Neuroscience and Biobehavioral Reviews 140 (2022) 104776

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

# Pre- and postnatal antibiotic exposure and risk of developing attention deficit hyperactivity disorder–A systematic review and meta-analysis combining evidence from human and animal studies

Katharina Otten [a,b,*], Lara Keller [c], Andrei A. Puiu [b], Beate Herpertz-Dahlmann [c], Jochen Seitz [c], Nils Kohn [d], J. Christopher Edgar [e,f], Lisa Wagels [b,g], Kerstin Konrad [a,h]

[a] Child Neuropsychology Section, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Faculty of Medicine, RWTH Aachen University, 52074 Aachen, Germany
[b] Department of Psychiatry, Psychotherapy and Psychosomatics, Faculty of Medicine, RWTH Aachen University, Aachen, Germany
[c] Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Faculty of Medicine, RWTH University Aachen, Aachen, Germany
[d] Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Centre, Nijmegen, the Netherlands
[e] Lurie Family Foundations MEG Imaging Center, Department of Radiology, The Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA
[f] Department of Radiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA
[g] Institute of Neuroscience and Medicine 10, Research Centre Jülich, Germany
[h] JARA-Brain Institute II, Molecular Neuroscience and Neuroimaging (INM-11), RWTH Aachen & Research Centre Jülich, 52428 Jülich, Germany

ARTICLE INFO

*Keywords:*
Antibiotics
Attention-deficit/hyperactivity disorder
Microbiome
Gut-brain axis
Neurodevelopment

ABSTRACT

This study investigated the effects of early antibiotic exposure on ADHD risk by (1) integrating meta-analytical evidence from human observational studies examining the association between prenatal or early postnatal antibiotic exposure on the risk of developing ADHD; and (2) reviewing evidence from experimental animal studies on the effects of early antibiotic exposure on behavior. Sixteen human studies and five rodent studies were reviewed. A quantitative meta-analysis with 10 human studies indicated an increased risk for ADHD after prenatal antibiotic exposure (summary effect estimate Hazard Ratio (HR) 1.23, 95% CI 1.09–1.38; N = 2,398,475 subjects) but not after postnatal exposure within the first two years of life (summary effect estimate HR 1.12, 95% CI 0.95–1.32; N = 1,863,867 subjects). The rodent literature suggested that peri-natal antibiotic exposure has effects on social behavior, anxiety and aggression, alongside changes in gut microbial composition. Human and rodent findings thus suggest prenatal antibiotic exposure as a possible risk factor for ADHD, and suggest that an early disruption of the gut microbiome by antibiotics may interfere with neurodevelopment.

## 1. Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most diagnosed neurodevelopmental disorders worldwide and is characterized by symptoms of inattention, and/ or hyperactivity/ impulsivity. Despite evidence for a strong genetic component, with heritability estimates from twin studies of 70–80% (Biederman, 2005), ADHD is not fully explained by genetics. Instead, ADHD is due to combination of genetic factors, environmental factors, and their interplay. In particular, non-shared environmental risk factors that act through interactions with genes and DNA variants that regulate gene expression - such as those in promoters, untranslated regions of genes or loci that encode microRNAs - seem to play an important role in ADHD (Faraone et al., 2015). Indeed, environmental factors that include psychosocial adversity, dietary factors or environmental toxins (Thapar et al., 2012) are thought to account for 10–40% of the variance in obtaining a diagnosis of ADHD (Sciberras et al., 2017). As a disorder with onset in early childhood, the investigation of environmental risks for ADHD has focused on pre- and early postnatal insults. Studies have, for example, identified maternal substance use (especially alcohol; see Eilertsen et al., 2017; Mick et al., 2002), stress during pregnancy (Grizenko et al., 2012), and pre-pregnancy obesity (Sanchez et al., 2018) as likely prenatal risk factors for ADHD.

Emerging evidence has also suggested an important role of the gut's

* Correspondence to: Child Neuropsychology Section, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Medical Faculty, RWTH Aachen University, 52074 Aachen, Germany.
*E-mail address:* kaotten@ukaachen.de (K. Otten).

https://doi.org/10.1016/j.neubiorev.2022.104776
Received 3 February 2022; Accepted 10 July 2022
Available online 14 July 2022

internal environment, or more specifically the gut microbiome, in the etiology of various mental disorders including Autism Spectrum Disorder (ASD) (e.g. Saurman et al., 2020), depression (e.g. Capuco et al., 2020), eating disorders (e.g. Seitz et al., 2020), and ADHD (e.g. Aarts et al., 2017; Mathee et al., 2020). The influence of the gut microbiome on human health and the brain is exerted via different pathways. First, the microbiome secrets various peptides and metabolites that affect and shape the stress response via the hypothalamic-pituitary-adrenal (HPA) axis (Checa-Ros et al., 2021; Cryan and Dinan, 2012; Foster et al., 2017). Second, certain bacteria have the capacity to produce different neurotransmitters and neuromodulators and thereby influence neurotransmitter concentrations (Cryan and Dinan, 2012). The metabolism and availability of tryptophan – the sole precursor of the neurotransmitter serotonin – is, for example, strongly influenced by the gut microbiota (Gao et al., 2020). Additionally, the gut microbiome is critical for the development and functioning of the immune system (Checa-Ros et al., 2021; Gensollen et al., 2016; Shamriz et al., 2016). This is of note as elevated markers of inflammation have been reported for various neuropsychiatric disorders in children and adolescents, including ADHD (Mitchell and Goldstein, 2014). Lastly, gut bacteria can directly influence vagus nerve signaling to the brain. The vagus nerve is involved in processes related to homeostasis, and increasing evidence highlights its role in mood regulation, stress reactivity, anxiety-related behavior and cognition (Breit et al., 2018; Fülling et al., 2019). Indeed, certain gut bacteria influence vagal nerve signaling and can thereby alter cognition and behavior (Fülling et al., 2019). In a nutshell, the gut microbiome influences health, cognition and behaviour and thus likely plays a role in the development of various neurodevelopmental disorders (Rogers et al., 2016).

With regard to ADHD, preliminary evidence shows that gut microbial profiles differ between patients with ADHD and neurotypical controls (Aarts et al., 2017; Prehn-Kristensen et al., 2018). Moreover, several conditions that are associated with ADHD have been associated with alterations in the gut microbiota composition. For example, atopic diseases, such as asthma or eczema, are more common in ADHD patients compared to healthy controls (Deckert et al., 2014; Kaas et al., 2021), and a link between these conditions and the composition of the intestinal microbiome has been demonstrated (Zimmermann et al., 2019). Further evidence for a role of the gut microbiome in ADHD comes from a recent study in which transferring fecal bacteria from ADHD patients into germ-free mice resulted in "ADHD-like" changes in brain structure and function as well as changed animal behavior (Tengeler et al., 2020). Given the heterogeneous findings, however, it is not yet possible to pin down a specific ADHD microbial profile (Checa-Ros et al., 2021).

One approach to better understand the ADHD microbial profile is to consider a disruption of the gut's bacterial homeostasis via the use of antibiotics. Such research has focused on developmental periods with high vulnerability for deviant brain development = the prenatal and early postnatal time windows. These early windows are not only critical for neurodevelopment but also coincide with the initial colonization of the gut (Borre et al., 2014). As the gut microbiome is involved in shaping the immune system, hormone secretion, and metabolism, disruptions during developmentally critical time windows likely affect neurodevelopment (Shamriz et al., 2016).

With respect to the initial colonization of the gut, non-human animal studies have shown that brain development as well as behavior are altered in germ-free mice, demonstrating the interaction of gut colonization and brain development early in life (Heijtz et al., 2011). Additionally, in early human development, cognitive outcomes of infants have been linked to three distinct bacterial composition clusters, demonstrating the importance of the microbiome on cognition in infancy (Carlson et al., 2018). Both findings suggest that antibiotic administration might impact neurodevelopment, such as increasing the risk for ADHD via disrupting the normal development of the microbiome (Azad et al., 2016; Bokulich et al., 2016).

Antibiotics prescriptions during early postnatal years and during pregnancy are common. A Danish study reported that more than 40% of pregnant women were administered antibiotics in 2010 (Broe et al., 2014), which results in large-scale modulation of the maternal microbiota composition. With respect to ADHD, Ai et al. (2021) conducted a meta-analysis that investigated the risk of developing ADHD after antibiotic exposure. They concluded that whereas maternal antibiotic exposure may be associated with an increased risk for ADHD, there was insufficient evidence for an association between postnatal antibiotic exposure and ADHD (Ai et al., 2021).

The present study sought to build upon Ai et al. (2021) by investigating prenatal antibiotic exposure and postnatal exposure within the first two years of life on the subsequent risk for ADHD by adopting a two-pronged approach: assessing human as well are non-human studies. As human studies are observational in nature, the effects of antibiotics are inseparable from the effects caused by the underlying reason for antibiotic administration. As such, evidence from experimental animal studies is needed to test potential effects and to identify underlying mechanisms. Thus, the current study investigated whether early exposure to antibiotics is related to an increased risk of ADHD by integrating (1) meta-analytical evidence from human observational studies examining the association between prenatal or early postnatal antibiotic exposure and the risk for developing ADHD; and (2) evidence from experimental animal studies investigating the effects of early antibiotic exposure on behavior and the gut microbiome.

## 2. Methods

The present systematic review and meta-analysis was registered on the International Prospective Register of Systematic Reviews PROSPERO under the registration number CRD42021234888 (http://www.crd.york.ac.uk/PROSPERO).

### 2.1. Search strategy and selection criteria

This systematic review was performed in accordance with recent PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines. A PRISMA 2020 checklist for systematic reviews is available in Supplemental Table 1 (Moher et al., 2009). Pubmed, Embase, and Scopus were screened for relevant studies that were written in English and published before January of 2021. The search string and search strategy are reported in Table 1. Additionally, the reference lists from identified articles were also screened for relevant citations.

Human as well as non-human studies were included and reviewed. Human studies were included if they investigated an association between pre- and postnatal antibiotic exposure within the fist two years of life and subsequent ADHD diagnosis. Studies assessing antibiotic exposure after the second year of life, or with no reported age of exposure, were excluded. Studies that focused on antibiotic exposure in breastfeeding mothers, thereby only indirectly affecting the child, were also excluded.

The outcome of interest was the diagnosis of ADHD during childhood. Studies with no categorical ADHD diagnosis but with a dimensional assessment of ADHD symptoms (such as by parental or teacher questionnaires using the Conners Rating Scales or the Strengths and Difficulties Questionnaires) were also included. Study types included cohort, case-control and cross-sectional studies. The main effect

**Table 1**
The Search Strategy used to search the databases PubMed, Embase and Scopus. The search was limited to "Title or Abstract".

| | |
|---|---|
| #1 | Antibiotic* OR antimicrob* OR antibacterial* OR "antibiotic exposure" |
| #2 | ADHD OR "attention deficit" OR "attention deficit hyperactivity disorder" OR impulsivity OR externalizing OR hyperactivity |
| #3 | Fetus OR newborn OR pregnancy OR prenatal OR postnatal OR neonate OR maternal OR offspring |
| #4 | #1 AND #2 AND #3 |

measures for the outcome criterium - the risk to develop ADHD diagnosis or elevated ADHD symptoms - were hazard ratios (HR), odds ratios (OR), mean difference and regression coefficients.

Non-human studies were included if they investigated the effect of prenatal or early postnatal antibiotic exposure on the offspring's behavior. For animal studies, only studies with a controlled experimental design were included.

Reviews, meta-analyses, case-studies or commentaries or publications written in languages other than English were excluded.

### 2.2. Study selection

The first screening included titles and abstracts of all identified articles. Subsequently, the full texts of all articles that were identified either as potentially relevant or with an unclear relevance were retrieved and the eligibility of the articles assessed. Data extraction and eligibility screening was conducted by one reviewer, and study eligibility additionally checked by a second reviewer. Disagreements were resolved through consensus and discussion. A flow chart diagram of the study selection process is depicted in Fig. 1.

### 2.3. Data extraction and risk of bias assessment

The following information was extracted for each included human study: year, country, sample size, study design, definition of the exposure including type and time of antibiotic use, specification of outcome including the time of outcome assessment, confounding factors and related results. If studies reported multiple outcomes on the effect of antibiotic use on ADHD risk from the same or from an overlapping sample, only the most adjusted measure for the final analysis was considered. If adjustment was equal, the most generalizable measure was selected (i.e., the measure coming from the largest subsample). All

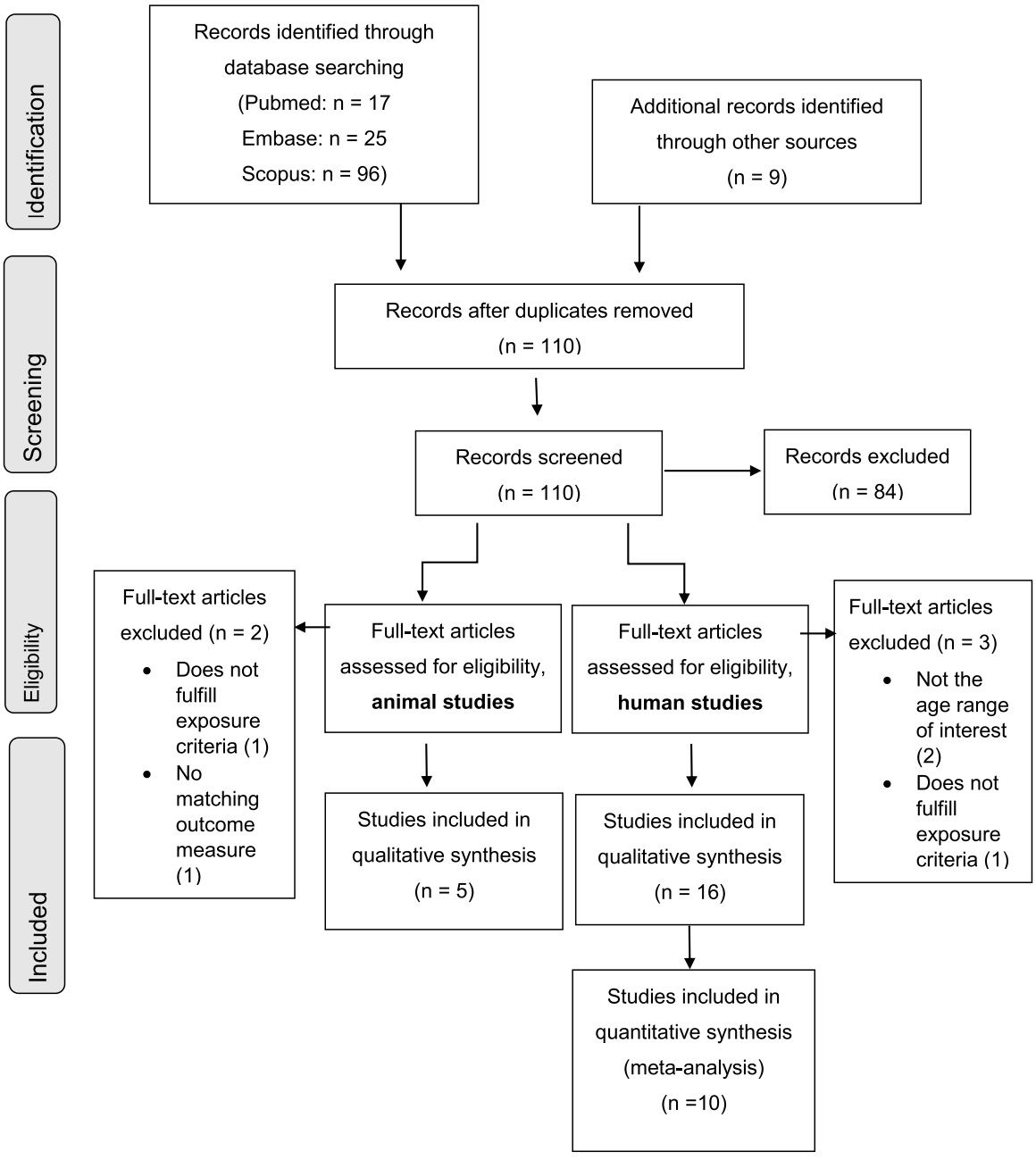


**Fig. 1.** This Prisma Flow Diagram illustrates the step-wise selection of articles.

measures were included if studies reported different measures for non-overlapping samples.

Animal studies were separately reviewed. Extracted data included: study design, animal model, details about the intervention including type, dose and timing of antibiotic exposure, details about the outcomes including the time point of behavioral testing, which tests were applied, which additional measures were reported in the study, and the associated results.

Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) (Wells et al., 2011). The NOS is a validated tool developed for the assessment of the quality of nonrandomised studies in a meta-analysis or a systematic review. Studies are evaluated on the selection of the sample, the comparability of the groups, and the identification of the exposure or outcome of interest depending on the study type. In total, a maximum of nine stars can be achieved and studies with at least eight stars are considered high-quality. Studies rated six or seven stars are considered to have a medium risk of bias, and studies with five or less stars are considered to have a high risk of bias. Two independent reviewers conducted the NOS assessment. Disagreements were resolved via consensus and discussion.

### 2.4. Data analysis

For the human studies, a meta-analysis was performed if at least two studies of the same exposure period (prenatal vs postnatal) reported the same risk measure. The effect measures used was the adjusted odds ratio (OR) or the adjusted hazard ratio (HR). The crude effect measure was used if no adjusted effect was provided. Separate meta-analyses were performed for studies reporting different effect measures.

Analyses were run using Review Manager 5.4 by the Cochrane Collaboration (Review Manager (RevMan) Version 5.4, The Cochrane Collaboration, 2020). Generic inverse variance models with random effects were used to account for possible variability in the intervention effects. Heterogeneity was quantified using the $I^2$ and $T^2$ statistics.

Sensitivity analysis was performed for prenatal analysis by excluding the study of Lydholm et al. (2019) as this study focused on treated infections and not directly on antibiotic exposure. For the postnatal analysis, the studies of Leviton et al. (2018) and Rand et al. (2016) were excluded as they were conducted in preterm infants.

## 3. Results

### 3.1. Overall study characteristics

In total, 138 articles were identified through database searching, and nine additional records by reference screening. After duplicates removal, 110 articles remained for title and abstract screening, of which 84 were excluded. Therefore, a total of 26 full-text articles were assessed for eligibility, of which 19 articles were human studies and seven were animal studies. Of the 19 human studies, two were excluded as they did not fit the predefined exposure age range, and a third study was excluded as it did not investigate the effects of antibiotic medication but of an antimicrobial chemical found in consumer products. Two studies were excluded from the seven non-human studies. One for having the exposure times during adolescent period (35 postnatal days in a Wistar rat model) instead of early childhood, and the second for not having an ADHD-related behavioral outcome measure. Details of the excluded studies are found in Supplementary Table 3. In sum, twenty-one studies met the inclusion criteria and were included in this review. A graphical overview of the selection process is depicted in Fig. 1. The main study characteristics and results are tabulated in Tables 2 and 3 for the human studies and the animal studies, respectively.

Concerning the human studies, five studies reported data exclusively on prenatal antibiotic exposure and six studies presented data only on postnatal antibiotic exposure. Four studies reported data for pre- as well as postnatal exposure. Another study grouped both types of exposure together as perinatal exposure, which did not allow categorisation as either pre- or postnatal. The studies of Slykerman et al. (2017) and Thompson et al. (2014) were conducted in New Zealand and reported data from the same cohort. One study grouped the outcome of ADHD together with other behavioral and emotional disorders and a separate measure for ADHD only could not be provided upon request (Lydholm et al., 2019).

Across studies, reporting of the type of antibiotic exposure and exact exposure time was highly heterogeneous and exposure assessment varied between studies, including record linkage systems and registries as well as parental reports (for more information see Table 2.).

Approximately half of the included studies reached a high NOS rating, with five studies reaching a nine-star rating and one study an eight-star rating. A medium risk of bias was reported for three studies with a seven-star rating and three studies with a six-star rating, and a high risk of bias was found for four studies only reaching five stars or less on the NOS. Details of the risk of bias assessment are presented in Table 4. Additionally, all reported confounding factors used in adjusted analyses are reported in Supplementary Table 2.

### 3.2. Prenatal antibiotic exposure

Of the nine studies that reported data on prenatal antibiotic exposure, five were conducted in population-based cohorts (Aversa et al., 2021; Fan et al., 2020; Hamad et al., 2020; Lavebratt et al., 2019; Lydholm et al., 2019), two were conducted with preterm born infants (Downey et al., 2015; Kenyon et al., 2008) and the two studies from New-Zealand performed analyses on a local cohort from a prior study (Slykerman et al., 2017b; Thompson et al., 2014). All five population-based cohort studies reported an adjusted HR (aHR) after prenatal antibiotic exposure. The meta-analysis was conducted by pooling the data from the population-based cohort studies except for Fan et al. (2020) (Fig. 2). The latter study was excluded as it provided risk estimates only for the effects of macrolide antibiotics relative to penicillin instead of estimates for exposed compared to unexposed individuals. Pooling the data resulted in a significant association between prenatal antibiotic exposure and ADHD diagnosis (summary effect estimate 1.23, 95% CI 1.09–1.38, N = 2398,475) with considerable heterogeneity ($I^2$=92). A sensitivity analysis leaving out the results from Lydholm et al. (2019) showed that the conclusions did not change and the effect remained significant (summary effect estimate 1.27, 95% CI 1.05–1.55, N = 1192,275).

### 3.3. Postnatal antibiotic exposure

Of the ten studies assessing early postnatal antibiotic exposure, five were conducted with population-based cohorts (Aversa et al., 2021; Axelsson et al., 2019; Hamad et al., 2019; Lavebratt et al., 2019), three were conducted in preterm infants (Downey et al., 2015; Leviton et al., 2018; Rand et al., 2016) and two were conducted in local cohorts from prior studies (Slykerman et al., 2017a, 2019). Meta-analyses were conducted separately for studies reporting HR and for studies reporting OR. Pooling cohort studies that reported aHR did not result in any significant effects (summary effect estimate HR 1.12, 95% CI 0.95–1.32, $I^2$=91, N = 1,863,867) (Fig. 3). Meta-analytic results of studies that reported an OR in a second analysis also did not show any effect (summary effect estimate OR 1.88, 95% CI 0.97–3.65, $I^2$=77, N = 34,762) (Fig. 4). In a sensitivity analysis, leaving out the two studies conducted with preterm infants did not change the results (summary effect estimate OR 1.37, 95% CI 0.71–2.67, $I^2$=67, N = 34,069).

Finally, a separate subgroup analysis with the two studies reporting results for preterm born infants did show a significant association between early antibiotic use and later ADHD diagnosis (summary effect estimate OR 3.42, 95% CI 1.78–6.59, $I^2$=0, N = 693).

**Table 2**
Characteristics of human studies.

| Study | Study Population | Antibiotic Exposure | Exposure Time | Outcome | Outcome measure | Results |
|---|---|---|---|---|---|---|
| **Prenatal Exposure** | | | | | | |
| Aversa et al. (2021) US, Minnesota | **14,572** children born between 2003 and 2011 | Records-linkage system | Whole pregnancy | Diagnosis of ADHD | ICD-9 or ICD-10 | HR (95% CI): 1.53 (1.36–1.72) |
| Downey et al. (2015) US | **826** extremely preterm children born between 2002 and 2004 | Medical records of antibiotics | Whole pregnancy | Attention problems | CBCL at an age of 24 months | 41% of children with attention problem received prenatal antibiotics;<br>30% of children with no attention problem received prenatal antibiotics |
| Fan et al. (2020) UK | **104,605** children born between 1990 and 2016 | British National Formulary | Between four gestational weeks and delivery | ADHD diagnosis | Diagnosis or $\geq$ 2 occurrence of prescription based on British National Register | Any trimester:<br>HR (95%CI): 1.05(0.78–1.42)<br>//HR based on comparison between penicillin and macrolide antibiotics |
| Hamad et al. (2020) Canada | **187,605** children born between 1998 and 2017 | Drug Program Information Network | Whole pregnancy | ADHD diagnosis | ICD-9 or ICD-10 | Overall cohort:<br>aHR (95% CI): 1.22 (1.18–1.26)<br>Sibling-controlled cohort:<br>aHR (95% CI): 1.06 (0.99–1.13) |
| Kenyon et al. (2008) UK | **3196** preterm born children | Factorial randomized design | Up to 10 days before birth | ADHD symptoms | Strengths and Difficulties Questionnaire; Parental report | Erythromicin:<br>OR (95% CI) 1.00 (0.77–1.31)<br>Co-Amoxiclav:<br>OR (95%CI) 1.20 (0.92–1.57) |
| Lavebratt et al. (2019) Finland | **990,098** children born between 1996 and 2012 | Finnish Register on Reimbursement Drugs | Whole pregnancy | ADHD and Conduct Disorder | ICD-10 codes F90-F91 | Broad spectrum antibiotics:<br>aHR (99% CI): 1.29 (1.17–1.41) |
| Slykerman et al. (2017) New Zealand | **871** children born between 1995 and 1997 | Parental Reports | Whole pregnancy | ADHD symptoms | Conners Rating Scale Revised | Mean Difference of Conners ADHD index between exposed and unexposed group not significantly different at age 7 or 11 |
| Thompson et al. (2014) New Zealand | **871** children born between 1995 and 1997 | Parental Reports | Whole pregnancy | ADHD symptoms | Strengths and Difficulties Questionnaire | Mean Difference of Strengths and Difficulties scores between exposed and unexposed group not significantly different at age 7 or 11<br>//same cohort as Slykerman et al. (2016) |
| Lydholm et al. (2019) Denmark | **1206,200** children born between 1996 and 2015 | National Prescription Registry | 40 weeks before birth until birth | ADHD grouped with behavioral and emotional disorders | ICD-10 codes F90-F99 | Maternal prescriptions:<br>aHR (95% CI): 1.13 (1.09–1.17) |
| **Perinatal Exposure** | | | | | | |
| Firestein et al. (2019) USA | **66** premature infants | Electronic medical record | Exposure either prenatal or postnatal during hospitalization | ADHD symptoms | CBCL for ages 1,5 years- 5 years | Exposed children differed significantly from unexposed for the attention problems subscale of the CBCL (P = .014), the scores of the Externalizing Behaviors Subscale (P = .04) and on the CBCL Total Problems Scale (P = .043) |
| **Postnatal Exposure** | | | | | | |
| Aversa et al. (2021) US | **14,572** children born between 2003 and 2011 | Record Linkage | First 2 years | ADHD diagnosis | ICD-9 or ICD-10 | Overall:<br>aHR (95% CI):1.32 (1.15–1.53)<br>Females:<br>aHR (95% CI): 1.53 (1.16–2.02)<br>Males:<br>aHR (95% CI): 1.25 (1.10–1.41) |
| Axelsson et al. (2019) Denmark | **671.592** children born between 1997 and 2010 | Danish National Prescription Registry | First 2 years | ADHD diagnosis | ICD-8 or ICD-10 | Standard model:<br>aHR (95% CI): 1.23 (1.19–1.28)<br>Between-within sibling model:<br>aHR (95% CI): 0.99 (0.92–1.06) |
| Downey et al. (2015) US | **826** extremely preterm children born between 2002 and 2004 | Record Linkage | Postnatal week 2–4 | Attention problems | CBCL at an age of 24 months | 86% of children with attention problem received antibiotics in week 2–4;<br>78% of children with no attention problem received antibiotics in week 2–4 |
| Hamad et al. (2019) Canada | **187,605** children born between 1998 and 2017 | Drug Program Information Network | First year of life | ADHD diagnosis | ICD-9 or ICD-10 | Overall cohort:<br>aHR (95% CI): 1.02 (0.97–1.08)<br>Sibling-controlled cohort:<br>aHR (95% CI): 0.96 ( 0.89–1.03) |
| | | Finnish Register on Reimbursement Drugs | First 2 years of life | | ICD-10 codes F90-F91 | Exposure in the first 6 months:<br>aHR (99% CI): 1.16 (1.11–1.22) |

(*continued on next page*)

**Table 2** (*continued*)

| Study | Study Population | Antibiotic Exposure | Exposure Time | Outcome | Outcome measure | Results |
|---|---|---|---|---|---|---|
| Lavebratt et al. (2019) Finland | **990.098** births between 1996 and 2012 | | | ADHD and Conduct Disorder | | Exposure between 6 and 12 months: aHR (99% CI): 1.12 (1.08–1.16) Exposure between 12 and 24 months: aHR (99% CI): 1.26 (1.20–1.33) |
| Leviton et al. (2018) USA | **583 extremely preterm** infants | Parental Reports | Postnatal week 2–4 | ADHD symptoms | Child Symptoms Inventory-4 | OR (95% CI): 3.6 (1.3–9.5) |
| Rand et al. (2016) New Zealand | **110 preterm** children born between 1998 and 2000 | Information collected from medical charts | During hospitalization after birth | ADHD | Development and Well-being Assessment (DAWBA) interview with parents | aOR (95% CI): 3.3 (1.4–7.7) |
| Slob et al. (2020) Netherlands, Sweden | **25,781** from a Dutch cohort and **7946** from a Swedish cohort | Parental reports (Dutch cohort) or Prescribed Drug Register (Swedish cohort) | First 2 years | ADHD diagnosis | Conners Parental Rating Scale Revised (Dutch Cohort); parent questionnaires or ICD-10 from national registers (Swedish cohort) | Unmatched Case-Control Design: aOR (95% CI): 1.10 (1.02–1.17) Matched Co-Twin control analysis: aOR (95% CI): 0.82 (0.62–1.08) |
| Slykerman et al. (2019) New Zealand | **342** children | Parental Reports | First 2 years | ADHD symptoms | Conners-3 parent form, Strengths and Difficulties Questionnaire | Exposure in first 6 months: aOR (95% CI): 4.0 (1.4–11.4) Exposure between 6 and 12 months: aOR (95% CI): 1.3 (0.5–3.5) Exposure between 12 and 24 months: aOR (95% CI): 1.3 (0.5–3.6) // estimates based on Conners-3 ADHD predominantly inattentive type |
| Slykerman et al. (2017) New Zealand | **871** children born between 1995 and 1997 | Parental Reports | First year | ADHD symptoms | Conners Rating Scale Revised | Exposed children differed significantly from unexposed children for parent assessment of Conners ADHD index (P = .037) at an age of 11. |

### 3.4. Animal studies

Five animal studies were included in this review, of which four were conducted in mice and one in rats. Only one of the five studies examined early postnatal antibiotic exposure (Kayyal et al., 2020). The other studies investigated prenatal exposure. Complicating comparisons, in one study the exposure was peri-conceptual starting before breeding until gestational day 15 (Degroote et al., 2016), and in another study the exposure was considered perinatal, starting during pregnancy and lasting until the weaning of the pups (Leclercq et al., 2017). All studies reported behavioral effects in the offspring with a decrease in sociability (Champagne-Jorgensen et al., 2020; Degroote et al., 2016; Kayyal et al., 2020; Leclercq et al., 2017), a decrease in anxiety (Champagne--Jorgensen et al., 2020; Leclercq et al., 2017) and a change in aggressive behavior (Champagne-Jorgensen et al., 2020; Leclercq et al., 2017) as the most consistently observed effects. Four studies additionally reported significant differences in microbiome composition between exposed and unexposed animals.

## 4. Discussion

The present review and meta-analyses investigated the effect of prenatal and early postnatal antibiotic exposure on the subsequent risk for developing ADHD. Twenty-one studies, of which 16 were human and five were rodent were included. Meta-analytic results from a very large sample (N = 2398,575) indicated that prenatal antibiotic use increases the risk of developing ADHD by 1.23 on average. Early postnatal antibiotic exposure only affects the ADHD risk in preterm born infants.

Results and the quality of prior studies were mixed for prenatal and postnatal exposure, underscoring the need for a systematic investigation across studies. In the meta-analysis with studies that reported an aHR, evidence for an increased ADHD risk after prenatal antibiotic exposure was found. It is hypothesized that this effect is mediated via the gut microbiome; more precisely, via a non-optimal microbiome transmission from mother to child at birth as maternal intrapartum antibiotics have been associated with a decreased transmission rate of Lactobacillus to the newborn (Keski-Nisula et al., 2013). However, these results should be considered with caution as only four studies were included in the analysis and heterogeneity was high. Also, underlying infections of the mother (the reason antibiotics were administered) could have influenced the offspring's likelihood of developing ADHD. For example, there is accumulating evidence that prenatal exposure to a wide variety of viral and bacterial infections - or simply inflammation- may subtly alter fetal brain development, leading to neuropsychiatric consequences for the child later in life (al-Haddad et al., 2019). Indeed, a recent meta-analysis by Zhu et al. (2022) suggests a small increase in the risk of ADHD after maternal infection during pregnancy (Zhu et al., 2022). Generally, observational human studies make it difficult to disentangle the effects of the antibiotics from the underlying cause of the prescription. More refined study designs and experimental evidence from animal studies is required to make strong conclusions.

Contrary to prenatal findings, evidence for an increased risk for ADHD after early postnatal antibiotic exposure was not observed. Indeed, results from three population-based cohort studies suggested that positive findings related to postnatal antibiotic exposure were due to residual genetic confounding. In particular, all three studies reported significant effects that disappeared after additional sibling-controlled analyses (Axelsson et al., 2019; Hamad et al., 2019; Slob et al., 2020). This replicates the findings of Yu et al. (2021) who concluded that associations between early life antibiotics and ADHD risk may be overestimated (Yu et al., 2021).

Several studies included in the current review were conducted in preterm born infants and should be considered carefully. Although preterm birth is a risk factor for ADHD (Franz et al., 2018), the studies included in the current meta-analysis separated this effect from the risk of antibiotic exposure by comparing only preterm born children of

**Table 3**
Characteristics of animal studies.

| Study | Animal Model | Antibiotic exposure | Exposure Time | Time point of behavioral testing | Results | Behavioral Tests Applied | Additional Findings |
|---|---|---|---|---|---|---|---|
| Champagne-Jorgensen et al. (2020) | BALB/c mice (N = 59) | Low dose penicillin in- water solution | Prenatal exposure: maternal exposure from gestational day 15 until birth | Testing began on postnatal day 43 | Sig decrease in anxiety in females; Sig decrease in sociability in males | Open field test Light dark box Three chamber social behavior Elevated plus maze Microdefeat/ Aggressor Avoidance | Microbial Findings were sig different between treatment groups. Sig differences in immune regulation and brain gene expression levels in treated males |
| Degroote et al. (2016) | Wistar rats (N = 36) | Diet supplemented with 1% SuccinylSulfaThiazole (SST) | Peri-conceptual exposure: maternal exposure one month before breeding until gestational day 15 | Around postnatal day 50 | Sig decrease in sociability | Open field test Social interactions Marble Burying Elevated Plus Maze PrePulse Inhibition of the acustic startle reflex | / |
| Kayyal et al. (2020) | BALB/c mice (N = 89) | Orally delivered penicillin or penicillin supplemented with lactobacillus rhamnosus | Postnatal exposure: exposure to pups from postnatal day 14 until day 21 | Tests started after postnatal day 42 | Sig decrease in sociability in males | Open field test Elevated plus maze Three chamber social behavior | Microbial Findings were sig different between treatment groups. Sig differences in brain gene expression level and in immune regulation. |
| Leclercq et al. (2017) | BALB/c mice (N = 72) | Penicillin or penicillin supplemented with lactobacillus rhamnosus | Perinatal exposure: one week before delivery until weaning of pups (postnatal day 21) | Tests started after postnatal day 42 | Sig decrease in anxiety in males; sig decrease in sociability; sig increase in aggression in males | Open field test Three chamber social behavior Elevated plus maze Microdefeat stress/ Social avoidance test | Sig differences in Microbiome composition between groups. Sig differences in brain gene expression level |
| Tochitani et al. (2016) | C57BL/ 6 J mice (N = 47) | Non-absorbable antibiotic solution containing neomycin trisulfate salt hydrate, bacitracin, pimaricin, acetic acid | Prenatal exposure: exposure to mother from gestational day 9 until day 16 | Tested in postnatal week 4 or in postnatal week 7–8 | Sig lower activity and less exploratory behavior in offspring in postnatal **week** 4 | 24-h home cage activity Open field test Three chamber social behavior | / |

**Table 4**
NOS rating.

| | Selection | Comparability | Outcome | Total |
|---|---|---|---|---|
| Aversa 2021 | * ** * | * * | * ** | 9 |
| Axelsson 2018 | * ** * | * * | * ** | 9 |
| Downey 2015 | * ** | | * | 4 |
| Fan 2020 | * ** * | * * | * ** | 9 |
| Firestein 2019 | * ** | * * | * | 6 |
| Hamad 2019 | * ** * | * * | * ** | 9 |
| Hamad 2020 | * ** * | * * | * ** | 9 |
| Kenyon 2008 | * * | | * * | 4 |
| Lavebratt 2019 | * ** * | * * | * * | 8 |
| Leviton 2018 | * ** | * * | * | 6 |
| Lydholm 2019 | * ** | * * | * * | 7 |
| Rand 2016 | * ** | * * | * * | 7 |
| Slob 2020 | * ** | * * | * | 6 |
| Slykerman 2017 | * * | | * * | 4 |
| Slykerman 2019 | * ** | * * | * * | 7 |
| Thompson 2014 | * * | | * * | 4 |

identical gestational age with and without early postnatal antibiotic exposure. However, preterm and term infants might be differently affected by antibiotics. Following our hypothesis that the effects of antibiotics on ADHD risk are mediated via the gut microbiome, the effects might depend on the initial microbiome composition. Studies have shown that the microbiome composition of preterm and term infants differ (Chernikova et al., 2018; Underwood and Sohn, 2017). Moreover, the microbial composition of preterm infants is not only significantly different after birth but also progresses differently than the microbiome of term infants (La Rosa et al., 2014; Lu and Claud, 2019). It is a possibility that the composition of microbiota in the gut of preterm and term born infants might be differently affected by antibiotics. This might lead to further perturbation in microbial development and related homeostatic functions.

However, it is also possible that preterm infants suffer from the underlying infection that gave reason for administering antibiotics, and that this infection or its consequences might be associated with an increased risk of ADHD. We conducted a separate subgroup analysis with the two studies that reported an OR for preterm born infants that were exposed to antibiotics postnatal after birth and found a significant result. This suggests that postnatal antibiotics in preterm born infants could increase the risk of developing ADHD. Nonetheless, only two studies (a total of 693 subjects) were included in the subgroup analysis and more research is needed to support the hypothesis that antibiotic exposure increases the risk for ADHD in preterm born infants.

Some limitations need to be considered regarding the human studies. First, only a small number of studies assessed ADHD risk after antibiotic exposure and the methods of data reporting was highly heterogeneous. This limited the possibilities for data synthesis. However, it would have

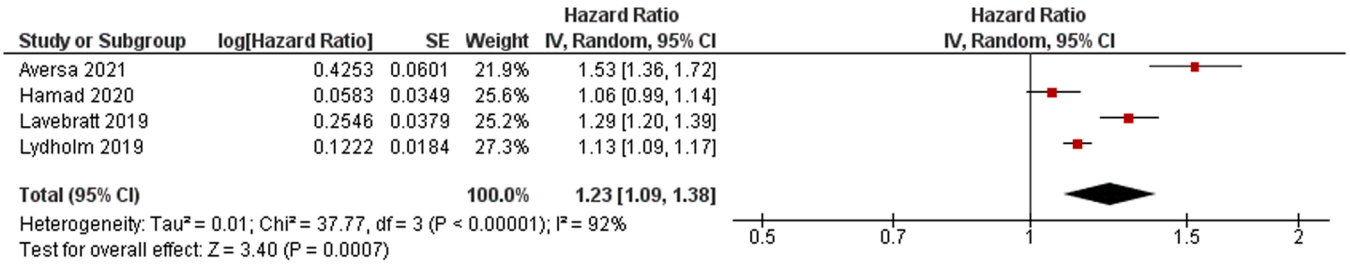


**Fig. 2.** Meta-analysis of studies reporting aHRs on prenatal antibiotic exposure.

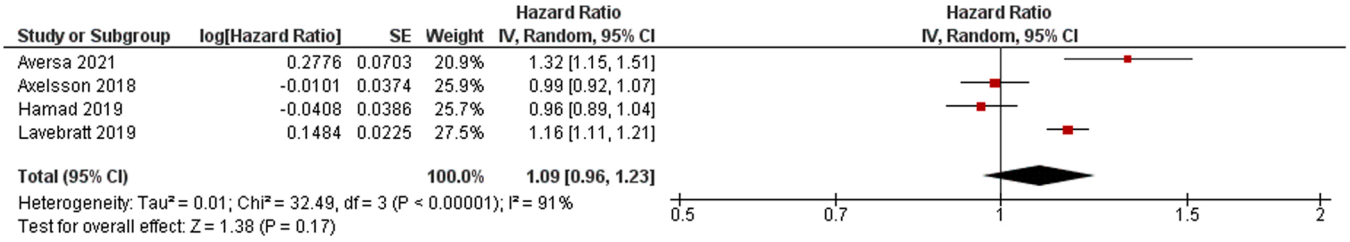


**Fig. 3.** Meta-analysis of studies reporting aHRs on postnatal antibiotic exposure.

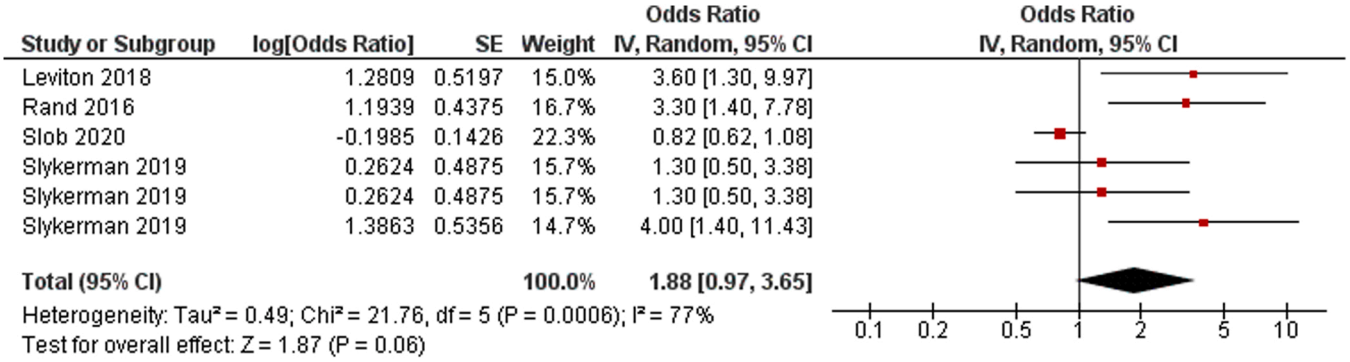


**Fig. 4.** Meta-analysis of studies reporting ORs on postnatal antibiotic exposure.

been interesting to investigate smaller exposure windows by assessing the influence of antibiotic exposure in different pregnancy trimesters or only in the first six months after birth. Slykerman et al. (2019) suggested that an earlier timing of antibiotic exposure has a stronger influence on ADHD related cognitive outcomes. In their study, they found significant effects only for children exposed to antibiotics within the first six months of life but not for children that received their antibiotic treatment between six and 12 or 12 and 24 months (Slykerman et al., 2019). Given the dynamic changes of the microbiome composition within the first two years of life (Bäckhed et al., 2015; Tamburini et al., 2016) it is possible that there is a specific time in which antibiotics may particularly disrupt the microbiome in such as way that influences the risk of developing ADHD. However, as exposure windows differed widely across studies, it was only possible to assess overall exposure during the first two years of life, for which no significant effect was observed.

Second, information on the details of antibiotic exposure in terms of duration, number of antibiotic courses or the type of antibiotic was not consistently reported across studies and thus not possible to include in a meta-analysis. Third, the assessment of exposure across studies was heterogeneous, and some studies utilized parental report to assess antibiotic exposure. Self-reports are, however, subject to a certain risk of bias. This should be taken into account, even though we do not consider this a limitation as our meta-analyses were based on population-based cohort studies that utilized medical registries to obtain objective information on antibiotic exposure.

Finally, all included studies were observational, making it impossible to separate effects of antibiotic exposure from any effects due to the underlying cause of the prescription. As previously noted, it is possible that reported effects are not due to antibiotic exposure but rather to the underlying maternal infection in case of prenatal exposure.

For this last reason, the findings from experimental animal studies is a crucial part of this review. Animal studies are experimentally controlled, and the effects of antibiotics can be investigated without the presence of an underlying infection. Only a small number of non-human studies, however, investigated the effects of prenatal or early postnatal antibiotic exposure on animal behavior. Moreover, although the rodent studies reported results of various behavioral tests, none directly targeted behaviors related to the ADHD core symptoms of impulsivity, hyperactivity or attention deficits. Likewise, none were conducted with an animal model of ADHD. However, animal studies can provide valuable insights into the effects of early antibiotic exposure on the offspring. Therefore, these studies were reviewed in order to explore potentially relevant mechanisms of risk.

Of the five rodent studies, only one examined postnatal antibiotic exposure. The others assessed prenatal, peri-conceptual or peri-natal exposure. The most consistently observed effect was a decrease in sociability, a finding reported in four of the five studies (Champagne-Jorgensen et al., 2020; Degroote et al., 2016; Kayyal et al., 2020; Leclercq et al., 2017). Further, decreases in anxiety and changed aggressive behavior were reported in two of the five studies

(Champagne-Jorgensen et al., 2020; Leclercq et al., 2017). These findings strongly support a causal effect of perinatal antibiotic exposure on offspring behavior. It remains difficult, however, to directly translate the rodent finding to humans.

Observations from animal studies have implications for future human studies. First, three rodent studies reported significant sex effects, with these findings indicating that early antibiotic exposure may have sex-specific effects. To our knowledge, only one human study has investigated the effects of antibiotics separately for girls and boys, with this study reporting a higher aHR risk for ADHD after antibiotic prescriptions in the first two years of life for girls than boys (Aversa et al., 2021). More studies are needed to investigate possible sex differences. Second, in two rodent studies it was found that adverse behavioral effects were prevented if a probiotic was supplemented along with the antibiotics (Kayyal et al., 2020; Leclercq et al., 2017). This indicates a potential protective effect of an early probiotic intervention. The observation that behavioral effects of antibiotics are prevented by probiotic supplementation provides strong support for the hypothesis that effects are caused by a disruption of the gut microbiome. A study by Pärtty et al. (2015) extends these finding to humans by concluding from a randomized trial of 75 infants that probiotic supplementation during the first six month of life may reduce the risk of developing a neuropsychiatric disorder during childhood (Pärtty et al., 2015).

Results from rodent studies also suggest that early antibiotic exposure not only impacts behavior but also gene expression levels in the developing brain (Champagne-Jorgensen et al., 2020; Kayyal et al., 2020; Leclercq et al., 2017). For example, a study assessing the effects of early-life penicillin exposure on newborn mice found substantial changes in microbial composition as well as significant effects on gene expression in the frontal cortex and amygdala (Volkova et al., 2021). These regions are implicated in numerous neuropsychiatric and neurodevelopmental disorders (Schumann et al., 2011), suggesting that early exposure to antibiotics could constitute a general risk factor for various neurodevelopmental disorders rather than being specific to ADHD. In line with the above, it was also found that one-month-old infants exposed to antibiotics right after birth showed altered event-related potentials related to auditory processing and recognition memory compared to unexposed infants, with this finding thus also suggesting an effect of early antibiotic exposure on cognition (Hickey et al., 2021). Nevertheless, the interplay between antibiotics, the microbiome, and other environmental factors is highly complex, and more research is needed to better understand how early antibiotics affect the microbiome and in turn the brain gene expression and neurodevelopment.

In conclusion, the present results show (1) an association between prenatal antibiotic exposure and an increased risk of developing ADHD, and (2) no association between postnatal antibiotic exposure within the first two years of life and an increased susceptibility to ADHD. However, the evidence regarding preterm birth points to the possibility that postnatal antibiotics increase the risk for ADHD in preterm infants (or that the increased risk is associated with the underlying infection). Rodent studies demonstrate microbial effects alongside behavioral effects after peri-natal antibiotic exposure and support the notion that an increased risk for ADHD after antibiotic exposure might be caused by a disruption of the gut microbiome. More carefully controlled studies are needed to further investigate this association.

## Declaration of Competing Interest

None.

## Acknowledgements

Funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) –269953372/GRK2150.

### *Authors contribution*

Author KO and KK worked on the research question and the study protocol. KO conducted the systematic search, data extraction, risk of bias assessment and wrote the manuscript. LK checked the study eligibility, the data extraction and the risk of bias assessment. All other authors contributed by providing input on the rationale for the study and by providing their input on the manuscript.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2022.104776.

## References

Aarts, E., Ederveen, T.H.A., Naaijen, J., Zwiers, M.P., Boekhorst, J., Timmerman, H.M., Smeekens, S.P., Netea, M.G., Buitelaar, J.K., Franke, B., van Hijum, S.A.F.T., Arias Vasquez, A., 2017. Gut microbiome in ADHD and its relation to neural reward anticipation. PLOS ONE 12 (9), e0183509. https://doi.org/10.1371/journal.pone.0183509.

Ai, Y., Zhao, J., Shi, J., Zhu, T.T., 2021. Antibiotic exposure and childhood attention-deficit/hyperactivity disorder: systematic review and meta-analysis. Psychopharmacology 238 (11), 3055–3062. https://doi.org/10.1007/s00213-021-05989-3.

al-Haddad, B.J.S., Jacobsson, B., Chabra, S., Modzelewska, D., Olson, E.M., Bernier, R., Enquobahrie, D.A., Hagberg, H., Östling, S., Rajagopal, L., Adams Waldorf, K.M., Sengpiel, V., 2019. Long-term risk of neuropsychiatric disease after exposure to infection in utero. JAMA Psychiatry 76 (6), 594. https://doi.org/10.1001/jamapsychiatry.2019.0029.

Aversa, Z., Atkinson, E.J., Schafer, M.J., Theiler, R.N., Rocca, W.A., Blaser, M.J., LeBrasseur, N.K., 2021. Association of infant antibiotic exposure with childhood health outcomes. Mayo Clin. Proc. 96 (1), 66–77. https://doi.org/10.1016/j.mayocp.2020.07.019.

Axelsson, P.B., Clausen, T.D., Petersen, A.H., Hageman, I., Pinborg, A., Kessing, L.V., Bergholt, T., Rasmussen, S.C., Keiding, N., Løkkegaard, E.C.L., 2019. Investigating the effects of cesarean delivery and antibiotic use in early childhood on risk of later attention deficit hyperactivity disorder. J. Child Psychol. Psychiatry Allied Discip. 60 (2), 151–159. https://doi.org/10.1111/jcpp.12961.

Azad, M.B., Konya, T., Persaud, R.R., Guttman, D.S., Chari, R.S., Field, C.J., Sears, M.R., Mandhane, P.J., Turvey, S.E., Subbarao, P., Becker, A.B., Scott, J.A., Kozyrskyj, A.L., 2016. Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: a prospective cohort study. BJOG Int. J. Obstet. Gynaecol. 123 (6), 983–993. https://doi.org/10.1111/1471-0528.13601.

Bäckhed, F., Roswall, J., Peng, Y., Feng, Q., Jia, H., Kovatcheva-Datchary, P., Li, Y., Xia, Y., Xie, H., Zhong, H., Khan, M.T., Zhang, J., Li, J., Xiao, L., Al-Aama, J., Zhang, D., Lee, Y.S., Kotowska, D., Colding, C., Wang, J., 2015. Dynamics and stabilization of the human gut microbiome during the first year of life. Cell Host Microbe 17 (5), 690–703. https://doi.org/10.1016/j.chom.2015.04.004.

Biederman, J., 2005. Attention-deficit/hyperactivity disorder: a selective overview. Biol. Psychiatry 57 (11), 1215–1220. https://doi.org/10.1016/j.biopsych.2004.10.020.

Bokulich, N.A., Chung, J., Battaglia, T., Henderson, N., Jay, M., Li, H.D., Lieber, A., Wu, F., Perez-Perez, G.I., Chen, Y., Schweizer, W., Zheng, X., Contreras, M., Dominguez-Bello, M.G., Blaser, M.J., 2016. Antibiotics, birth mode, and diet shape microbiome maturation during early life. Sci. Transl. Med. 8 (343), 343ra82. https://doi.org/10.1126/scitranslmed.aad7121.

Borre, Y.E., O'Keeffe, G.W., Clarke, G., Stanton, C., Dinan, T.G., Cryan, J.F., 2014. Microbiota and neurodevelopmental windows: implications for brain disorders. Trends Mol. Med. 20 (9), 509–518. https://doi.org/10.1016/j.molmed.2014.05.002.

Breit, S., Kupferberg, A., Rogler, G., Hasler, G., 2018. Vagus nerve as modulator of the brain-gut axis in psychiatric and inflammatory disorders. Front. Psychiatry 9, 44. https://doi.org/10.3389/fpsyt.2018.00044.

Broe, A., Pottegård, A., Lamont, R.F., Jørgensen, J.S., Damkier, P., 2014. Increasing use of antibiotics in pregnancy during the period 2000–2010: prevalence, timing, category, and demographics. BJOG: Int. J. Obstet. Gynaecol. 121 (8), 988–996. https://doi.org/10.1111/1471-0528.12806.

Capuco, A., Urits, I., Hasoon, J., Chun, R., Gerald, B., Wang, J.K., Kassem, H., Ngo, A.L., Abd-Elsayed, A., Simopoulos, T., Kaye, A.D., Viswanath, O., 2020. Current perspectives on gut microbiome dysbiosis and depression. Adv. Ther. 37 (4), 1328–1346. https://doi.org/10.1007/s12325-020-01272-7.

Carlson, A.L., Xia, K., Azcarate-Peril, M.A., Goldman, B.D., Ahn, M., Styner, M.A., Thompson, A.L., Geng, X., Gilmore, J.H., Knickmeyer, R.C., 2018. Infant gut microbiome associated with cognitive development. Biol. Psychiatry 83 (2), 148–159. https://doi.org/10.1016/j.biopsych.2017.06.021.

Champagne-Jorgensen, K., Mian, M.F., Kay, S., Hanani, H., Ziv, O., McVey Neufeld, K.-A., Koren, O., Bienenstock, J., 2020. Prenatal low-dose penicillin results in long-term sex-specific changes to murine behaviour, immune regulation, and gut microbiota. Brain Behav., Immun. 84, 154–163. https://doi.org/10.1016/j.bbi.2019.11.020.

Checa-Ros, A., Jeréz-Calero, A., Molina-Carballo, A., Campoy, C., Muñoz-Hoyos, A., 2021. Current evidence on the role of the gut microbiome in ADHD pathophysiology

and therapeutic implications. Nutrients 13 (1), 249. https://doi.org/10.3390/nu13010249.
Chernikova, D.A., Madan, J.C., Housman, M.L., Zain-ul-abideen, M., Lundgren, S.N., Morrison, H.G., Sogin, M.L., Williams, S.M., Moore, J.H., Karagas, M.R., Hoen, A.G., 2018. The premature infant gut microbiome during the first 6 weeks of life differs based on gestational maturity at birth. Pediatr. Res. 84 (1), 71–79. https://doi.org/10.1038/s41390-018-0022-z.
Cryan, J.F., Dinan, T.G., 2012. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat. Rev. Neurosci. 13 (10), 701–712. https://doi.org/10.1038/nrn3346.
Deckert, S., Kopkow, C., Schmitt, J., 2014. Nonallergic comorbidities of atopic eczema: an overview of systematic reviews. Allergy 69 (1), 37–45. https://doi.org/10.1111/all.12246.
Degroote, S., Hunting, D.J., Baccarelli, A.A., Takser, L., 2016. Maternal gut and fetal brain connection: Increased anxiety and reduced social interactions in Wistar rat offspring following peri-conceptional antibiotic exposure. Prog. Neuro Psychopharmacol. Biol. Psychiatry 71, 76–82. https://doi.org/10.1016/j.pnpbp.2016.06.010.
Downey, L.C., O'Shea, T.M., Allred, E.N., Kuban, K., McElrath, T.F., Warner, D.D., Ware, J., Hecht, J.L., Onderdonk, A., Leviton, A., 2015. Antenatal and early postnatal antecedents of parent-reported attention problems at 2 years of age. J. Pediatr. 166 (1), 20–25. https://doi.org/10.1016/j.jpeds.2014.08.004.
Eilertsen, E.M., Gjerde, L.C., Reichborn-Kjennerud, T., Ørstavik, R.E., Knudsen, G.P., Stoltenberg, C., Czajkowski, N., Røysamb, E., Kendler, K.S., Ystrom, E., 2017. Maternal alcohol use during pregnancy and offspring attention-deficit hyperactivity disorder (ADHD): a prospective sibling control study. Int. J. Epidemiol. 46 (5), 1633–1640. https://doi.org/10.1093/ije/dyx067.
Fan, H., Gilbert, R., O'Callaghan, F., & Li, L. (2020). Associations between macrolide antibiotics prescribing during pregnancy and adverse child outcomes in the UK: Population based cohort study. The BMJ, 368((Fan H.; Gilbert R.; Li L.) Population, Policy and Practice Programme, Great Ormond Street Institute of Child Health, University College London, London, United Kingdom). Embase. https://doi.org/10.1136/bmj.m33.
Faraone, S.V., Asherson, P., Banaschewski, T., Biederman, J., Buitelaar, J.K., Ramos-Quiroga, J.A., Rohde, L.A., Sonuga-Barke, E.J.S., Tannock, R., Franke, B., 2015. Attention-deficit/hyperactivity disorder. Nat. Rev. Dis. Prim. 1 (1), 15020. https://doi.org/10.1038/nrdp.2015.20.
Firestein, M.R., Myers, M.M., Austin, J., Stark, R.I., Barone, J.L., Ludwig, R.J., Welch, M. G., 2019. Perinatal antibiotics alter preterm infant EEG and neurobehavior in the Family Nurture Intervention trial. Dev. Psychobiol. 61 (5), 661–669. https://doi.org/10.1002/dev.21820.
Foster, J.A., Rinaman, L., Cryan, J.F., 2017. Stress & the gut-brain axis: regulation by the microbiome. Neurobiol. Stress 7, 124–136. https://doi.org/10.1016/j.ynstr.2017.03.001.
Franz, A.P., Bolat, G.U., Bolat, H., Matijasevich, A., Santos, I.S., Silveira, R.C., Procianoy, R.S., Rohde, L.A., Moreira-Maia, C.R., 2018. Attention-deficit/hyperactivity disorder and very preterm/very low birth weight: a meta-analysis. Pediatrics 141 (1). https://doi.org/10.1542/peds.2017-1645.
Fülling, C., Dinan, T.G., Cryan, J.F., 2019. Gut microbe to brain signaling: what happens in vagus. Neuron 101 (6), 998–1002. https://doi.org/10.1016/j.neuron.2019.02.008.
Gao, K., Mu, C., Farzi, A., Zhu, W., 2020. Tryptophan metabolism: a link between the gut microbiota and brain. Adv. Nutr. 11 (3), 709–723. https://doi.org/10.1093/advances/nmz127.
Gensollen, T., Iyer, S.S., Kasper, D.L., Blumberg, R.S., 2016. How colonization by microbiota in early life shapes the immune system. Science 352 (6285), 539–544. https://doi.org/10.1126/science.aad9378.
Grizenko, N., Fortier, M.-E., Zadorozny, C., Thakur, G., Schmitz, N., Duval, R., Joober, R., 2012. Maternal stress during pregnancy, ADHD symptomatology in children and genotype: gene-environment interaction. J. Can. Acad. Child Adolesc. Psychiatry 21 (1), 9–15.
Hamad, A.F., Alessi-Severini, S., Mahmud, S.M., Brownell, M., Kuo, I.F., 2019. Antibiotic exposure in the first year of life and the risk of attention-deficit/hyperactivity disorder: a population-based cohort study. Am. J. Epidemiol. 188 (11), 1923–1931. https://doi.org/10.1093/aje/kwz178.
Hamad, A.F., Alessi-Severini, S., Mahmud, S., Brownell, M., Kuo, I.F., 2020. Prenatal antibiotic exposure and risk of attention-deficit/hyperactivity disorder: a population-based cohort study. CMAJ. https://doi.org/10.1503/cmaj.190883.
Heijtz, R.D., Wang, S., Anuar, F., Qian, Y., Björkholm, B., Samuelsson, A., Hibberd, M.L., Forssberg, H., Pettersson, S., 2011. Normal gut microbiota modulates brain development and behavior. Proc. Natl. Acad. Sci. 108 (7), 3047–3052. https://doi.org/10.1073/pnas.1010529108.
Hickey, M.K., Miller, N.C., Haapala, J., Demerath, E.W., Pfister, K.M., Georgieff, M.K., Gale, C.A., 2021. Infants exposed to antibiotics after birth have altered recognition memory responses at one month of age. Pediatr. Res. 89 (6), 1500–1507. https://doi.org/10.1038/s41390-020-01117-7.
Kaas, T.H., Vinding, R.K., Stokholm, J., Bønnelykke, K., Bisgaard, H., Chawes, B.L., 2021. Association between childhood asthma and attention deficit hyperactivity or autism spectrum disorders: a systematic review with meta-analysis. Clin. Exp. Allergy 51 (2), 228–252. https://doi.org/10.1111/cea.13750.
Kayyal, M., Javkar, T., Firoz Mian, M., Binyamin, D., Koren, O., Neufeld, K.-A.M., Forsythe, P., 2020. Sex dependent effects of post-natal penicillin on brain, behavior and immune regulation are prevented by concurrent probiotic treatment. Sci. Rep. 10 (1), 10318. https://doi.org/10.1038/s41598-020-67271-4.
Kenyon, S., Pike, K., Jones, D., Brocklehurst, P., Marlow, N., Salt, A., Taylor, D., 2008. Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the ORACLE II trial. Lancet 372 (9646), 1319–1327. https://doi.org/10.1016/S0140-6736(08)61203-9.
Keski-Nisula, L., Kyynäräinen, H.-R., Kärkkäinen, U., Karhukorpi, J., Heinonen, S., Pekkanen, J., 2013. Maternal intrapartum antibiotics and decreased vertical transmission of *Lactobacillus* to neonates during birth. Acta Paediatr. 102 (5), 480–485. https://doi.org/10.1111/apa.12186.
La Rosa, P.S., Warner, B.B., Zhou, Y., Weinstock, G.M., Sodergren, E., Hall-Moore, C.M., Stevens, H.J., Bennett, W.E., Shaikh, N., Linneman, L.A., Hoffmann, J.A., Hamvas, A., Deych, E., Shands, B.A., Shannon, W.D., Tarr, P.I., 2014. Patterned progression of bacterial populations in the premature infant gut. Proc. Natl. Acad. Sci. 111 (34), 12522–12527. https://doi.org/10.1073/pnas.1409497111.
Lavebratt, C., Yang, L.L., Giacobini, M.B., Forsell, Y., Schalling, M., Partonen, T., Gissler, M., 2019. Early exposure to antibiotic drugs and risk for psychiatric disorders: A population-based study (Embase). Transl. Psychiatry 9 (1). https://doi.org/10.1038/s41398-019-0653-9.
Leclercq, S., Mian, F.M., Stanisz, A.M., Bindels, L.B., Cambier, E., Ben-Amram, H., Koren, O., Forsythe, P., Bienenstock, J., 2017. Low-dose penicillin in early life induces long-term changes in murine gut microbiota, brain cytokines and behavior. Nat. Commun. 8 (1), 15062. https://doi.org/10.1038/ncomms15062.
Leviton, A., Hooper, S.R., Hunter, S.J., Scott, M.N., Allred, E.N., Joseph, R.M., O'Shea, T. M., Kuban, K., 2018. Antecedents of screening positive for attention deficit hyperactivity disorder in ten-year-old children born extremely preterm. Pediatr. Neurol. 81, 25–30. https://doi.org/10.1016/j.pediatrneurol.2017.12.010.
Lu, J., Claud, E.C., 2019. Connection between gut microbiome and brain development in preterm infants. Dev. Psychobiol. 61 (5), 739–751. https://doi.org/10.1002/dev.21806.
Lydholm, C.N., Köhler-Forsberg, O., Nordentoft, M., Yolken, R.H., Mortensen, P.B., Petersen, L., Benros, M.E., 2019. Parental infections before, during, and after pregnancy as risk factors for mental disorders in childhood and adolescence: a nationwide danish study. Biol. Psychiatry 85 (4), 317–325. https://doi.org/10.1016/j.biopsych.2018.09.013.
Mathee, K., Cickovski, T., Deoraj, A., Stollstorff, M., Narasimhan, G., 2020. The gut microbiome and neuropsychiatric disorders: implications for attention deficit hyperactivity disorder (ADHD. J. Med. Microbiol. 69 (1), 14–24. https://doi.org/10.1099/jmm.0.001112.
Mick, E., Biederman, J., Faraone, S.V., Sayer, J., Kleinman, S., 2002. Case-control study of attention-deficit hyperactivity disorder and maternal smoking, alcohol use, and drug use during pregnancy. J. Am. Acad. Child Adolesc. Psychiatry 41 (4), 378–385. https://doi.org/10.1097/00004583-200204000-00009.
Mitchell, R.H.B., Goldstein, B.I., 2014. Inflammation in children and adolescents with neuropsychiatric disorders: a systematic review. J. Am. Acad. Child Adolesc. Psychiatry 53 (3), 274–296. https://doi.org/10.1016/j.jaac.2013.11.013.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., for the PRISMA Group, 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 339 (jul21 1), b2535. https://doi.org/10.1136/bmj.b2535.
Pärtty, A., Kalliomäki, M., Wacklin, P., Salminen, S., Isolauri, E., 2015. A possible link between early probiotic intervention and the risk of neuropsychiatric disorders later in childhood: a randomized trial. Pediatr. Res. 77 (6), 823–828. https://doi.org/10.1038/pr.2015.51.
Prehn-Kristensen, A., Zimmermann, A., Tittmann, L., Lieb, W., Schreiber, S., Baving, L., Fischer, A., 2018. Reduced microbiome alpha diversity in young patients with ADHD. PloS One 13 (7), e0200728. https://doi.org/10.1371/journal.pone.0200728.
Rand, K.M., Austin, N.C., Inder, T.E., Bora, S., Woodward, L.J., 2016. Neonatal infection and later neurodevelopmental risk in the very preterm infant. J. Pediatr. 170, 97–104. https://doi.org/10.1016/j.jpeds.2015.11.017.
Rogers, G.B., Keating, D.J., Young, R.L., Wong, M.-L., Licinio, J., Wesselingh, S., 2016. From gut dysbiosis to altered brain function and mental illness: Mechanisms and pathways. Mol. Psychiatry 21 (6), 738–748. https://doi.org/10.1038/mp.2016.50.
Sanchez, C.E., Barry, C., Sabhlok, A., Russell, K., Majors, A., Kollins, S.H., Fuemmeler, B. F., 2018. Maternal pre-pregnancy obesity and child neurodevelopmental outcomes: A meta-analysis. Obes. Rev.: Off. J. Int. Assoc. Study Obes. 19 (4), 464–484. https://doi.org/10.1111/obr.12643.
Saurman, V., Margolis, K.G., Luna, R.A., 2020. Autism spectrum disorder as a brain-gut-microbiome axis disorder. Dig. Dis. Sci. 65 (3), 818–828. https://doi.org/10.1007/s10620-020-06133-5.
Schumann, C.M., Bauman, M.D., Amaral, D.G., 2011. Abnormal structure or function of the amygdala is a common component of neurodevelopmental disorders. Neuropsychologia 49 (4), 745–759. https://doi.org/10.1016/j.neuropsychologia.2010.09.028.
Sciberras, E., Mulraney, M., Silva, D., Coghill, D., 2017. Prenatal risk factors and the etiology of ADHD-review of existing evidence. Curr. Psychiatry Rep. 19 (1), 1. https://doi.org/10.1007/s11920-017-0753-2.
Seitz, J., Dahmen, B., Keller, L., Herpertz-Dahlmann, B., 2020. Gut feelings: how microbiota might impact the development and course of anorexia nervosa. Nutrients 12 (11), 3295. https://doi.org/10.3390/nu12113295.
Shamriz, O., Mizrahi, H., Werbner, M., Shoenfeld, Y., Avni, O., Koren, O., 2016. Microbiota at the crossroads of autoimmunity. Autoimmun. Rev. 15 (9), 859–869. https://doi.org/10.1016/j.autrev.2016.07.012.
Slob, E.M.A., Brew, B.K., Vijverberg, S.J.H., Dijs, T., van Beijsterveldt, C.E.M., Koppelman, G.H., Bartels, M., Dolan, C.V., Larsson, H., Lundström, S., Lichtenstein, P., Gong, T., Maitland-van der Zee, A.H., Kraneveld, A.D., Almqvist, C., Boomsma, D.I., 2020. Early-life antibiotic use and risk of attention-deficit hyperactivity disorder and autism spectrum disorder: results of a discordant twin study. Int. J. Epidemiol. https://doi.org/10.1093/ije/dyaa168.

Slykerman, R.F., Thompson, J., Waldie, K.E., Murphy, R., Wall, C., Mitchell, E.A., 2017. Antibiotics in the first year of life and subsequent neurocognitive outcomes. Acta Paediatrica 87–94. https://doi.org/10.1111/apa.13613.

Slykerman, R.F., Coomarasamy, C., Wickens, K., Thompson, J.M.D., Stanley, T.V., Barthow, C., Kang, J., Crane, J., Mitchell, E.A., 2019. Exposure to antibiotics in the first 24 months of life and neurocognitive outcomes at 11 years of age. Psychopharmacology 236 (5), 1573–1582. https://doi.org/10.1007/s00213-019-05216-0.

Tamburini, S., Shen, N., Wu, H.C., Clemente, J.C., 2016. The microbiome in early life: implications for health outcomes. Nat. Med. 22 (7), 713–722. https://doi.org/10.1038/nm.4142.

Tengeler, A.C., Dam, S.A., Wiesmann, M., Naaijen, J., van Bodegom, M., Belzer, C., Dederen, P.J., Verweij, V., Franke, B., Kozicz, T., Arias Vasquez, A., Kiliaan, A.J., 2020. Gut microbiota from persons with attention-deficit/hyperactivity disorder affects the brain in mice. Microbiome 8 (1), 44. https://doi.org/10.1186/s40168-020-00816-x.

Thapar, A., Cooper, M., Jefferies, R., Stergiakouli, E., 2012. What causes attention deficit hyperactivity disorder. Arch. Dis. Child. 97 (3), 260–265. https://doi.org/10.1136/archdischild-2011-300482.

Thompson, J.M.D., Waldie, K.E., Wall, C.R., Murphy, R., Mitchell, E.A., 2014. Associations between acetaminophen use during pregnancy and ADHD symptoms measured at ages 7 and 11 years. PLoS One 9 (9), e108210. https://doi.org/10.1371/journal.pone.0108210.

Tochitani, S., Ikeno, T., Ito, T., Sakurai, A., Yamauchi, T., Matsuzaki, H., 2016. Administration of Non-Absorbable Antibiotics to Pregnant Mice to Perturb the Maternal Gut Microbiota Is Associated with Alterations in Offspring Behavior. PloS One 11 (1), e0138293. https://doi.org/10.1371/journal.pone.0138293.

Underwood, M.A., Sohn, K., 2017. The microbiota of the extremely preterm infant. Clin. Perinatol. 44 (2), 407–427. https://doi.org/10.1016/j.clp.2017.01.005.

Volkova, A., Ruggles, K., Schulfer, A., Gao, Z., Ginsberg, S.D., Blaser, M.J., 2021. Effects of early-life penicillin exposure on the gut microbiome and frontal cortex and amygdala gene expression. IScience 24 (7), 102797. https://doi.org/10.1016/j.isci.2021.102797.

Yu, H., Zhou, Y., Pan, L., Zhang, X., Jiang, H., 2021. Early life antibiotic exposure and the subsequent risk of autism spectrum disorder and attention deficit hyperactivity disorder: a systematic review and meta-analysis. J. Autism Dev. Disord. https://doi.org/10.1007/s10803-021-05121-6.

Zhu, C., Jiang, H., Sun, J., 2022. Maternal infection during pregnancy and the risk of attention-deficit/hyperactivity disorder in the offspring: a systematic review and meta-analysis. Asian J. Psychiatry 68, 102972. https://doi.org/10.1016/j.ajp.2021.102972.

Zimmermann, P., Messina, N., Mohn, W.W., Finlay, B.B., Curtis, N., 2019. Association between the intestinal microbiota and allergic sensitization, eczema, and asthma: a systematic review. J. Allergy Clin. Immunol. 143 (2), 467–485. https://doi.org/10.1016/j.jaci.2018.09.025.