and implications for DSM-V’, *Psychiatric Clinics of North America*, 32(3), pp. 483–524.

4. Bercik, P. et al. (2011) ‘The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice’, *Gastroenterology*, 141(2), pp. 599–609.
5. Bitsko, R.H. et al. (2018) ‘Epidemiology and impact of health care provider-diagnosed anxiety and depression among US children’, *Journal of Developmental and Behavioral Pediatrics*, 39(5), pp. 395–403.
6. Blaser, M.J. and Bello, M.G. (2014) ‘Maternal antibiotic use and risk of asthma in offspring’, *The Lancet Respiratory Medicine*, 2(10), pp. e16.
7. Braithwaite, E.C., Murphy, S.E. and Ramchandani, P.G. (2014) ‘Prenatal risk factors for depression: a critical review of the evidence and potential mechanisms’, *Journal of Developmental Origins of Health and Disease*, 5(5), pp. 339–350.
8. Busfield, J. (2011) *Mental illness*. Cambridge: Polity Press.
9. Cook, B.L. et al. (2019) ‘A review of mental health and mental health care disparities research: 2011–2014’, *Medical Care Research and Review*, 76(6), pp. 683–710.
10. Delara, M. et al. (2021) ‘Early life exposure to antibiotics and the risk of mood and anxiety disorders in children and adolescents: A population-based cohort study’, *Journal of Psychiatric Research*, 137, pp. 621–633.
11. Di Martino, M. et al. (2017) ‘Prevalence of antibiotic prescription in pediatric outpatients in Italy: the role of local health districts and primary care physicians in determining variation’, *BMC Public Health*, 17(1), p. 886.
12. Duko, B., Gebeyehu, A. and Ayano, G. (2015) ‘Prevalence and correlates of depression and anxiety among patients with tuberculosis’, *BMC Psychiatry*, 15, p. 214.
13. Fan, H. et al. (2020) ‘Associations between macrolide antibiotics prescribing during pregnancy and adverse child outcomes in the UK’, *BMJ*, 368, p. m331.
14. Farzi, A., Fröhlich, E.E. and Holzer, P. (2018) ‘Gut microbiota and the neuroendocrine system’, *Neurotherapeutics*, 15(1), pp. 5–22.
15. Garb, H.N. (2021) ‘Race bias and gender bias in the diagnosis of psychological disorders’, *Clinical Psychology Review*, 90, p. 102087.
16. Gareau, M.G. (2014) ‘Microbiota-gut-brain axis and cognitive function’, *Advances in Experimental Medicine and Biology*, 817, pp. 357–371.
17. Ghandour, R.M. et al. (2019) ‘Prevalence and treatment of depression, anxiety, and conduct problems in US children’, *The Journal of Pediatrics*, 206, pp. 256–267.
18. Global Burden of Disease Collaborators (2020) ‘Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019’, *The Lancet*, 396(10258), pp. 1204–1222.
19. Henderson, M. et al. (2011) ‘Work and common psychiatric disorders’, *Journal of the Royal Society of Medicine*, 104(5), pp. 198–207.
20. Hu, K. et al. (2022) ‘Use of antibiotics and risk of psychiatric disorders in newly diagnosed cancer patients’, *Cancer Epidemiology, Biomarkers & Prevention*, 31(3), pp. 528–535.
21. Ishii, W., Komine-Aizawa, S. and Hayakawa, S. (2016) ‘Antibiotics or infection itself? The possible importance of inflammatory cytokines on mental states’, *The Journal of Clinical Psychiatry*, 77(12), p. e1653.
22. Jang, H.M. et al. (2018) ‘Evidence for interplay among antibacterial-induced gut microbiota disturbance, neuro-inflammation, and anxiety in mice’, *Mucosal Immunology*, 11(5), pp. 1386–1397.
23. Johnson, S. and Marlow, N. (2011) ‘Preterm birth and childhood psychiatric disorders’, *Pediatric Research*, 69(5), pp. 11R–18R.
24. Kendler, K.S., Zachar, P. and Craver, C. (2011) ‘What kinds of things are psychiatric disorders?’, *Psychological Medicine*, 41(6), pp. 1143–1150.
25. Klein, E.Y. et al. (2018) ‘Global increase and geographic convergence in antibiotic consumption between 2000 and 2015’, *PNAS*, 115(15), pp. E3463–E3470.
26. Klein, E.Y. et al. (2021) ‘Assessment of WHO antibiotic consumption and access targets in 76 countries, 2000–15’, *The Lancet Infectious Diseases*, 21(1), pp. 107–115.
27. Kohler, O. et al. (2017) ‘Infections and exposure to anti-infective agents and the risk of severe mental disorders’, *Acta Psychiatrica Scandinavica*, 135(2), pp. 97–105.
28. Köhler-Forsberg, O. et al. (2019) ‘A nationwide study in Denmark of the association between treated infections and the subsequent risk of treated mental disorders in children and adolescents’, *JAMA Psychiatry*, 76(3), pp. 271–279.
29. Kozyrskyj, A.L. et al. (2016) ‘Fetal programming of overweight through the microbiome: boys are disproportionately affected’, *Journal of Developmental Origins of Health and Disease*, 7(1), pp. 25–34.
30. Krystal, J.H. and State, M.W. (2014) ‘Psychiatric disorders: diagnosis to therapy’, *Cell*, 157(1), pp. 201–214.
31. Kushak, R.I. and Winter, H.S. (2020) ‘Gut microbiota and gender in autism spectrum disorders’, *Current Pediatric Reviews*, 16(4), pp. 249–254.
32. Langdon, A., Crook, N. and Dantas, G. (2016) ‘The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation’, *Genome Medicine*, 8(1), p. 39.
33. Lavebratt, C. et al. (2019) ‘Early exposure to antibiotic drugs and risk for psychiatric disorders: a population-based study’, *Translational Psychiatry*, 9(1), p. 317.
34. Lee, J.W., Lee, H. and Kang, H.Y. (2021) ‘Association between depression and antibiotic use: analysis of population-based National Health Insurance claims data’, *BMC Psychiatry*, 21(1), p. 536.
35. Leclercq, S. et al. (2017) ‘Low-dose penicillin in early life induces long-term changes in murine gut microbiota, brain cytokines and behavior’, *Nature Communications*, 8, p. 15062.
36. Liang, X. et al. (2021) ‘Long-term antibiotic use during early life and risks to mental traits’, *Neuropsychopharmacology*, 46(6), pp. 1086–1092.
37. Liao, C.H. et al. (2015) ‘High prevalence of herpes zoster in patients with depression’, *The Journal of Clinical Psychiatry*, 76(9), pp. e1099–e1104.
38. Liu, X., Zhang, J., Sang, Y., Liu, K., Zhu, Y., Yang, L., Wang, S., Sheng, J., Wang, Q., Zhang, D., Cao, H. and Tao, F., 2021. Antibiotic exposure and potential risk of depression in the Chinese elderly: a biomonitoring-based population study. Environmental Science and Pollution Research International, 28(21), pp.26794-26806. https://doi.org/10.1007/s11356-021-12560-2

39. Ljungqvist, I. et al. (2016) 'Money and mental illness: a study of the relationship between poverty and serious psychological problems', *Community Mental Health Journal*, 52(7), pp. 842–850.
40. Lurie, I. et al. (2015) 'Antibiotic exposure and the risk for depression, anxiety, or psychosis', *The Journal of Clinical Psychiatry*, 76(11), pp. 1522–1528.
41. Lyte, M. (2014) 'Microbial endocrinology and the microbiota-gut-brain axis', *Advances in Experimental Medicine and Biology*, 817, pp. 3–24.
42. Mensah, K.B. et al. (2017) 'Antibiotic use during pregnancy: a retrospective study of prescription patterns and birth outcomes', *Journal of Pharmaceutical Policy and Practice*, 10, p. 24.
43. Murphy, J.R. et al. (2018) 'Maternal peripartum antibiotic exposure and the risk of postpartum depression', *Research in Nursing & Health*.
44. Pan, S.W., Yen, Y.F., Feng, J.Y., Su, V.Y., Kou, Y.R. and Su, W.J., 2015. The Risk of Depressive Disorder Among Contacts of Tuberculosis Patients in a TB-endemic Area: A Population-based Cohort Study. Medicine (Baltimore), 94(43), p.e1870. https://doi.org/10.1097/MD.0000000000001870
45. Pan American Health Organization (PAHO) (n.d.) Noncommunicable diseases and mental health data portal. Available at: https://www.paho.org/en/noncommunicable-diseases-and-mental-health (Accessed: 15 August 2023).
46. Pfau, M.L. et al. (2018) 'Inflammatory mediators in mood disorders: therapeutic opportunities', *Annual Review of Pharmacology and Toxicology*, 58, pp. 411–428.
47. Prichett, L.M. et al. (2022) 'Relationship between antibiotic exposure and subsequent mental health disorders in a primary care health system', *Brain, Behavior, & Immunity - Health*, 21, p. 100430.
48. Seminog, O.O. and Goldacre, M.J. (2013) 'Risk of pneumonia and pneumococcal disease in people with severe mental illness', *Thorax*, 68(2), pp. 171–176.
49. Skoog, I. (2011) 'Psychiatric disorders in the elderly', *The Canadian Journal of Psychiatry*, 56(7), pp. 387–397.
50. Slykerman, R.F. et al. (2017) 'Antibiotics in the first year of life and subsequent neurocognitive outcomes', *Acta Paediatrica*, 106(1), pp. 87–94.
51. Slykerman, R.F. et al. (2019) 'Exposure to antibiotics in the first 24 months of life and neurocognitive outcomes at 11 years of age', *Psychopharmacology*, 236(5), pp. 1573–1582.
52. Stokholm, J. et al. (2013) 'Prevalence and predictors of antibiotic administration during pregnancy and birth', *PLoS ONE*, 8(12), p. e82932.
53. Stokholm, J. et al. (2014) 'Maternal propensity for infections and risk of childhood asthma', *The Lancet Respiratory Medicine*, 2(8), pp. 631–637.
54. Sun, J. et al. (2019) 'Antibiotics use and risk of amyotrophic lateral sclerosis in Sweden', *European Journal of Neurology*, 26(11), pp. 1355–1361.
55. Tsirgiotis, J.M. et al. (2022) 'A mixed-methods investigation of diagnostician sex/gender-bias and challenges in assessing females for autism spectrum disorder', *Journal of Autism and Developmental Disorders*, 52(10), pp. 4474–4489.
56. Verdú, E.F. et al. (2006) 'Specific probiotic therapy attenuates antibiotic-induced visceral hypersensitivity in mice', *Gut*, 55(2), pp. 182–190.
57. World Health Organization (WHO) (2021) *Depression*. Available at: https://www.who.int/news-room/fact-sheets/detail/depression (Accessed: 15 August 2023).