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Review

Early antibiotic exposure and risk of psychiatric and neurocognitive outcomes: systematic review and meta-analysis

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Background

The prenatal and early-life periods pose a crucial neurodevelopmental window whereby disruptions to the intestinal microbiota and the developing brain may have adverse impacts. As antibiotics affect the human intestinal microbiome, it follows that early-life antibiotic exposure may be associated with later-life psychiatric or neurocognitive outcomes.

Aims

To explore the association between early-life (in utero and early childhood (age 0–2 years)) antibiotic exposure and the subsequent risk of psychiatric and neurocognitive outcomes.

Method

A search was conducted using Medline, PsychINFO and Excerpta Medica databases on 20 November 2023. Risk of bias was assessed using the Newcastle-Ottawa scale, and certainty was assessed using the grading of recommendations, assessment, development and evaluation (GRADE) certainty assessment.

Results

Thirty studies were included ($n = 7\,047\,853$ participants). Associations were observed between *in utero* antibiotic exposure and later development of autism spectrum disorder (ASD) (odds ratio 1.09, 95% CI: 1.02–1.16) and attention-deficit hyperactivity disorder (ADHD) (odds ratio 1.19, 95% CI: 1.11–1.27) and early-childhood exposure and later development of ASD (odds ratio 1.19, 95% CI: 1.01–1.40), ADHD (odds ratio 1.33, 95% CI: 1.20–1.48) and major depressive disorder (MDD) (odds ratio 1.29, 95% CI: 1.04–1.60). However, studies that used sibling control groups showed no significant association between early-life exposure and ASD or ADHD. No studies in MDD used sibling controls. Using the GRADE certainty assessment, all meta-analyses but one were rated very low certainty, largely owing to methodological and statistical heterogeneity.

Conclusions

While there was weak evidence for associations between antibiotic use in early-life and later neurodevelopmental outcomes, these were attenuated in sibling-controlled subgroup analyses. Thus, associations may be explained by genetic and familial confounding, and studies failing to utilise sibling-control groups must be interpreted with caution.
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Keywords

Antibiotics; neurodevelopment; psychiatry; autism spectrum disorder; attention-deficit hyperactivity disorder.

The prenatal and early-life periods are a crucial neurodevelopmental window. Early disruptions to the developing brain and relevant systems may potentially influence neurocognitive or psychiatric outcomes.[1] The intestinal microbiota have an impact on brain health and functioning.[1] Animal studies indicate that the early intestinal microbiota, both in pregnancy and early life, influence brain development and behaviour.[2–5] Compelling preclinical data demonstrate that disruptions to the early-life intestinal microbiota through antibiotics result in changes in psychiatric and neurocognitive symptoms.[2–6] *In utero*, antibiotic exposure has been associated with changes in brain structure and memory in mouse models,[7] while postnatal antibiotic exposure was associated with increased anxiety-like behaviours compared with controls.[8] Perinatal antibiotic exposure in rodents has been associated with anxiety- and depression-like behaviours,[3,6] with effects being both gender- and time-dependent.[9] Animal studies have also demonstrated relationships between antibiotic exposure occurring outside the early-life period and later depressive or anxiety-like symptoms, and changes to biological markers associated with stress.[10–14]

In humans, recent studies also report an association between early-life intestinal microbiota and emotional, behavioural, temperamental and cognitive outcomes.[15–18] Differences in a range of long-term health outcomes, including autism spectrum disorder (ASD),[19] attention-deficit hyperactivity disorder (ADHD)[20,21] and autoimmune and allergic conditions, have also been observed between infants delivered via caesarean section compared with vaginal delivery.[22] These differences may represent an effect of differential microbial acquisition.[23] Antibiotics have a clear and potentially lasting[24] impact on the human intestinal microbiome, with exposure in the first 3 years of life resulting in decreased diversity at both the species and strain levels.[25] Korpela et al[24] demonstrated that following a single prescription of amoxycillin, infants' intestinal microbiota composition never returned to pre-antibiotic composition; rather, it moved towards a more mature composition characterised by low *Bifidobacterium* abundance. It follows that *in utero* or early-life antibiotic exposure (representing a critical neurodevelopmental window) may be associated with later-life psychiatric or neurocognitive outcomes.

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Prior literature

Six previous systematic reviews and meta-analyses have been conducted, evaluating the association between *in utero* and/or childhood antibiotic exposure and later development of ASD or ADHD.[26–31] The findings of these reviews are inconsistent, owing to a steadily expanding evidence base, differing search strategies and eligibility criteria, with most reviews limited to a very small number of included papers. In saying this, prior reviews all identified potential associations between prenatal antibiotic exposure and ASD[27,28,30] and ADHD.[26,29,30] With respect to postnatal exposure, these reviews reported increased odds of later development of ASD[27,28,31] and ADHD.[26,29,31] However, in the two reviews that specifically examined sibling-controlled studies,[28,31] both reported that sibling-controlled studies attenuated any associations observed between pre- or postnatal antibiotic exposure and later development of ASD or ADHD. Hence, genetic or familial confounding may explain these associations, where common gene(s) drive the susceptibility to both infections (and associated antibiotic use) and mental health disorders,[32] or shared factors within the family (for example, frequent attendance by healthcare professionals) predispose to both use of antibiotics and psychiatric or neurocognitive diagnoses; however, this needs to be confirmed.

Study rationale

For a number of reasons, including antibiotic resistance and the mounting evidence linking intestinal microbiota with health, efforts have been made towards responsible antibiotic stewardship.[33] To inform these efforts, we need a clearer understanding of whether *in utero* (prenatal) or early childhood (postnatal) antibiotic exposure is associated with psychiatric and/or neurodevelopmental outcomes in later life. To date, there are no published reviews broadly evaluating psychiatric or neurocognitive outcomes other than ASD and ADHD, pointing to important gaps in the literature. Furthermore, the evidence base has expanded substantially since the time of previously published reviews,[26,28,31] with around 30% of the literature in this field having been published after 2022, and more recent literature being of higher quality and more likely to include sibling controls. In addition, none of the prior reviews conducted a certainty assessment, which would be recommended for interpretation of the findings.

Study objectives

This systematic review aims to update and address the gap in the literature, with respect to the clinical question of whether *in utero* or early-life antibiotic exposure is associated with neurocognitive or psychiatric outcomes. The *in utero* and early childhood exposure periods are evaluated separately, to disentangle the specific risks associated with each exposure period. This will best inform clinical implications for each exposure period. This review also includes sibling-controlled studies, given the potential importance of genetic and familial confounding highlighted in prior research. Finally, this review uses a grading of recommendations, assessment, development and evaluation (GRADE) certainty assessment to assist with interpretation of results.

Method

This systematic review was reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[34] and the protocol was preregistered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42022304128).

Search strategy and study selection criteria

A series of electronic database searches were completed, with the initial search conducted on 17 January 2023 and the final search performed on 20 November 2023 using the Excerpta Medica (EMBASE), Ovid Medline and PsychINFO databases. The search was limited to studies conducted in English and with human participants only. The keywords used are available in the Supplementary Material (available at https://doi.org/10.1192/bjp.2024.121).

To be eligible, studies needed to meet the following inclusion criteria: (a) peer reviewed full text studies conducted in English and in humans only; (b) observational studies, cohort studies or case–control studies; (c) participants with a documented exposure to antibiotics *in utero* or the first 2 years of life compared with unexposed controls; (d) participants with a documented history or assessment of a psychiatric or neurocognitive outcome, or a documented absence of these outcomes.

Data extraction and management

The process of data collection commenced on 17 January 2023. Primary screening was conducted independently by J.E.G., S.D. and A.W. using the web application, Rayyan.[35] Full text secondary review was performed in duplicate by J.E.G., S.D. and A.W. Reference lists of relevant publications were reviewed for studies not identified in the database search. Where there were conflicts, consensus was achieved through discussion. J.E.G. extracted data into a Microsoft Excel sheet. For data verification purposes, E.T. independently extracted data for 20% of included studies, and was blinded to J.E.G.'s data.

Data extracted included study details, demographic data, outcome data, exposure data and data sources. Studies were grouped by outcomes including (a) ASD; (b) ADHD; (c) other psychiatric or behavioural outcomes, such as mood disorders, psychotic disorders, anxiety disorders and internalising/externalising behaviours in children; and (d) other neurocognitive outcomes, such as developmental delay and educational outcomes.

Data synthesis and statistical analysis

Meta-analyses (and subgroup meta-analyses) were performed where study data, such as patient groups, type of exposure (i.e. prenatal or early life) and outcome measures, were sufficiently similar to allow for synthesis. In addition, at least three studies relating to a particular outcome measure were required to meet the minimum number to justify synthesis for each meta-analysis. Random-effects meta-analyses were performed for each outcome investigating prenatal exposure and postnatal exposure separately using comprehensive meta-analysis.[36] Where there were insufficient data to perform a meta-analysis, the results were synthesised descriptively.

Where data were sufficient, subgroup analyses were performed for the following: (a) sibling-controlled studies, which consisted of studies that used a non-exposed sibling as a control, in contrast to the primary analysis, which used non-sibling controls that may or may not have been matched; (b) study design, comparing the impact of case–control and cohort studies; (c) maternal or childhood infection; (d) antibiotic types/categories; and (e) specific time windows for antibiotic exposure in pregnancy (e.g. trimester) or childhood (e.g. age range below 2 years).

To test the robustness of the meta-analyses, a leave-one-out meta-analysis was performed for all meta-analyses. This leave-one-out approach involves conducting multiple separate meta-analyses for each subset of the studies in which one study was excluded each time, demonstrating the impact of each individual study on the overall odds ratio.[37]

Hazard ratios and odds ratios were used interchangeably and combined for the purpose of the meta-analyses when the incidence

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of the outcome was less than 10%, in keeping with the rare outcome rule.[38] When odds ratios were not presented in the study, but sufficient data were available, odds ratios were manually calculated using an online calculator.[39] When outcomes were only available graphically, then data estimates were extracted using webplotdigitiser.[40]

Where studies presented stratified data with respect to the outcome of interest (e.g. by childhood age or antibiotic category), these results were combined into a single odds ratio using a separate fixed effects meta-analysis for that study only. This single (pooled) odds ratio was then used to represent the study in the main meta-analysis, so as to avoid using one study multiple times in a single meta-analysis.

Heterogeneity of included studies was evaluated clinically, methodologically and statistically. Evaluation of clinical heterogeneity involved consideration of participant characteristics, study design, conditions/outcomes being studied and definition of exposure. Statistical heterogeneity was considered to be significant if an I^2 value of greater than 50% was found. Methodological heterogeneity was assessed using the Newcastle-Ottawa scale (NOS).[41] Publication bias was assessed using funnel plots and Egger's intercept, wherein $P < 0.05$ indicated a significant difference.

Quality assessment

Risk of bias was assessed with the NOS.[41] The NOS was completed independently by J.E.G. and E.T., who were blind to each other's ratings. Conflicts were resolved later through verbal consensus, with S.D. acting as a third reviewer. Each study was rated separately for every outcome of interest (ADHD, ASD, other psych/behavioural outcomes and cognitive/educational outcomes). Follow-up times were rated depending on study outcomes, which were determined based on the average age at which the disorder of interest is usually diagnosed. Studies were given a one star rating if ≥80% of participants were followed up for the minimum time based on disorder/outcome (ASD: 4 years minimum;[42] ADHD: 5 years minimum;[43] other psychiatric or behavioural outcomes: 14 years minimum;[44] other outcomes: nil set point, but decided on a case-by-case basis depending on the outcome selected). With respect to comparability, studies were awarded zero stars when the odds ratio or hazard ratio for the outcome of interest was unadjusted or was only adjusted for one covariate. One star was awarded if two or three common factors (e.g. age, gender, mode of delivery and socioeconomic status) were adjusted for. Two stars were awarded if more than three of these factors were adjusted for.

Certainty was assessed using the GRADE certainty assessment[45] for each outcome.

Results

The systematic search yielded 1879 de-duplicated studies, of which 30 met eligibility criteria and were included in the systematic review (see Fig. 1).

Overall characteristics

The following outcomes were reported across the 30 included studies: ASD ($n = 21$), ADHD ($n = 14$), other psychiatric or behavioural outcomes ($n = 7$), of which four specifically related to major depressive disorder (MDD) outcomes and cognitive or educational outcomes ($n = 4$) (see Supplementary Table 1). Regarding exposure period, 11 studies related to *in utero* exposure, 13 studies to childhood exposure and five to both *in utero* and childhood exposure periods. With respect to age of exposure to antibiotics, there were insufficient data to perform a subgroup meta-analysis comparing the risk of exposure in the first to the second year of life. Data were also insufficient to perform a subgroup analysis by antibiotic type. Seven used a case–control design and 23 were cohort studies. A total of 7 047 853 participants were enrolled in the included studies, with sample sizes ranging from 66 to 1 601 689, and a median of 51 755. It was not possible to report follow-up data owing to missing or not clearly reported data. Antibiotic exposure was determined through medical records, prescription data or parental report. Outcomes of interest were identified either through diagnostic labels or coding in medical records, parental report using various condition-specific rating scales or a researcher-administrated assessment. Demographic data were inconsistently and infrequently presented, with few studies reporting on the same demographic data types; for example, some reported only maternal demographics, whilst others reported only offspring demographics. This study was primarily focused on data pertaining to offspring. Twenty-seven of the 30 included studies reported gender of offspring; a total of 51.4% of included participants were male. Ethnicity was reported in only eight of the 30 included studies.

Autism spectrum disorder

Prenatal antibiotic exposure and likelihood of later development of ASD

A significant association was observed between prenatal antibiotic exposure and likelihood of later development of ASD (odds ratio 1.09, 95% CI: 1.02–1.16, $I^2 = 75\%$, $\text{tau}^2 = 0.006$, $Q = 39.748$, d.f. = 10, $P < 0.001$; Fig. 2). A leave-one-out analysis demonstrated robustness of the outcomes, with no one study accounting for a substantial difference in outcome (see Supplementary Fig. 1). When separated by study design, a lower odds ratio was observed in the case–control studies ($n = 4$, odds ratio 0.13, 95% CI: −0.20–0.44) than the cohort studies ($n = 7$, odds ratio 1.10, 95% CI: 1.05–1.14).

Critically, the two studies that accounted for genetic and familial confounding by using a sibling control found no significant association between prenatal antibiotic exposure and later development of ASD (hazard ratio 1.08, 95% CI: 0.90–1.30;[52] hazard ratio 1.04, 95% CI: 0.92–1.01[54]).

Childhood antibiotic exposure and likelihood of later development of ASD

A significant association was observed between childhood antibiotic exposure and likelihood of later development of ASD (odds ratio 1.19, 95% CI: 1.01–1.40, $I^2 = 96\%$, $\text{tau}^2 = 0.0034$, $Q = 199.64$, d.f. = 7, $P < 0.001$; Fig. 3). A leave-one-out analysis identified that removal of Grossi et al,[60] Grossi et al[61] and Bittker[59] resulted in relatively large changes to the overall odds ratio, reducing it by 0.03, 0.02 and 0.04, respectively (see Supplementary Fig. 2). However the largest impact was made by Njotto et al,[56] which, when removed, reduced the total odds ratio by 0.11. When separated by study design, the effect was stronger in the case–control subgroup ($n = 3$, odds ratio 1.60, 95% CI: 1.26–2.03) than the cohort subgroup ($n = 5$, odds ratio 1.09, 95% CI: 0.92–1.30).

A subgroup meta-analysis of sibling-controlled studies showed no significant association between antibiotic exposure in childhood and ASD risk (odds ratio 1.03, 95% CI: 0.91–1.16, $I^2 = 20\%$, $Q = 5.00$, d.f. = 4, $P = 0.29$; Supplementary Fig. 3). Heterogeneity was lower in the sibling-matched subgroup analysis than the primary analysis. In the sibling-controlled subgroup analyses, a leave-one-out strategy demonstrated that the results were robust (see Supplementary Fig. 4). When separated by study design, subgroup meta-analyses did not reveal a significantly different outcome from either group to the pooled odds ratio.

Attention-deficit and hyperactivity disorder

Prenatal antibiotic exposure and likelihood of later development of ADHD

A significant association was demonstrated between prenatal antibiotic exposure and likelihood of later development of ADHD (odds ratio 1.19, 95% CI: 1.11–1.27, $I^2 = 91$, $Q = 44.24$, d.f. = 4, $P < 0.001$; Fig. 4). A leave-one-out analysis demonstrated robustness of the

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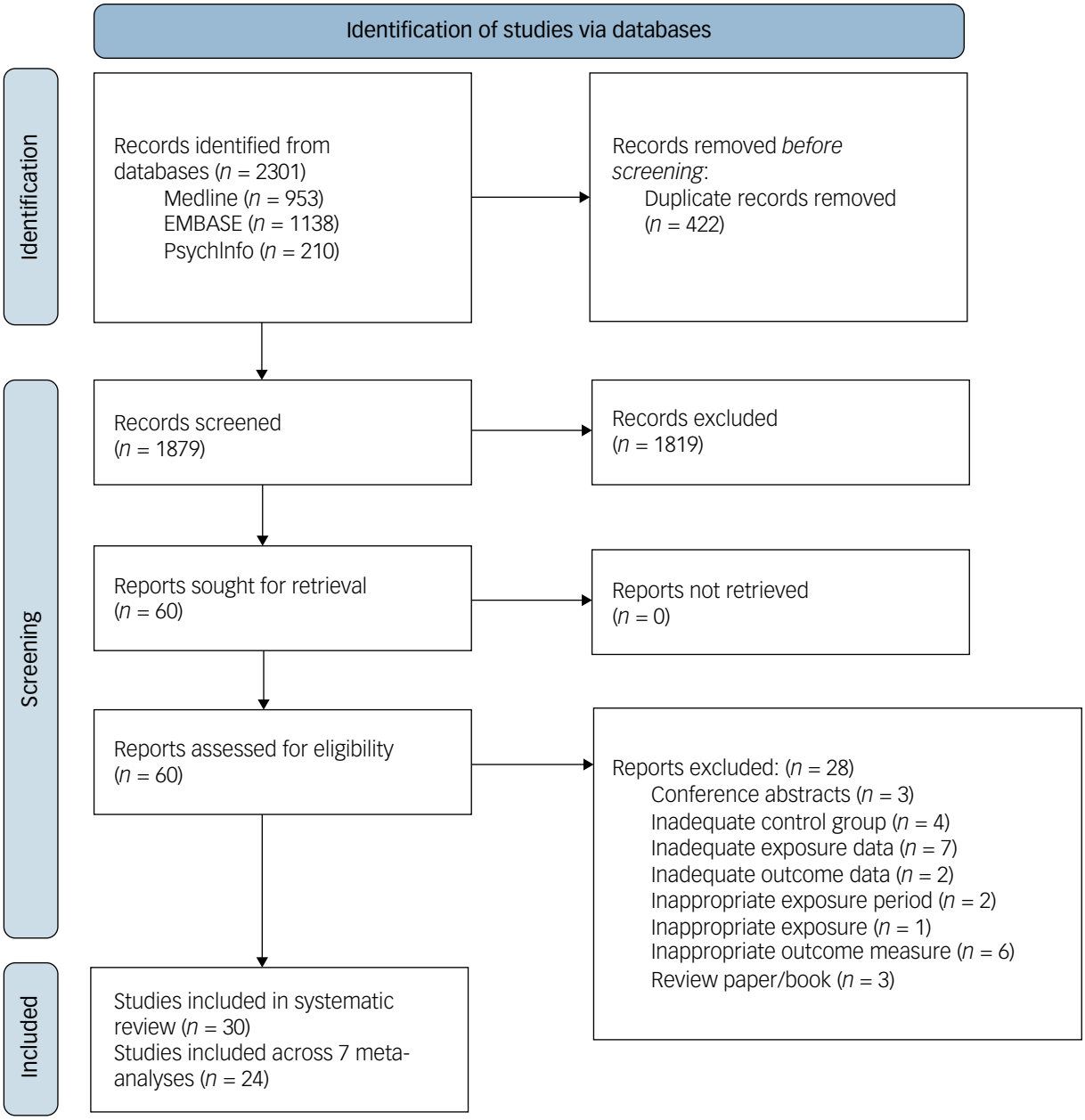

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses flowchart.
EMBASE, Excerpta Medica.

outcomes, with no one study accounting for a substantial difference in outcome (see Supplementary Fig. 5). A subgroup analysis by study type was not performed as all included studies were cohort studies.

Firestein et al[65] was not included in the meta-analysis as no definitive cut-off/definition of ADHD was specified. Consistent with the present meta-analysis, Firestein et al[65] reported that prenatal antibiotic exposure was associated with poorer scores on the attention problems subscale of the Child Behavior Checklist (CBCL) ($F(1, 31) = 6.04$, $P = 0.01$).

The one study that corrected for genetic or familial confounding using a sibling control group reported a reduced and non-significant hazard ratio for ADHD (hazard ratio 1.06, 95% CI: 0.99–1.13).[63]

Childhood antibiotic exposure and likelihood of later development of ADHD

A meta-analysis of eight studies found increased odds of ADHD following childhood exposure (odds ratio = 1.33, 95% CI: 1.20–1.48, $I^2 = 99\%$, $Q = 470.108$, d.f. = 7, $P < 0.001$; Fig. 5). A leave-one-out analysis revealed that no single study substantially changed the pooled odds ratio, demonstrating robustness of results (see Supplementary Fig. 6). A subgroup analysis by study type was not performed as all studies were cohort studies. However, this association was attenuated in a subgroup meta-analysis including only sibling-controlled studies: (odds ratio 0.97, 95% CI: 0.93–1.01, $I^2 = 0\%$, $Q = 1.65$, d.f. = 2; Supplementary Fig. 7). A leave-one-out analysis demonstrated that no one study appeared to substantially change the final pooled odds ratio (see Supplementary Fig. 8).

Other psychiatric and behavioural outcomes

Prenatal and childhood antibiotic exposure and likelihood of later development of psychiatric disorders

Studies exploring the likelihood of psychiatric disorders following prenatal or childhood antibiotic exposure were heterogeneous with respect to psychiatric outcomes, including anxiety disorders.

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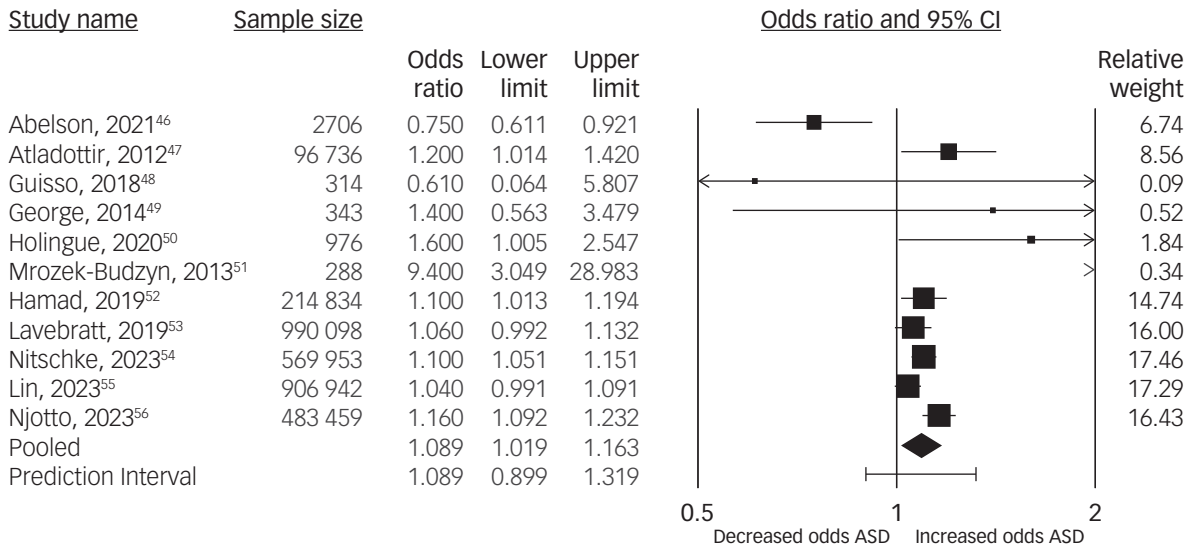

Fig. 2 Prenatal antibiotic exposure and likelihood of later development of autism spectrum disorder (ASD).

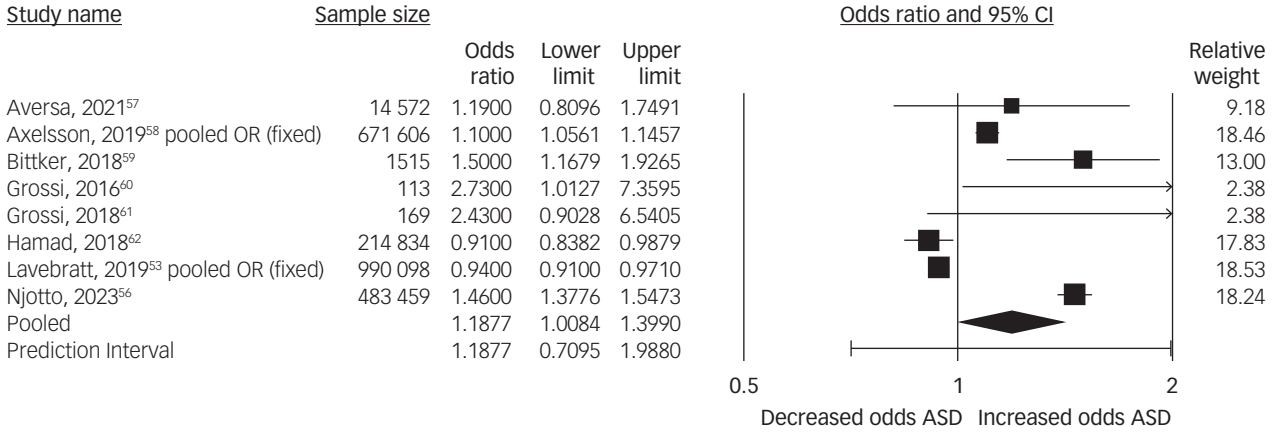

Fig. 3 Childhood antibiotic exposure and likelihood of later development of autism spectrum disorder (ASD).

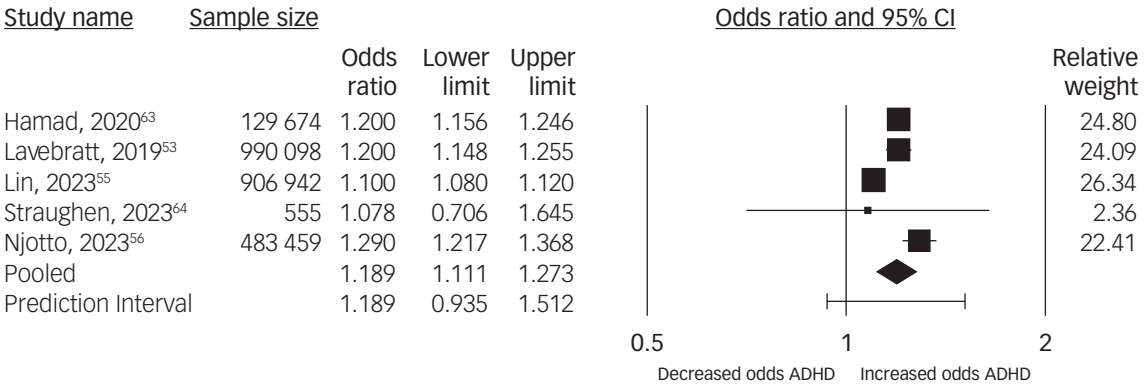

Fig. 4 Prenatal antibiotic exposure and likelihood of later development of attention-deficit hyperactivity disorder (ADHD).

Hence, with the exception of MDD, meta-analyses were not possible. Psychiatric outcome measures included a diagnosis of a psychiatric disorder as reported in a participant's electronic medical record, prescription of psychotropic medications, attachment type and scores on various scales, including the CBCL, measuring emotional and behavioural problems, the Centre for Epidemiological Studies Depression Scale (CES-DC), measuring depressive symptoms, and the Multidimensional Anxiety Scale for Children 2nd Edition (MASC-2), measuring anxiety symptoms.

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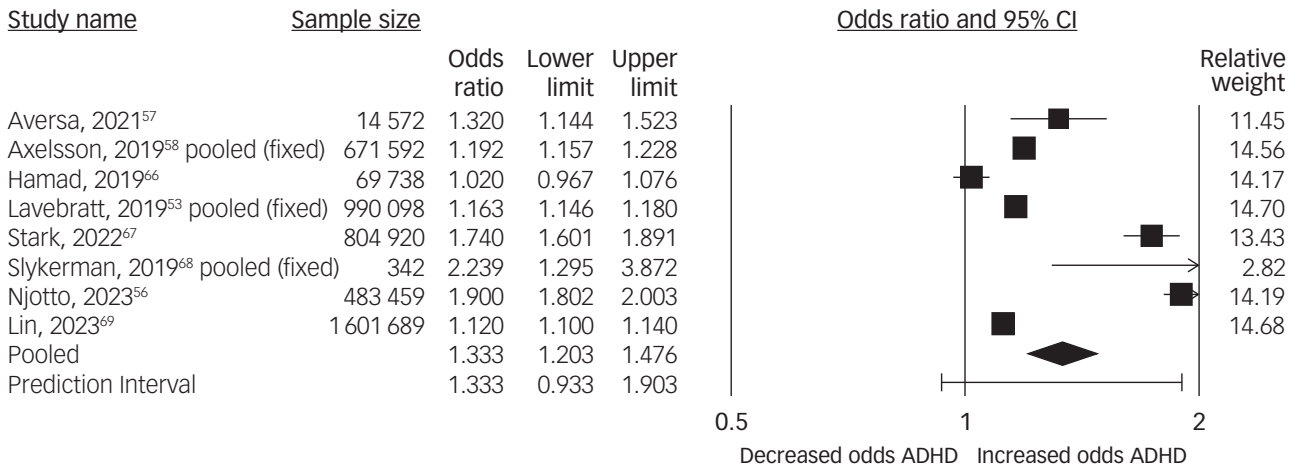

Fig. 5 Childhood antibiotic exposure and likelihood of later development of attention-deficit hyperactivity disorder (ADHD).

The four studies that evaluated psychiatric outcomes following prenatal exposure all showed increased likelihood of later psychiatric outcomes.[53,65,71,72] Oszvar et al[71] reported an association between *in utero* (or labour) exposure to antibiotics and later development of eating disorders (adjusted hazard ratio (aHR) = 1.09, 95% CI: 1.03–1.15). Delara et al[70] reported an increased likelihood of mood and anxiety disorders following prenatal antibiotic exposure (aHR = 1.08, 95% CI: 1.03–1.13). Lavebratt et al[53] reported an association between *in utero* antibiotic exposure and later development of any psychiatric diagnosis (using ICD codes in medical records) (aHR = 1.16, 95% CI: 1.14–1.18). Firestein et al[65] reported higher (representing worse) total problems score on the CBCL in offspring who had been exposed to antibiotics *in utero* compared with unexposed controls ($F(1, 60) = 4.476$, $P = 0.039$).

Five studies evaluated the likelihood of psychiatric symptoms or disorders following childhood antibiotic exposure.[53,67,68,70,72] Two studies reported an increased hazard ratio of a psychiatric disorder[53] or psychotropic prescription[67] associated with childhood antibiotic exposure. Lavebratt et al[53] reported an increased risk of all psychiatric disorders (using ICD codes in medical records) in children exposed to antibiotics compared with unexposed controls (age 0–6 months: hazard ratio 1.15 [95% CI: 1.12–1.17], 6–12 months: hazard ratio 1.10 [95% CI: 1.08–1.11], 1–2 years hazard ratio 1.16 [95% CI: 1.13–1.18]). Stark et al[67] reported increased use of psychotropic medications in exposed compared with unexposed children (aHR = 1.17, 95% CI: 1.59–1.84). The remaining three studies found no significant difference in psychiatric diagnoses, specifically mood and anxiety disorders[70] or symptoms measured by CES-DC scores, parent-rated Strengths and Difficulties Questionnaire (SDQ) scores and MASC-2 scores[68,72] in exposed compared with unexposed children.

Childhood antibiotic exposure and likelihood of later development of major depressive disorder

The data from four studies were sufficiently homogenous to perform a meta-analysis of the odds ratio of MDD following early-life antibiotic exposure. These studies used various measurements of MDD, including a documented diagnosis of mood or anxiety disorder in the patient's medical record,[70] prescription of antidepressant medication[53,67] or scoring ≥24 on the CES-DC.[68]

Figure 6 shows an association between childhood antibiotic exposure and risk of MDD (odds ratio 1.29, 95% CI: 1.04–1.60, $I^2 = 94\%$, $Q = 49.81$, d.f. = 3, $P < 0.001$). A leave-one-out analysis was performed, indicating the findings were robust (see Supplementary Fig. 9). No sibling-controlled studies evaluated the association between childhood antibiotic exposure and MDD.

Prenatal or childhood antibiotic exposure and likelihood of later development of cognitive or educational outcomes

No studies were identified that evaluated risk of cognitive or educational outcomes (e.g. IQ scores, intellectual disabilities or reading scores) following prenatal antibiotic exposure.

Four studies reported on educational/cognitive outcomes following early childhood.[57,68,72,73] These studies were heterogeneous

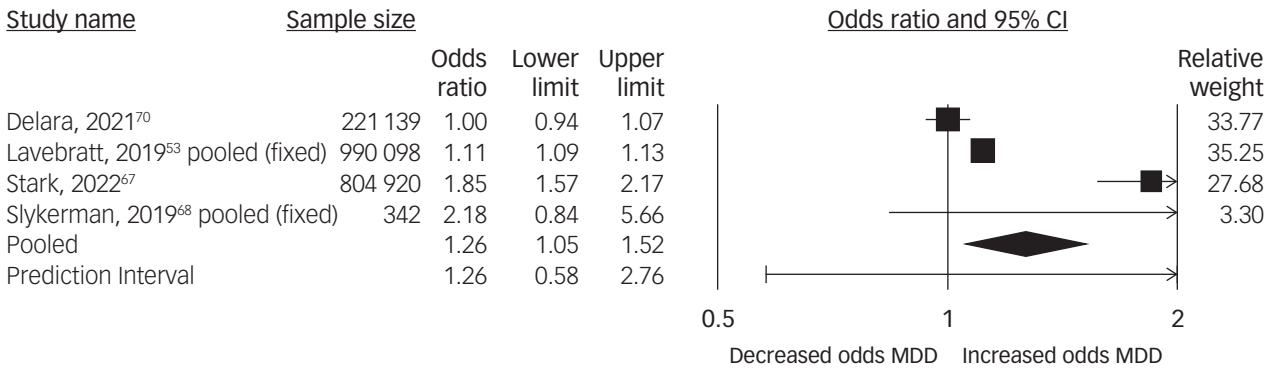

Fig. 6 Childhood antibiotic exposure likelihood of later development of major depressive disorder.

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with respect to outcome measures used, and thus could not be pooled and a meta-analysis was not performed. Aversa et al[57] reported that early exposure was associated with an increased risk in intellectual disorders (hazard ratio 1.21, 95% CI: 1.03–1.43). Slykerman et al[72] found no significant difference in IQ scores at age 11 or reading scores at age 7 associated with childhood antibiotic exposure. Slykerman et al[68] reported a small reduction in IQ scores for antibiotic exposed compared with unexposed children at age 11: Wechsler Intelligence Scale for Children – Fourth Edition (estimated mean difference, adjusted) at 0–6 months: −4.8 (95% CI: −9.4 to −0.3); 6–12 months: −3.6 (95% CI: −7.5–0.3); 12–24 months: −0.6 (95% CI: −4.6–3.4). Slykerman et al[73] reported increased behavioural difficulties (higher SDQ scores) and decreased performance in a receptive language task at 4.5 years in children exposed to antibiotics in the first year of life compared to unexposed children (or those who had been exposed after age 1).

No studies measuring cognitive/educational outcomes following *in utero* or childhood antibiotic exposure used sibling controls.

Time period for childhood antibiotic exposure and likelihood of ASD or ADHD

Whilst data were insufficient for a meta-analysis, three studies presented data allowing for comparison between antibiotic exposure in the first year of life compared with the second year of life and subsequent likelihood of ADHD[53,66] or ASD.[53,62] All three reported a reduced risk of ASD and ADHD following antibiotic exposure in the first year of life compared with the second.[53,62,66]

Antibiotic type

Regarding antibiotic types, 13 of the 30 included studies presented data stratified by antibiotic types. However, antibiotic data were inconsistently presented across study types, for example, some grouped by indication type (e.g. airway, urinary tract), others grouped by narrow versus broad spectrum, whilst others broke antibiotic types down into various different types/groupings (e.g. penicillin, other beta-lactam-based antibiotics, macrolides). In addition, none of the data stratified by antibiotic type also controlled for siblings. As such, it was not possible to perform a subgroup analysis for antibiotic type.

An attempt was also made to provide a descriptive synthesis relating to antibiotic types across different exposure periods and outcomes. However, the results were highly heterogenous, and no antibiotic type clearly emerged as showing significantly different risk for any outcome compared to the other antibiotic types. Owing to the heterogeneity and limitations of available data, it was not possible to comment on whether specific antibiotic types were associated with differing likelihoods of later development of neurocognitive or psychiatric outcomes.

Risk of bias

The overall mean NOS score across both case–control and cohort study types was 6.9, indicating intermediate risk (see Supplementary Table 2). Risk of bias scores for case–control studies ranged from 2 to 7, with a mean score of 4.4, representing intermediate. For case–control studies, the representativeness of cases was low, with several studies using specific populations, such as a medical community, specific ethnic population or premature births, the results from which are not easily generalisable. Several studies failed to adjust for confounding factors, which limited comparability. Ascertainment of the exposure may also be biased, as several studies determined diagnosis/outcome from parental interview rather than medical records.

For cohort studies, scores ranged from 4 to 9, with a mean score of 7.6, representing low risk. The adequacy of follow up may have been biased as numerous studies had significant missing data or loss to follow up. Even though studies were graded separately for each study outcome, no difference in NOS scores for any study between different outcomes were observed, hence Supplementary Table 2 is not separated by outcomes.

Certainty assessment

Using the GRADE framework, there was very low certainty for all seven meta-analyses, indicating that these results are unlikely to reflect the true effect (see Table 1). Reasons for downgrading certainty across these outcomes included significant statistical and methodological heterogeneity, lack of adjustment for key confounders (particularly sibling controls), inadequate length of follow up and gaps in data.

Discussion

Key findings

Significant associations were observed between *in utero* antibiotic exposure and both ASD and ADHD. However, whilst there were insufficient studies to perform sibling subgroup analyses for these exposures/outcomes, the studies that did use sibling control groups showed no significant associations. Similarly, significant associations were observed between exposure to antibiotics in the first 2 years of life and later development of ASD, ADHD and MDD. Here, there were sufficient data to perform sibling-controlled subgroup analyses for ASD and ADHD, and these analyses also showed no significant associations. Data were absent with respect to sibling-controlled analyses for MDD. Thus sibling-controlled analyses appeared to attenuate any associations observed between *in utero* or early childhood antibiotic exposure and ASD or ADHD, suggesting that any associations observed may arise from genetic or familial confounding factors. With respect to other psychiatric or neurocognitive outcomes, the data were too heterogeneous to perform any meta-analyses or draw any clear conclusions. However, the four studies that evaluated psychiatric outcomes following *in utero* antibiotic exposure indicated an increased likelihood of a psychiatric disorder.[53,65,70] This was not the case for childhood antibiotic exposure, where two[53,67] of the five studies reported an association between childhood exposure and later psychiatric disorder, and the remaining three showed no significant associations.[68,70,72]

There were no studies that evaluated any cognitive or educational outcomes following *in utero* antibiotic exposure. Studies evaluating early childhood exposure and educational/cognitive outcomes were mixed and inconclusive: three studies showed an association between childhood antibiotic exposure and poorer cognitive/educational outcomes[57,68,73] and one showed no association.[72]

No studies evaluating psychiatric or other cognitive outcomes used sibling controls to correct for genetic or familial confounding, which may have attenuated any associations seen, as was the case with ASD and ADHD. These findings therefore need to be interpreted with caution and indicate a critical gap in data in this area.

There were only three studies that presented data stratified by time bracket of antibiotic exposure in childhood.[53,62,66] However, all reported a reduced risk of ASD or ADHD following antibiotic exposure in the first year of life compared with the second.[53,62,66] This supports the contention that the association between childhood antibiotic exposure and likelihood of ASD or ADHD demonstrated in our meta-analyses may be explained by confounding by indication, genetics or familial factors, and that there is likely no true association between childhood antibiotic exposure and later development of ASD or ADHD. There were insufficient data to comment on other outcomes. It should be noted that all but one

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Table 1 Grading of recommendations, assessment, development and evaluation certainty assessment of the evidence supporting the statement 'early antibiotic exposure is associated with an increased risk of psychiatric or neurocognitive outcomes'

Certainty assessment							Effect		
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)	Absolute (95% CI)	Certainty
Certainty assessment of the statement: prenatal antibiotic exposure is associated with an increased risk of ASD									
11	Non-randomised studies	Not serious[a]	Very serious[b]	Serious[c]	Not serious[d]	None	Odds ratio 1.09 (1.02–1.16)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low
Certainty assessment of the statement: childhood antibiotic exposure is associated with an increased risk of ASD									
8	Non-randomised studies	Serious[e]	Very serious[b]	Very serious[f]	Not serious[d]	None	Odds ratio 1.19 (1.01–1.40)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low
Certainty assessment of the statement: childhood antibiotic exposure is associated with an increased risk of ASD in sibling-controlled studies only									
5	Non-randomised studies	Not serious[g]	Not serious[h]	Not serious[i]	Not serious[d]	None	Odds ratio 1.03 (0.91–1.16)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕◯◯ Low
Certainty assessment of the statement: prenatal antibiotic exposure is associated with an increased risk of ADHD									
5	Non-randomised studies	Not serious[j]	Very serious[b]	Not serious[k]	Not serious[d]	None	Odds ratio 1.19 (1.11–1.27)	1 fewer per 1000 (from 1 fewer to 1 fewer)	⊕◯◯◯ Very low
Certainty assessment of the statement: childhood antibiotic exposure is associated with an increased risk of ADHD									
8	Non-randomised studies	Not serious[j]	Very serious[b]	Very serious[l]	Serious[m]	None	Odds ratio 1.33 (1.20–1.48)	1 fewer per 1000 (from 1 fewer to 1 fewer)	⊕◯◯◯ Very low
Certainty assessment of the statement: childhood antibiotic exposure is associated with an increased risk of ADHD in sibling-controlled studies only									
3	Non-randomised studies	Not serious[j]	Not serious[h]	Not serious[k]	Not serious[d]	Publication bias strongly suspected[n]	Odds ratio 0.97 (0.93–1.01)	1 fewer per 1000 (from 1 fewer to 1 fewer)	⊕◯◯◯ Very low
Certainty assessment of the statement: childhood antibiotic exposure is associated with an increased risk of MDD									
4	Non-randomised studies	Very serious[o]	Very serious[b]	Very serious[p]	Very serious[m]	None	Odds ratio 1.29 (1.04–1.60)	1 fewer per 1000 (from 2 fewer to 1 fewer)	⊕◯◯◯ Very low

ASD, autism spectrum disorder; ADHD, attention-deficit hyperactivity disorder; MDD, major depressive disorder.
a. Newcastle-Ottawa scale (NOS) risk of bias was low for the seven cohort studies that contributed 92.31% towards the pooled estimate. The remaining four case–control studies had moderate risk of bias but only contributed 7.69%.
b. $I^2 \geq 75$.
c. Six studies that contributed 18% of the weighting towards the final pooled estimate had a number of methodological issues, including unrepresentative samples, potential for recall bias, missing data and small sample sizes. The remaining studies, contributing 82%, did not appear to have any major issues.
d. Narrow confidence interval.
e. The three case studies that contributed 18% to the final pooled estimate were at high risk of bias, but the remaining five cohort studies that contributed 82% were low risk.
f. There were a number of methodological limitations from papers weighted more heavily, including low sample sizes, selection/recruitment bias, recall bias, missing data and inadequate follow-up times.
g. Whilst three included studies had high risk of bias according to NOS scores, the two that contributed 94% were at low risk of bias.
h. $I^2 < 50$.
i. Two studies that contributed heavily to the final outcome (94% weighting) did not have any significant methodological issues.
j. The overall risk of bias was low across studies.
k. Nil significant limitations in the included papers.
l. Substantial heterogeneity relating to determination of ADHD outcome, with studies using prescription data, diagnostic codes and scores in symptom rating scales.
m. Wide confidence interval.
n. The Egger's intercept was significant ($P < 0.05$).
o. Two studies that were rated as very low risk of bias constituted 69% of the weighting towards the overall pooled estimate; however, the remaining two studies, contributing 31%, were of moderate risk of bias.
p. There were methodological inconsistencies and limitations across studies, relating to heterogeneous definitions of MDD (e.g. prescription data, mood and anxiety disorders not distinguished from one another, rating scales and diagnoses in medical records), representativeness of the study cohort and missing data.

of the meta-analysis findings listed above were rated as very low certainty using the GRADE certainty assessment. The one exception was the certainty of the statement 'childhood antibiotic exposure is associated with an increased risk of ASD in sibling-controlled studies only', which was rated as low. It should be noted, however, that using the GRADE certainty system, meta-analyses of observational data always begin at low quality as a default owing to the widely recognised limitations of observational data.[74] The certainty can only be upgraded in the case of a very large effect size (for example, a two-fold increase in risk) or a dose–response gradient (which was not possible to assess in this review owing to a lack of data).[74] The reason for ratings of very low certainty across most findings was largely because of methodological heterogeneity regarding ascertainment of outcome measures and exposures, high I^2 results (five of the seven meta-analyses with >75% I^2 values), lack of generalisability of study populations and gaps in data. Even though a number of significant associations are reported, the prediction intervals associated with all findings were wide and crossed the null. In saying this, when using the NOS for individual study quality assessments, most of the included studies were of low risk (meaning a NOS score of 7 or greater), particularly the cohort studies, which represented most included studies ($n = 23$), with a mean NOS score of 7.6. We also conducted leave-one-out analyses and performed separate subgroup analyses by study type for each meta-analysis, which demonstrated robustness of the findings. The reason for the discrepancy between poor GRADE scores but high NOS scores for individual studies arose from heterogeneity between studies, meaning whilst study quality was overall high for individual studies, it was difficult to synthesise and interpret the studies as a whole owing to methodological differences reflected in high statistical heterogeneity.

Possible mechanisms

There are several key mechanisms by which antibiotic exposure may be associated with psychiatric or neurocognitive outcomes. The first pertains to disruptions to the gut–brain–microbiota axis caused by antibiotics. Antibiotics clearly affect the intestinal microbiome, reducing microbial diversity,[25] a variable thought to be associated with a number of neuropsychiatric disorders including ASD, anxiety, schizophrenia, Parkinson's disease and Alzheimer's disease.[1] It is therefore plausible that early antibiotic exposure may result in increased risk of mental health disorders through their impact on the intestinal microbiota of the infant and subsequent influence on neurodevelopment.[32] The intestinal microbiota directly and indirectly communicate with and influence the central nervous system through a number of well-documented pathways, including maternal microbiota-derived extracellular vesicles *in utero*,[75] vagal nerve stimulation and synthesis of neuroactive agents and other products that modulate immune and inflammatory pathways.[1] Most brain tissue is white matter, which is largely comprised of immune cells and other cells that support neuronal activity.[76] Hence, any processes that affect the immune system or cause inflammatory changes have implications for brain functioning and development.[77] There are human data in preterm infants suggesting white matter injury resulting from elevated levels of cytokines and oxidative stress is associated with disruptions to the intestinal microbiota.[77]

It is also possible that other microbiota-influencing factors may modify the effect of antibiotics (either increasing or decreasing the impact of antibiotics on the intestinal microbiota) with implications for risk of outcomes believed to be associated with microbiota changes. For example, breast milk exposure has been found to function as an effect modifier that substantially mitigates antibiotic-associated microbiota disruption and associated asthma risk.[78] This has implications for familial confounding, discussed below.

Other potential mechanisms include familial confounding or confounding by genetics. Familial confounding refers to the idea that shared familial factors may account for both increased likelihood of an exposure and a particular outcome. For example, shared familial exposure to infections or environmental risk factors such as air pollution may increase risk of both the outcomes of interest and the risk of antibiotic use. Air pollution arising from residing close to a freeway has been linked with increased likelihood of ASD,[79] and has also been linked with the increased prevalence of certain pathogens, which may be associated with infection and need for antibiotic use.[80] Healthcare utilisation is another example, as families that present more frequently to health services are more likely to be prescribed and use antibiotics, as well as receive a diagnosis of a psychiatric or neurocognitive disorder. In addition, cohabiting individuals are known to share microbiota.[80] Hence, antibiotic use in one family member may reduce diversity of the gut microbiome across the household.[82] If household gut microbiota composition operates as an underlying mechanism, then antibiotic use may be considered a shared household exposure, which may potentially bias the results towards the null. Further research is needed to investigate the gut microbiome as a shared exposure, along with the temporal relevance of any antibiotic-induced microbial changes on subsequent mental health outcomes in children.

Confounding by genetics refers to the idea that a common gene drives susceptibility to both infections (and associated antibiotic use) and psychiatric/neurocognitive disorders.[32] For example, there is evidence of increased frequency of ear infections in children with ASD compared to the general population.[83,84] High levels of heritability have been observed across a range of psychiatric and neurocognitive disorders,[85] so studies that do not account for genetic confounding are susceptible to spurious associations. Only five[47,48,58,70,86] of the 30 included studies attempted to account for genetic confounding by using parental history of the outcome of interest as a covariate and, of these, one study looked at maternal history only.[70] However, even this strategy has limitations. We note the increasing recognition, identification and diagnosis of psychiatric and neurocognitive disorders at this time compared with one generation ago, also affected by the change in the diagnostic criteria for most of these disorders over time with new editions of DSM and ICD.[87] As such, even taking parental diagnosis into account, it is likely that this strategy may lead to under-recognition of psychiatric and neurocognitive disorders in parents. Using parental psychiatric history as a covariate also fails to account for familial confounding. We suggest therefore that the optimal way to account for confounding by genetics and familial factors is through use of sibling-control groups. This review found that the use of sibling controls attenuated associations observed between prenatal and childhood antibiotic exposure and both ASD and ADHD, indicating that confounding by genetics or familial factors is a likely explanatory factor.

Another potential mechanism is confounding by indication, wherein the infection itself may have had a causal role in the later development of mental health disorders.[32] Antibiotics are generally used in the context of confirmed or suspected infection, and it may therefore be the infection itself (maternal or early childhood), or infection-related factors such as fever/inflammatory response, that are associated with any later neuropsychiatric outcomes observed rather than the antibiotics. Potential mechanisms may include direct neurotoxicity of the pathogen, which may cross the blood–brain barrier,[32] immune activation,[88–90] elevated acute phase reactants[91,92] or fever.[47,93–95] In animal models, maternal immune activation is used to elicit ASD-like phenotypes.[96] In humans, prenatal viral infections were shown to be associated with schizophrenia in offspring.[97,98]

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Owing to a lack of data, this review was unable to evaluate infection-related confounding factors (e.g. infection type, duration of illness, admission to hospital, presence of fever and complications). This meant it was not possible to separate the effect of the underlying infection from the effect of the antibiotics themselves, resulting in potential confounding by indication. Another consideration is that if it is indeed the underlying infection that is the factor driving increased risk for mental health conditions, then antibiotics may be protective. As the data do not separate the key factors of antibiotic exposure, versus the underlying infection, or the possible interplay between these factors, this association is poorly understood at this stage. Further research is needed to investigate this type of confounding.

Strengths and limitations

This systematic review has numerous strengths. It is among the first to broadly examine the association between early-life and *in utero* antibiotic exposure and all psychiatric and neurocognitive outcomes. Being broad in nature, this review was able to identify key gaps in the body of literature. Notably, these gaps related to the following: (a) studies evaluating psychiatric and cognitive/educational outcomes; (b) studies evaluating *in utero* antibiotic exposure; and (c) studies utilising sibling controls. With respect to studies evaluating psychiatric outcomes, these outcomes varied significantly with respect to outcome measures used, meaning it was not possible to pool data for most psychiatric and cognitive/educational outcomes. The breadth of this review is a key strength as it allows for an overarching synthesis in data in this field of related disorders/outcomes, and the identification of literature gaps and directions for future research. Importantly, the review included sibling-controlled data, which previous reviews identified as a critical confounding factor.[31]

This review also identified several limitations of the available data. Studies lacking sibling controls were a key limitation, as this review found that use of sibling-control groups appeared to attenuate the findings of increased risk of ADHD and ASD following childhood antibiotic exposure. It is therefore possible that similar findings may also have been observed for MDD, and the other psychiatric and neurocognitive outcomes. Thus, any findings that did not use a sibling control group should be interpreted with caution. With respect to exposure period, only three studies evaluating *in utero* exposure also accounted for early childhood exposure as a covariate,[52,57,86] and no studies investigating early childhood exposure accounted for the influence of *in utero* exposure as a covariate, which may have biased the outcomes. There was also a critical lack of sibling-controlled data assessing *in utero* antibiotic exposure, arguably the most important period for evaluation. Childhood exposure assumes that early-life factors may modify disease risk, whereas the disorder (or predisposition to the disorder) may have already been present at the time of exposure. This may be the case for any psychiatric or neurocognitive outcome but particularly for ASD, which can manifest before age 2 but is often undiagnosed owing to the challenges of early diagnosis.[99,100] Unfortunately, the data relating to antibiotic types were limited and inconsistent and stratified by exposure window for childhood antibiotic exposure, again with a critical absence of sibling-controlled data. However, it is theoretically possible that different antibiotic types may be associated with different risks of psychiatric or neurocognitive outcomes following early-life exposure. In Parkinson's disease, for example, one study has reported a strong association with macrolides and lincosamides.[101] In addition, as mentioned above, statistical and methodological heterogeneity were observed across both the exposure and outcome data.

Finally, many of the population-based cohort studies utilised retrospective service-level administrative data. Administrative records are likely to capture antibiotic prescription and dispensation. However, without a prospective study design, actual antibiotic use remains uncertain, and may be overestimated as individuals prescribed or dispensed antibiotics may not take the medication. Moreover, the use of administrative data may miss, misclassify and/or underestimate psychiatric outcomes if diagnoses occurred at other services or were never formally assessed and thus would bias our results towards the null hypothesis.

Clinical implications and directions for future research

Taken as a whole, particularly considering the low and very low levels of certainty and non-significant prediction intervals, at this stage there is no convincing evidence to suggest a causal link between *in utero* or early-life antibiotic exposure and later development of psychiatric or neurocognitive outcomes and no definitive conclusions can be made.

To better inform clinical practice with respect to prescribing and informed consent for antibiotic use in the prenatal and early-life periods, future studies must at the very least include sibling-control groups. To mitigate bias arising from reliance on administrative data, further large prospective cohort studies are needed, which systematically assess psychiatric outcomes and confounders or effect modifiers, such as sibling exposure and outcomes, mode of delivery, breastfeeding, antibiotic type, infection type/severity, health service utilisation, gender and socioeconomic status.

Studies should also correct for the influence of unaccounted-for antibiotic exposure, for example, studies of early childhood antibiotic exposure should also measure and correct for *in utero* exposure and *vice versa*. We recommend studies present sibling-controlled antibiotic type data, stratified by specific antibiotic categories such as penicillin, macrolides and tetracyclines, to allow for greater understanding of differential magnitudes of association by antibiotic type rather than stratifying by broad spectrum versus narrow spectrum antibiotics, or other broader groupings. We also recommend studies endeavour to stratify data by exposure windows, particularly for childhood exposure as the limited data available to date suggests there may be significant differences in risk of later development of psychiatric/neurocognitive outcomes (e.g. 0–6, 6–12, 12–24 months).

Future studies of antibiotic risk associated with neurocognitive/psychiatric outcomes should also take infection type and severity into account where possible to correct for confounding by infection. For example, contrasting the use of antibiotics for low-grade infections, such as a mild upper-respiratory tract or lower-urinary tract infection, with their use in severe infection and adjusting for severity factors, such as fever or admission to hospital, or if these data were missing, providing a justification for the lack of data.

Associations were observed between *in utero* antibiotic exposure and ASD and ADHD, and early childhood antibiotic exposure and ASD, ADHD and MDD. However (with the exception of MDD, for which no sibling-controlled data were available), these associations were all attenuated in studies that used sibling-control groups. The data are therefore supportive of the hypothesis that associations observed between antibiotic use in early life and later neurodevelopmental may be attributable to shared genetics or familial factors.

The findings of this systematic review pave the way for future study designs that incorporate sibling controls, as well as those that focus on *in utero* antibiotic exposure, for which the evidence is sparser. In addition, we note the critical absence of psychiatric and cognitive educational outcomes, and the heterogeneity of studies that do evaluate these. We recommend investment of

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high-quality prospective cohort studies that systematically assess psychiatric diagnoses, augmenting symptoms scales as a measure of psychiatric outcomes.

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Supplementary material

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Data availability

Data, analytic code and research material availability are not applicable to this article as no new data, analytic codes or research material were created or analysed in this study.

Author contributions

J.E.G. drafted the manuscript, incorporated edits from authors, prepared the manuscript for submission and completed the primary and secondary reviews, data extraction, quality assessments and all statistical analyses. A.W., W.M. and S.D. provided oversight and advice during the drafting process. A.W. and S.D. also acted as a secondary reviewers. E.T. completed data extraction pertaining to 20% of the included studies for quality assurance, and was a second reviewer for the quality assessment. S.D. and F.N.J. were senior authors. All authors read and approved the final document.

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