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The relationship of prenatal and infant antibiotic exposure with childhood overweight and obesity: a systematic review

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Review

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Abstract

This study aimed to assess the evidence regarding the relationship between early-life antibiotic exposure and childhood overweight/obesity by reviewing observational studies on prenatal antibiotic exposure and systematic reviews on infant antibiotic exposure. A search in Pubmed, Embase and Google Scholar covering the period 1st January till 1st December 2018 led to the identification of five studies on prenatal antibiotic exposure and four systematic reviews on infant antibiotic exposure. Positive trends between prenatal antibiotic exposure and overweight/obesity were reported in all studies; two studies reported a significant overall relationship and the other three reported significant relationships under certain conditions. Effect sizes ranged from odds ratio (OR): 1.04 (0.62–1.74) to relative risk (RR): 1.77 (1.25–2.51). Regarding infant antibiotics, one review concluded there was substantial evidence that infant antibiotic exposure increased the risk of childhood overweight/obesity [pooled effect sizes: RR: 1.21 (1.09–1.33) for overweight and RR: 1.18 (1.12–1.25) for obesity]. Two reviews concluded there was some evidence for a relationship [pooled effect sizes: OR: 1.05 (1.00–1.11) and OR: 1.11 (1.02–1.20)]. The fourth review concluded the studies were too heterogeneous for meta-analyses and the evidence regarding the relationship between infant antibiotic exposure and childhood overweight/obesity was inconclusive. More well-designed studies are needed that include data on intra-partum antibiotics and address important potential confounders (including maternal and childhood infections). This review points to some evidence of a relationship between early-life antibiotic exposure and childhood overweight/obesity; this is especially evident in certain children (i.e. exposed to multiple and broad-spectrum antibiotics, earlier postnatal exposure and male gender) and merits further research.

Background

Chronic diseases including obesity are on the rise worldwide, many of which already start to manifest during childhood.[1] According to the World Health Organization (2018), the prevalence of overweight and obesity worldwide among children from 5 to 19 years of age was 18% in 2016, compared with just 4% in 1975.[2] In the United States, 31.8% of all children from 2 to 19 years of age were estimated to be either overweight or obese in 2011–2012[3] and in the Netherlands, 13.4% of children between the ages of 4 and 20 were overweight or obese in 2016.[4] Childhood overweight and obesity can persist into adulthood, increasing the risk of cardiovascular diseases, diabetes and various cancers later in life.[5] Overweight can affect every system in the body and is therefore associated with an increased risk of other health issues including joint problems, fractures, sleeping disorders, hypertension, nonalcoholic fatty liver disease, depression and anxiety.[6]

Modifiable early-life risk factors found in a systematic review by Woo Baidal *et al.*[7] for childhood overweight include not only prenatal factors, such as maternal pre-pregnancy and excess gestational weight gain, smoking during pregnancy, high birth weight, but also postnatal factors, such as premature solid food introduction and infant antibiotics. The human gut microbiome may play a substantial underlying role in these early risk factors for overweight and obesity.[8]

One of the factors that can disrupt the gut microbiome and may contribute to the development of childhood overweight and obesity is early-life antibiotic administration.[9] In the early 1950s, farmers had already started adding low doses of antibiotics to the food of various animals, including chickens and pigs, following the discovery that antibiotic administration could significantly increase their growth.[10] Later experimental studies in mice also demonstrate the likelihood of a critical window in which antibiotics could impose lasting effects; mice exposed to antibiotics in early life before weaning were more likely to become overweight than mice that were not exposed, or mice that were exposed to antibiotics after weaning.[11,12] Several observational studies have reported that alterations to the early developing microbiome may also be making children susceptible to overweight or obesity.[13] Although the microbiome may eventually return to its original composition after the completion of antibiotic administration, the disruption caused by antibiotics may lead to permanent changes in metabolic and immune development.[8,14]

Antibiotics are commonly administered to women during pregnancy for urinary and respiratory infections and just prior to or during delivery, to prevent neonatal Group B Streptococcus fever and maternal infections, including chorioamnionitis and infections arising from surgical wounds after caesarean sections.[15] Stokholm *et al.*[16] estimated antibiotic administration to be 37% for pregnancy and 33% during delivery in Denmark. In the Netherlands, 20.8% of women are estimated to have antibiotics during pregnancy,[17] but the proportion of intra-partum antibiotics is unknown. Antibiotics are given to over 50% of children in high-income countries, during their first years of life to treat mainly ear and respiratory tract infections.[9,18]

As overweight and obesity rates are rising with such detrimental consequences and antibiotics are so commonly administered to women and children, it is important to ascertain whether and to what extent antibiotic exposure, a potentially modifiable factor, does increase the risk of developing childhood overweight. An initial review of the literature revealed that a substantial number of studies have been conducted on the relationship between infant antibiotic administration and childhood overweight, and far fewer studies have been conducted on prenatal antibiotic exposure and childhood overweight. This review therefore has two main aims: (1) to review the evidence reported by observational studies between 2008 and 2018 that have investigated prenatal antibiotic exposure and overweight or obesity in children up to 18 years of age and (2) to review the evidence that has been reported by systematic reviews between 2008 and 2018 that have investigated infant antibiotic exposure and overweight or obesity in children up to 18 years of age.

Methods

The databases Pubmed, Embase and Google Scholar were searched from the period 1st January 2008 till 1st December 2018. Search terms adjusted to the databases Pubmed and Embase (see Box S1) were used to identify the titles and abstracts of relevant English language publications. Various combinations of the same keywords were entered into Google Scholar to check for any additional publications. The titles and abstracts that were retrieved were screened by RB for potential inclusion in this review. The full texts of the selected titles/abstracts were then read and assessed independently by RB and MT to determine whether they were eligible for this review. The inclusion and exclusion criteria, quality assessments and data extraction methods differed somewhat for the two types of review conducted in this study and will therefore be described separately.

Prenatal antibiotic exposure

Inclusion and exclusion criteria

The inclusion criteria for study design were observational human studies, such as cohort, case-control or cross-sectional studies examining prenatal antibiotic exposure. We included only studies that were published, in order to have sufficient information to be able to conduct comparable assessments of the quality and findings of the studies. By including only studies that had been peer-reviewed, we aimed to increase the chance of our findings being accurate. Experimental animal studies and reviews were excluded.

The exposure for the review of prenatal antibiotic exposure was any type of antibiotic administered during pregnancy and during delivery; data could be obtained by means of medical databases or by maternal self-reports. All publications needed to report effect sizes, such as odds ratios, relative risks, body mass index (BMI) z-scores and their corresponding 95% confidence intervals. The outcome overweight or obesity could be measured at any time during childhood up to 18 years of age and determined by BMI (divided into weight categories, such as underweight/normal weight/overweight/obesity) or by BMI z-scores. These anthropometrics could be based on parental self-reports or measurements by trained personnel.

Quality assessment

To help determine how reliable the findings of the finally selected publications were on prenatal antibiotic exposure and childhood overweight, RB and MT independently assessed them for their risk of bias using the Newcastle–Ottawa Scale (NOS)[19] (Table 1). This scale evaluates observational studies and gives points for three categories: 'selection' (assessing how representative the sample is, and how objective the measurements are), 'comparability' (assessing how well potential confounders are taken into account) and 'outcome' (assessing follow-up time and how missing data are handled). The maximum number of points that can be awarded is 9, with publications scoring 8–9 points considered 'low risk', 6–7 points 'medium risk' and publications with <6 points evaluated as 'unclear'.

For the 'comparability' category, the main potential confounders we considered to be of importance due to their association with childhood overweight were caesarean section,[25] postnatal antibiotics,[13] maternal pre-pregnancy overweight,[26] childhood infections[27] and maternal infection (due to its association with childhood infections).[28]

Data extraction

Data were also extracted independently from each publication by RB and MT. The data extracted by RB and MT were compared and any disagreement was discussed until consensus was reached. These data consisted of the study design, country, definitions of the exposure and outcome measurements, the main findings (i.e. effect sizes and confidence intervals), additional relevant factors that were adjusted for or examined and the study authors' own conclusions. Information was collected on the potential confounding factors the studies had adjusted for, such as maternal infections and maternal BMI, and on whether authors had addressed multiple doses and types of antibiotics.

Infant antibiotic administration

Inclusion and exclusion criteria

The inclusion criteria were published systematic reviews that consisted of observational human studies examining the relationship between infant antibiotic exposure during the first 2 years of life and the development of childhood overweight or obesity. The

Table 1. Prenatal antibiotics exposure and childhood overweight/obesity

Study and authors' conclusions (relevant for this review)	Country	Population	–Timing of antibiotic exposure –Prevalence exposure	Health outcome/age and prevalence	Summary measures (HR, RR or OR) variables adjusted for	Influential factors		Risk of Bias using NOS
Wang *et al*.[20] Prospective cohort study *Prenatal antibiotic use was not associated with obesity or BMI z-score at age 4 years, but repeated exposure was associated with obesity at 7 years of age.*	United States	– 4 year olds: 33,228 – 7 year olds: 39,615 Study period: 1959–1976	– Pregnancy first/second/third trimester (self-reported), intrapartum antibiotics not included – Prevalence: 25.2% – Significance found only when exposure was in second trimester.	– Overweight/obesity – 4 year olds: Prevalence: 24.7%/8.9% – 7 year olds: Prevalence: 13.1%/4.6%	– 4 year olds: *Overweight:* OR: 1.01 (0.97–1.06) *Obesity:* 0.98 (0.90–1.06) – 7 years olds *Overweight:* OR: 1.04 (0.98–1.10) *Obesity:* 1.09 (0.98–1.20) Adjusted for the following: maternal age, race, socioeconomic index, smoking during pregnancy, prepregnancy BMI, parity and centre.	Dose-response relationship	Significant from two or more antibiotic exposures	Selection: 3/4 Comparability:1/2 Outcome:3/3 Total: 7 (medium risk)
						Intrapartum antibiotics	Unclear, but most likely excluded	
						Types of antibiotics	Broad-spectrum (tetracyclines and aminoglycosides) and narrow-spectrum antibiotics (only penicillin) significantly associated with obesity at 7 years with 2+ exposures	
						Childhood antibiotics usage	Not examined	
						Gender	No differences	
						Birth weight	Not examined	
						Delivery mode	Effect stronger in CS group than vaginal. Authors mention this may be due to intrapartum antibiotics	
						Maternal overweight	Adjusted for pre-pregnancy BMI	
						Breastfeeding	Not examined	
						Maternal infections	Not examined	
						Childhood infections	Not examined	

Table 1. (*Continued*)

Study and authors' conclusions (relevant for this review)	Country	Population	–Timing of antibiotic exposure –Prevalence exposure	Health outcome/age and prevalence	Summary measures (HR, RR or OR) variables adjusted for	Influential factors		Risk of Bias using NOS
Cassidy-Bushrow *et al*.[21] Prospective cohort study *There was an association between antibiotics and increased BMI z-score, mainly with exposure in the second trimester at age 2. There was no association between antibiotics and overweight/obesity in general, but exposure in first trimester was associated with overweight/obesity*.	United States	527 children Study period: 2003–2007	– Pregnancy first/second/third trimester – Prevalence: 57.5%	– Increased BMI z-score – Overweight/obesity – 2 years old Prevalence: 17.1%	Increased z-score: 0.20 ± 0.10 ($P = 0.046$) Overweight/obesity: OR: 1.04 (0.62–1.74) Only first trimester exposure associated with overweight /obesity: OR: 1.78 (1.07, 2.98) Adjusted for the following: infant gender, delivery mode, ever breastfed, maternal age, maternal race, maternal education, birth weight Z-score, child age at 2-year visit and BMI at first prenatal care visit.	Dose–response relationship	There was only an insignificant trend for BMI z-score, but for overweight/obesity not even a trend.	Selection: 4/4 Comparability: 1/2 Outcome: 2/3 Total: 7 (medium risk)
						Intrapartum Antibiotics	Yes, authors mention including delivery in the exposure period	
						Types of antibiotics	No differences associated with overweight/obesity, but BMI z-score was only associated with macrolides	
						Childhood antibiotics usage	In univariable analyses, there was no significant association with prenatal antibiotics, so not considered to be confounder.	
						Gender	Association did not vary between gender groups	
						Birth weight	Association did not vary between birth weight groups	
						Delivery mode	No association with higher BMI z-score in CS group. In VB group, association reached significance ($P = 0.064$)	
						Maternal overweight	Adjusted for	
						Breastfeeding	Association did not vary between breastfeeding groups	
						Maternal infections	Not examined	
						Childhood infections	Not examined	

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Poulsen *et al*.[22] Retrospective cohort study *Children's antibiotic use, but not prenatal antibiotic exposure is related to children's BMI at age 3 years.*	United States	8793 mothers/ child pairs Born from 2006 to 2012	– Conception date till delivery date. – Prevalence: 60.4%	– BMI z-score – 3 years old	BMI z-score 0.136 (−0.144 to 0.417) (not significant) No differences observed per trimester. Adjusted for the following: age, mother race/ethnicity, mother Medical Assistance, smoking during pregnancy, parity, and pre-gravid BMI	Dose-response relationship	3+ orders of antibiotics associated with increased BMI-z-score but not significant. Only the sample overweight/obese mothers taking 3+ antibiotic orders was significant	Selection: 4/4 Comparability: 1/2 Outcome: 2/3 Total: 7 (medium risk)
						Intrapartum Antibiotics	Collected separately to prenatal antibiotics, but not mentioned again later, unclear whether included in main analyses	
						Types of antibiotics	No differences in effect found	
						Childhood antibiotics usage	Not adjusted for, examined separately	
						Gender	Not examined	
						Birth weight	Not adjusted for, due to occurring after antibiotic exposure. Subgroup analyses conducted, but no effect modification	
						Delivery mode	Not adjusted for, due to occurring after antibiotic exposure. Subgroup analyses conducted, but no effect modification.	
						Maternal overweight	Subgroup analyses: Only significant association in sample of mothers with overweight/ obesity who had also taken 3+ antibiotic orders.	
						Breastfeeding	Not examined	
						Maternal infections	Not examined	
						Childhood Infections	Not examined	

Table 1. (*Continued*)

Study and authors' conclusions (relevant for this review)	Country	Population	–Timing of antibiotic exposure –Prevalence exposure	Health outcome/age and prevalence	Summary measures (HR, RR or OR) variables adjusted for	Influential factors		Risk of Bias using NOS
Mueller *et al*.[23] Prospective birth cohort *Exposure to antibiotics in the second or third trimester (adjusted for delivery mode) and caesarean section (adjusted for prenatal antibiotics) were independently associated with higher risk of childhood obesity*.	United States	436 children (mothers all African-American or Dominican) Pregnant women recruited between 1998 and 2006	– Pregnancy 1st/2nd/3rd trimester (self-reported), intrapartum antibiotics not included – Prevalence: 16% (2nd or 3rd trimester)	– Obesity – 7 years old – Prevalence: 25.2%	RR: 1.77 (1.25–2.51) (excluding mothers with gestational diabetes and pre-eclampsia) Adjusted for the following: sex, ethnicity, birth weight, maternal age, maternal pre-gravid BMI, receipt of public assistance during pregnancy, having breastfed in first year, and delivery mode.	Dose-response relationship	Not examined	Selection: 3/4 Comparability: 1/2 Outcome: 3/3 Total: 7 (medium risk)
						Intrapartum Antibiotics	Not included	
						Types of antibiotics	Not examined	
						Childhood antibiotics usage	Not examined	
						Gender	Adjusted for	
						Birth weight	Adjusted for	
						Delivery mode	Those with CS (adjusted for prenatal antibiotics, but (not intrapartum antibiotics) significantly more likely to have obesity than those with VB.	
						Maternal overweight	Adjusted for pre-pregnancy BMI	
						Breastfeeding	Adjusted for	
						Maternal infections	Not examined	
						Childhood infections	Not examined	

Mor *et al.*[24] Retrospective cohort study *Prenatal exposure to systemic antibacterials is associated with an increased risk of overweight and obesity at school age. The role of the underlying infection cannot be ruled out.*	Denmark	9886 Born between : 1994 and 1998	– 30 days before estimated conception data till childbirth – Prevalence: 33%	– 7–16 years old – Overweight: 7.8% – Obese: 3.1% – Prevalence: 10.9%	– Overweight: PR: 1.26 (1.10–1.45) – Obese: PR: 1.29 (1.03–1.62) Adjusted for the following: sex, maternal age group, smoking during pregnancy, marital status and multiple pregnancy.	Dose–response relationship	Only significant with ≥3 prescriptions	Selection: 4/4 Comparability: 1/2 Outcome: 3/3 Total: 8 (low risk)
						Intra-partum Antibiotics	Unclear	
						Types of antibiotics	Tetracyclines, Penicillins & Macrolides not significant.Sulfonamides and trimethoprim & a mix of antibiotics significantly associated with overweight.	
						Childhood antibiotics usage	Not examined	
						Gender	Subgroup analyses: Overweight only significant in sample of boys, although there was also a positive effect size (but lower) in girls.	
						Birth weight	Stratification analyses show greater risk for overweight, but not obesity in lower birth weight <3500 sample. only overweight significant for low birth weight.	
						Delivery mode	Stratification analyses show similar effect sizes between CS and VB groups, but only within the VB group, the relationship with overweight and obesity is significant.	
						Maternal overweight	Adjusted for an estimation of its prevalence	
						Breastfeeding	Not examined	
						Maternal infections	Not examined	
						Childhood infections	Not examined, but authors mention there being a possible genetic predisposition to obesity and infection.	

NOS, Newcastle-Ottawa Scale (low risk: 8–9 points, medium risk: 6–7 points, unclear risk: <6 points); CS, caesarean section; VB, vaginal birth; OR, odds ratio; RR, relative risk.

systematic reviews needed to report statistical effect sizes and confidence intervals.

Quality assessment

The assessments of the systematic reviews were based on a tested criteria appraisal tool for umbrella reviews[29] and on the tool Risk of Bias in Systematic Reviews (ROBIS)[30] (Tables S1a and S1b). The first tool consists of 10 questions about the methodology used in the systematic review with the following answer options which we adjusted to 'yes', 'no', 'unclear' and 'not applicable'. The ROBIS tool is used to help assess risk of bias in terms of four different domains: 'study eligibility' (i.e. the appropriateness of eligibility criteria), 'identification and selection of studies' (i.e. the appropriateness of methods used to identify publications), 'data collection and study appraisal' (i.e. efforts made to minimise error in data collection and risk of bias assessment) and 'synthesis and findings' (i.e. the appropriateness of the synthesis conducted).

Data extraction

Data were extracted from the systematic reviews on the authors, country, the number of studies included, whether a meta-analysis had been conducted, the main findings and pooled results, additional findings of influential factors, information about quality assessments conducted by the authors and the authors' own summary conclusions regarding the evidence on infant antibiotic exposure and childhood overweight/obesity.

Results

Five studies were identified investigating prenatal antibiotic exposure and childhood overweight/obesity and were published during the period 2015–2018 (see Figure S1 for search process). Four systematic reviews were identified investigating infant antibiotic exposure and childhood overweight/obesity and were published from 2017 to 2018. Three of the systematic reviews had additionally conducted meta-analyses and one systematic review included had examined prenatal as well as infant antibiotic exposure. The authors that had not conducted a meta-analysis referred to their study as a narrative review in the title, but they had followed the same reproducible procedures in their review as other systematic reviews.

Prenatal antibiotic exposure

Study characteristics

Five cohort articles were identified examining the relationship between prenatal antibiotic exposure and childhood overweight or obesity (Table 1). The studies were conducted in the United States ($n = 4$) or in Denmark ($n = 1$) and the sample sizes ranged from 436 to 39,615 mother–child pairs. The prevalence of prenatal antibiotic exposure was 16% when intra-partum antibiotics were excluded,[23] 57.5% in the study that included intra-partum antibiotics[21] and 25.2%–60.4% in the other three studies where it was unclear whether or not intra-partum antibiotics were included.[20,24,22] Childhood overweight/obesity ranged from 17.1% at 2 years of age[21] to 24.7/8.9% (overweight/obesity) at 4 years of age[20] to ranges of 10.9%–25.2% at the ages of 7 and older.[20,23,24]

Study findings

There were generally positive trends found in the relationship between any prenatal antibiotic exposure and childhood overweight, although this relationship was significant in just two of the five studies: that is, overweight: prevalence rate (PR): 1.26 (1.10–1.45); obesity: PR: 1.29 (1.03–1.62) in a Danish sample of 7–16 year olds[24] and relative risk (RR): 1.77 (1.25–2.51) in 7 year olds from a sample who had mothers identifying as African-American or Dominican[23] (Table 1). Another study did not find an association with overweight or obesity categories, but with an increased BMI z-score at 3 years of age.[22]

The significance of the relationship found in the study conducted by Mor *et al.*[24] was mainly driven by exposure to three or more antibiotic prescriptions. Although the other three studies found a general insignificant relationship between prenatal antibiotic exposure and childhood overweight/obesity, they all did reveal significant relationships under certain conditions, that is, the exposure consisted of multiple antibiotic prescriptions in a sample where mothers were overweight[22] and the exposure was multiple, mainly broad-spectrum antibiotic administration when overweight was measured at a later childhood age (7 versus 4 years of age[20]). Other conditions were that antibiotic exposure had occurred only during certain trimesters [i.e. only first trimester[21] or only second trimester for overweight at 7 years of age (but not at 4 years)[20]].

Three of the four studies that had examined evidence for a dose–response relationship found a significant relationship only after multiple courses (i.e. 2+ courses when outcome was measured at age 7[20], 3+ courses[24] and 3+ courses by overweight mothers[22]). Two studies examined antibiotic types and found that sulfonamides, trimethoprim and mixed antibiotics had a stronger effect size[24] and that macrolides were associated with a higher BMI z-score.[21]

Influential factors

Common potential confounders that were usually adjusted for were maternal age, ethnicity, indicators of socio-economic status (such as maternal education or receipt of public assistance), parity, infant gender, maternal BMI and delivery mode. Birth weight, breastfeeding, maternal and child infections and early childhood antibiotic administration were less frequently considered.

Delivery mode: Studies conducting subgroup analyses on delivery mode revealed varying results. Wang *et al.*[20] found a stronger relationship between prenatal antibiotic exposure and overweight/obesity in a subgroup of children who had been born by caesarean section, Cassidy-Bushrow *et al.*[21] found no difference in effect size in the two types of delivery mode and Mor *et al.*[24] found similar effect sizes, but the relationship was only significant in children born vaginally. Caesarean section was found to be a significant independent predictor besides prenatal antibiotic exposure.[23]

Pre-pregnancy maternal weight: This potential confounder was adjusted for in all studies but one; that study did not have information on maternal BMI, but did correct for estimates based on previous literature by Vidal *et al.*[31] and Whitaker *et al.*[32] Only Poulsen *et al.*[22] stratified by maternal weight and found that only mothers with overweight who had taken 3+ courses antibiotics were significantly likely to have a child with overweight or obesity.

Postnatal antibiotics: This factor was generally not examined as a possible confounder of prenatal antibiotic use and overweight. Poulsen *et al.*[22] had observed that there was a significant trend of postnatal antibiotic use with prenatal antibiotic exposure. In their study, they examined postnatal antibiotic use correcting for prenatal antibiotics, but did not correct for postnatal antibiotics when examining prenatal antibiotics. They found that postnatal antibiotics were and prenatal antibiotic exposure was not associated with childhood overweight and obesity.

Maternal and childhood infections: Maternal infections were not examined in any publications, but Mor *et al.*,[24] Wang *et al.*[20] and Cassidy-Bushrow *et al.*[21] did mention in their discussions that a possible underlying role of maternal infection could not be ruled out in the relationships they had found between prenatal antibiotics and overweight/obesity. Mor *et al.*[24] mentioned that there could be a genetic predisposition to infection and obesity. None of the studies adjusted for childhood infections in the relationship between prenatal antibiotic exposure and childhood overweight/obesity; however, Mueller *et al.*[23] did not find a significant relationship between prenatal and childhood infections.

Breastfeeding: Two of the five studies examining the relationship between prenatal antibiotic exposure and overweight/obesity adjusted for breastfeeding; in both studies, breastfeeding was defined as ever having breastfed. Other related child feeding practices with regard to weaning were never mentioned as possible confounders.

Gender: The gender of the infant was either adjusted for or examined in subgroup analyses. One study found that the relationship between prenatal antibiotic exposure and overweight in 7–16 year olds was only significant in boys,[24] although there was a positive but insignificant effect in girls.

Birth weight: Mor *et al.*[24] found a stronger relationship between prenatal antibiotic exposure and overweight within the lower birth weight sample than the higher birth weight sample.

Risk of bias in studies

Most studies had a medium risk of bias, usually scoring a 7 out 9, when assessed according to the NOS. Studies generally lost points by not taking important potential confounders into account (such as delivery mode, postnatal antibiotics or maternal and childhood infections) or by using self-reported as opposed to medically diagnosed measurements. There were other issues, however, that we believed could not be captured in the NOS scale, such as ambiguity at times about the types of analyses that had been conducted, and missing information, such as whether or not intra-partum antibiotics (administered just prior to or during delivery) had been included as part of the exposure prenatal antibiotics.

Heterogeneity between the studies on prenatal antibiotic exposure made them difficult to compare. There was heterogeneity with respect to the exposure (i.e. inclusion/exclusion of intra-partum antibiotics or inclusion not mentioned), various ages of outcome (ranging from age 2 in one study to 7–16 years in another study), the type of overweight measurements (i.e. BMI odd ratios versus z-scores) and the number and types of potential confounders taken into account.

Infant antibiotic administration

Study characteristics

The four systematic reviews that had been retrieved were conducted in Denmark, China, United Kingdom and Canada each covering between 12 and 17 publications on infant antibiotic administration. The latest date of the search period conducted by these four systematic reviews was October 2017. Nine publications were covered by all 4 reviews and 12 publications by at least 3 reviews (see Box S2).

Main findings

The four systematic reviews varied in their overall conclusions (see Table 2). One concluded there was substantial evidence for infant antibiotic exposure increasing the risk of childhood overweight/obesity,[33] two concluded there was a small association between infant antibiotic exposure and childhood overweight/obesity[49,34] and one concluded that there was no conclusive evidence of associations between infant antibiotic exposure and childhood overweight/obesity.[35] Reported pooled effect sizes found by the meta-analyses conducted in three of the systematic reviews were RR: 1.21 (1.09–1.33) for overweight and RR: 1.18 (1.12–1.25) for obesity (based on any exposure <24 months and any age of outcome from 2 to 12 years),[33] odds ratio (OR): 1.11 (1.02–1.20) [based on any exposure (0–2 years) and any age of outcome from >2 to 12 years][34] and OR: 1.05 (1.00–1.11) [based on earliest age of exposure (<24 months), latest age of outcome (2–18 years) and lowest number of prescriptions in each publication].[49]

Notable influential factors with greater effects, as reported by these reviews, were multiple doses of antibiotics (a few studies within the reviews also reporting dose–response relationships), broad-spectrum antibiotics (macrolides being most consistently reported[49]) and male gender.

Other factors investigated were the follow-up times. Miller *et al.*[49] found that shorter follow-up times (<5 years) were significant, whereas longer follow-up times up to 10 years and above 10 years had positive effects, but were insignificant.

The investigation of maternal overweight was only mentioned by Partap *et al.*[35] who found that in the two publications conducting sub-studies according to maternal weight, a significant association was only found in mothers of normal weight. Partap *et al.* also mentioned two twin studies that showed an insignificant relationship between infant antibiotics and childhood overweight.

The authors of the four systematic reviews all reported the potential confounders that had been adjusted for in each study; factors that were commonly adjusted for included gestational age, birth weight, maternal age, socio-economic status and breastfeeding. All authors of the systematic reviews acknowledged the likelihood of there being more potential confounders influencing the relationship between infant antibiotic administration and overweight/obesity, such as childhood infections.

Assessment of studies

Using the critical appraisal tool by Aromataris *et al.*[29] and the ROBIS to assess the methodology and synthesis, it was apparent the four systematic reviews varied in the criteria they adhered to (Tables S1a and S1b). Partap *et al.* were the most and Shao *et al.* the least stringent with regard to the methodology, study syntheses and evaluations. Three out of the four reviews assessed the studies using the NOS, with varying scores and evaluations. Shao *et al.* rated their included studies the most favourably, assigning scores from 7 to 9 to all the studies and evaluating scores of at least 7 as low risk of bias. More details on how the scores were obtained were not reported in their review. Their more relaxed criteria with regard to assessing articles, pooling findings from heterogeneous studies, interpreting publication bias and including them in their meta-analysis likely contributed to their more assertive conclusions that there is a causal relationship between early-life antibiotics and childhood overweight.

Miller *et al.* and Rasmussen *et al.* also assessed the included articles using the NOS and in general had similar proportions of scores [Miller: low risk (four studies), moderate risk (eight studies) and high risk (three studies) and Rasmussen: low risk (two studies), moderate risk (eight studies) and high risk (three studies)].

Miller assessed the 'comparability' category of the NOS (covering the adequacy of adjusting for confounders) in the

Table 2. Summary of systematic reviews examining infant antibiotic exposure and childhood overweight or obesity

Systematic review and authors' conclusions	No. of publications	Age of exposure and outcome	Findings	Additional analyses	Influential factors	Other comments	Authors' own quality assessments
Miller *et al*.[49] (November 2018) Country: Canada Title: **The association between antibiotic use in infancy and childhood overweight or obesity: a systematic review and meta-analysis** Conclusions: *There was a small association between antibiotic exposure and childhood overweight and obesity in some subgroups of children. The strongest associations were observed in boys versus girls and children exposed to multiple antibiotic courses or broad-spectrum drugs*.	17 articles covering 15 studies (cohort or case-control studies) 10 articles for meta-analysis Publications still 17 July 2017	Exposure <24 months Outcome: during childhood (2–18 years) Exposure grouped into 3, 6, 8, 12 or 24 months In studies categorising exposure in age at first exposure, <12 months had stronger effects than first exposure from 12 to 24 months.	Meta-analysis (based on earliest age of exposure, latest age of outcome and lowest number of prescriptions): **OR: 1.05 (1.00–1.11)** Authors' citation: "Our view is that the body of literature in this field is far too heterogeneous to conduct a meta-analysis and obtain meaningful summary estimates of effect."	Follow-up times: <5 years 5–10 years >10 years Insignificant associations for subgroups of follow-up times of 5–10 years and >10 years (although highest effect size). Significant pooled odds if length of follow-up is less than 5 years: **OR: 1.06 (1.01–1.12)**	• **Male gender**: (six studies) study with largest effect: within sample of boys at 12 years of age: **OR: 5.35 (1.94–14.72)** • **Multiple antibiotics**: ≥2 to 4 courses strongest effects (five studies). Some studies showed a dose–response relationship, but this was less clear than exposure to multiple antibiotics. • **Broad-spectrum antibiotics** (three out of four studies).Macrolides most consistent antibiotic with significant association (four out of five studies). • **Age at first exposure** was found to be more strongly associated with overweight or obesity than exposures grouped by set time intervals <24 months of life that were not related to age at first exposure. Generally, exposure before 12 months more likely to develop overweight than after 12 months.	Authors say that a comprehensive meta-analysis was constrained by substantial methodological heterogeneity (adjusted covariates, exposure and outcome ages, type and frequency of exposure, and differences in outcome measure) across studies. Authors recommend that studies should use more standardised methods to make comparability easier.	Authors were not stringent when evaluating studies for confounding by indication (i.e. they only required that there had to be adjustment for at least one childhood risk factor (birth weight, childhood infection, asthma or prematurity) and at least one maternal risk factor (breastfeeding, overweight, smoking and delivery mode) in the NOS category "comparability", meaning most studies fulfilled this requirement. Authors mention, however, in the discussion that untreated infections should also be considered a confounder (based on the study by Li *et al.*[29] Publication bias assessed: funnel plot suggested possible publication bias, but this did not appear to affect the pooled results. Studies lost somewhat more points for outcome (due to inadequate reporting of losses-to follow-up or non-response rates, or by data collected through self-report.

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Partap *et al.* [35] (October 2018) Country: United Kingdom Title: **Association between early-life antibiotic use and childhood overweight and obesity: a narrative review** Conclusions: *Overall, we found no consistent and conclusive evidence of associations between early-life antibiotic use and later child body mass.* *Most studies did not appropriately account for confounding by indication for antibiotic use. Further comparable studies using routine clinical data may help clarify this association.*	13 articles (cohort, case-control and cross-sectional studies) Publications till October 2017	Exposure <3 years Exposure during first 6 months (four studies)and up to ≥3 years (two studies) Outcomes reported ranged from continuous measures including BMI or BMI-for-age z-score, weight-for-length z-score, or weight for-age z-score and rate of weight gain to binary measures of overweight or obesity.	Due to wide variation in studies, authors did not perform a meta-analysis	Two studies were included that contained additional twin studies where twins were discordant for antibiotic exposure; these showed insignificant associations.	• **Male gender** stronger effect in three out of four studies. • **Exposure period**: eight studies examined this, five found stronger associations at 3–6 months than at later ages. (Two studies showed no differences, and one study showed a stronger effect up to 24 months than up to 6 months). • **Dose-response**: four out of seven studies found either a dose response relationship or an association only with two or more courses, two found no associations with multiple antibiotics courses, and one found a lower risk of overweight with fewer antibiotics. • **Broad-spectrum antibiotics** found to be stronger in 3/7 studies, two studies found no differences and one study found obesity risk at 5+ courses of antibiotics working against anaerobic bacteria. • **Maternal overweight:** only two studies examined this, finding only an association at 38 months and at 7 years, respectively in mothers of normal weight. • **Infections**: Examined or adjusted for by four studies. One study found a relationship between infections and obesity, but not between antibiotics and obesity in children with infections.	Authors mention that studies varied considerably with respect to a range of methodological aspects, including exposure and outcome definition and ascertainment, analytical strategy and inclusion of covariates.	Authors did not conduct an assessment with a standardised appraisal tool, but determined a list of variables that were potentially important confounders: early childhood infections, delivery mode, exclusive breastfeeding, preterm birth and birth weight, maternal smoking, socio-economic status, maternal BMI, current wheeze/asthma, lifestyle (diet and physical activity), siblingship. They concluded that none of the studies had accounted for all these factors, and most importantly for confounding by indication. Other quality issues according to authors were small sample sizes, and antibiotic exposure not always being reliable, for example, based on parent report or on prescriptions. Authors recommend studies using comparable study measures and similar types of analyses to previous studies, larger sample sizes, adjusting for all important confounders.

Table 2. (*Continued*)

Systematic review and authors' conclusions	No. of publications	Age of exposure and outcome	Findings	Additional analyses	Influential factors	Other comments	Authors' own quality assessments
Rasmussen *et al*.[34] (February 2018) Country: Denmark Title: **Antibiotic exposure in early life and childhood overweight and obesity: A systematic review and meta-analysis** Conclusions: *The present systematic review and meta-analysis found a somewhat increased risk of childhood overweight and obesity in individuals exposed to antibiotics either within the first 6 months of life, or when exposed to repeated treatments.*	13 articles (12 cohort and 1 case control) 7 articles used for meta-analyses Publications till March 2017	**Exposure**: Antibiotic exposure 0–4 2 months after birth **Outcome**: Overweight/obesity/ BMI z-scores 24 months–12 years old	Any exposure and any age >2–12 years (Based on 7 studies): OR: 1.11 (1.02–1.20) Studies examining BMI z-scores were also significant.	Exposure 1 treatment : **OR: 1.04 (0.99–1.10)** Exposure to >1 treatment: **OR: 1.24 (1.09–1.43)** Exposure first 6 months : **OR: 1.20 (1.04–1.37)** Exposure >6 months: **OR: 1.04 (0.95–1.14)**	• **Broad-spectrum antibiotics** showed stronger effects than narrow-spectrum antibiotics. • **Exposure period** Antibiotic exposure only before 6 months of age is significant. • **Dose-response relationship** was generally found Authors say the relationship found may be due to confounding by indication (i.e. those with obesity are more likely to have infections and therefore require antibiotics) Authors did not include infections as an essential potential confounder, but mentioned its possible importance in the discussion.	Authors mention a large amount of heterogeneity in the studies with regard to the definition of the outcome, the age of outcome (which varied from age 3 to 12 years across the studies) and in adjustment for confounders. They suggest that the present meta-analysis may be biased toward showing a positive association between antibiotics and childhood overweight.	Assessed using Risk Of Bias Assessment tool for Nonrandomised Studies and the NOS. Studies with high risk of bias were excluded from meta-analysis. Authors mention that all the articles had at a high risk of bias in at least one domain, and that there was insufficient adjustment for confounders. This study supports a causal relationship and a critical window of exposure, but reverse causation and confounding by indication cannot be ruled out. Funnel plot: some potential publication bias
Shao *et al*.[33] (July 2017) Country: China Title: **Antibiotic Exposure in Early Life Increases Risk of Childhood Obesity: A Systematic Review and Meta-Analysis** Conclusions: *Antibiotic exposure in early life significantly increased risk of childhood overweight, obesity, an increased BMI z-score and increase of weight gain. There was an obvious significant dose–response relationship between antibiotic exposure in early life and childhood adiposity. In conclusion, antibiotic exposure in early life significantly increases risk of childhood obesity.*	15 articles (cohort studies) Publications till February 2017 All publications used for various meta-analyses.	Exposure: during pregnancy and during the first 2 years after birth Outcomes: Overweight/obesity/ BMI z-scores 24 months – 12 years old	Based on longest follow-up time: Exposure during infancy and overweight: **RR: 1.21 (1.09–1.33)** Exposure during infancy and obesity: **RR: 1.18 (1.12–1.25)** BMI z-scores (seven studies) and weight gain z-scores (two studies) also show significant pooled associations.	Pooled results according to age of exposure **Overweight**: <6 months: **RR: 1.22 (1.09–1.36)** 6–12 months: **OR: 1.25 (1.10–1.42)** 12–24 months: **OR: 1.20 (1.01–1.43)** Pooled results according to age of exposure **Obesity:**<6 months: **OR: 1.15 (1.04–1.26)** 6–12 months: **OR: 1.07 (0.95–1.22)** 12–24 months: **OR: 1.06 (0.96–1.16)**	• **Dose–response relationships**: Pooled effects significant in the six studies examining this. • **Gender**: although subgroup analyses showed significance within both genders, the effect size was higher in males.	Authors mention that all publications are heterogeneous with respect to age of outcome, confounders adjusted for, etc. Authors do not mention how they treated different types of effect sizes; did they do any conversions? Authors say that the significant relationships shown in the meta-analysis prove that antibiotic exposure is an independent risk factor of childhood obesity.	Assessed articles with NOS: No mention on how these points were scored, or which confounders were considered important for the "comparability" section. All studies scored highly with NOS (7–9 points), which was interpreted as low risk of bias. Publication bias evaluated, but no obvious evidence found for publication bias.

studies they reviewed much more favourably, giving 12/15 of their studies the maximum of two points if relevant potential confounders had been adequately accounted for. Their criteria were adjusting for at least one childhood and at least one maternal risk factor to gain the full two points. They did mention in their discussion, however, that (untreated) infections should be treated as potential confounders in future studies. Rasmussen *et al.* only awarded 2 of 13 included studies the full 2 points for 'comparability', due to inadequate adjustment for confounding, although in their list of potential confounders, they did not include childhood infections. They did mention in their discussion, however, that infections were likely to be of importance and that most studies did not address this. The studies rated as high risk of bias were not included in their meta-analyses. Other points were often lost by the authors of these systematic reviews for inadequate reporting of loss-to-follow-up or non-response rates and self-reported data.

The most stringent assessment of publications was conducted by Partap *et al.*[35] who also had the most cautious conclusions regarding the association between infant antibiotic exposure and childhood overweight. The authors mentioned not conducting a meta-analysis, due to the heterogeneity of all the studies. Although they did not use a standardised method, such as the NOS to assess the studies, they did consider important potential confounders that studies should have adjusted for to obtain more reliable results. Important confounders mentioned in their review were early childhood infections, delivery mode, exclusive breastfeeding, preterm birth and birth weight, maternal smoking, BMI and socio-economic status, current wheeze/asthma, lifestyle and siblingship. None of the studies adjusted for all of these factors. They concluded that most studies did not sufficiently examine confounding by indication. Other critical points raised by this review were small sample sizes and parent-reported antibiotic use.

The three studies who conducted meta-analyses also created funnel plots to test for publication bias. One study concluded there was no indication of publication bias (Shao *et al.*, 2017),[33] one study mentioned there was possible publication bias, but this would unlikely affect the pooled results[49] and one study concluded there was some potential publication bias.[34]

Three of the four reviews recommended further studies using more standardised and similar measures in order to make comparability across the publications more clear and reliable.

The studies that were assessed by the authors of the systematic reviews had similar quality issues to the assessments we had made of the observational studies on prenatal antibiotic exposure, the majority scoring a 7 when assessed by the NOS (medium quality). Similar issues were encountered, including much heterogeneity in the studies (e.g. in exposure/outcome measurements and potential confounders), and the use of self-reported data.

Discussion

In this review, our two main aims were to summarise and assess the evidence regarding prenatal antibiotics exposure and the development of childhood overweight/obesity and to summarise and assess the systematic reviews of publications regarding infant antibiotic exposure and overweight/obesity. A search for publications in the last 10 years resulted in the retrieval of five studies on prenatal antibiotic exposure published during the period 2015–2018 and four systematic reviews on infant antibiotic administration published from 2017 to 2018.

Main findings

The five studies that were identified generally showed a positive trend in the relationship between any prenatal antibiotic exposure and childhood overweight/obesity, which was significant in two of the studies. The other three studies showed significant relationships with overweight/obesity under certain conditions, such as multiple antibiotic courses or prescriptions, broad-spectrum antibiotics, older children, overweight mothers and during varying trimesters where exposure occurred.

The four systematic reviews similarly tended to conclude that there was either a clear relationship,[33] there was some evidence of a relationship[49,34] and there was no clear evidence of a relationship[35] between infant antibiotic exposure and childhood overweight and obesity. All reviews mentioned there being much heterogeneity in the studies, and three reviews mentioned the lack of adjustment for confounding by infectious diseases in many studies as being a potential issue causing bias.

Overall, the studies examining both prenatal antibiotic exposure and infant antibiotic administration point to some evidence of a relationship with childhood overweight/obesity under certain circumstances, but these relationships cannot be concluded as definitive at this point.

The gut microbiome

Although we cannot conclude with certainty that early antibiotic exposure causes overweight or obesity in humans, there is some evidence that the gut microbiome may play a role in this relationship. The microbiome in the gut of overweight children is more likely to have a lower diversity and a higher ratio of firmicutes to bacteroidetes than normal weight children,[36] which in turn is associated with a higher BMI in later childhood.[37] A recent Norwegian cohort study showed that the composition of the gut microbiome during various times of the first 2 years of life predicted childhood BMI at 12 years old.[38] Antibiotic use during pregnancy is also associated with increased staphylococcus species,[39] which in turn is associated with increased risk of childhood overweight.[40]

Various factors are known to influence the colonisation of the gut microbiota of children early in life including maternal BMI and diet, smoking status and stress during pregnancy, preterm birth, hospitalisation, mode of birth (i.e. vaginal versus caesarean), type of milk feeding (i.e. breastfeeding versus formula), childhood infections and early antibiotic exposure.[41,42] Other drugs, such as acid-suppression medications, can also affect the microbiome and are associated with childhood diseases, such as obesity and allergies.[43,44]

Overweight and obesity are thought to occur through various bacterial mechanisms, including the bacterial role in increasing the efficiency of energy extraction from more food sources than normal weight children, influencing gastrohormonal changes in hunger and satiety, and increasing gut wall permeability leading to the higher plasma concentrations of lipopolysaccharides and liver fat, and increased production of proinflammatory cytokines. This subsequent low-grade inflammation is associated with a range of chronic diseases, including type 2 diabetes and obesity.[41,45,46]

Other influential factors

Some of the factors found by the studies in this review that may be influential in the relationship between prenatal antibiotic exposure and overweight/obesity fall in line with earlier studies. Caesarean section was found to have independent effects on the development of obesity, which corresponds with the findings of an earlier systematic review that CS was associated with childhood obesity.[25] It is difficult, however, to ascertain what extent of this relationship may be due to caesarean section itself, or due to intra-partum antibiotics often given to prevent post-surgical wounds,[9] or whether their effects correlate when it comes to disrupting the microbiome. Subgroup analyses on delivery mode in the studies in this review showed mixed findings; sometimes there was a stronger effect of prenatal antibiotics in children who had had caesarean sections (for instance, Wang *et al.*[20]) and sometimes there were only significant effects of antibiotics in children with vaginal births (for instance, Mor *et al.*[24]). These seemingly conflicting findings are plausible, however, if there are differences in intra-partum antibiotic policies in different medical settings with regard to caesarian sections,[47] or when studies differ in whether or not intra-partum antibiotics are included in the exposure measurement. More studies are needed that can distinguish these effects on the microbiome, for instance, by comparing children who have had CS and intra-partum antibiotics before cord clampage with those who have had antibiotics following cord clampage.

In the studies examining infant antibiotic administration, male gender was also a factor found to be relatively more at risk of developing overweight or obesity when exposed to antibiotics. Kozyrskyj *et al.*[48] found that boys were more likely to develop overweight and obesity than girls, when their microbiome was disrupted. Gender differences were also found in mouse studies, with early penicillin exposure having a greater impact on male mice than female mice.[12]

In the studies on both prenatal antibiotic exposure and infant antibiotic administration, little consideration was generally given to maternal or infant infections being possible confounders. A recent Australian study found that mothers who had been exposed to antibiotics before and especially during pregnancy had an increased risk of children being hospitalised for infections.[49] Infections in turn are also associated with childhood overweight.[27,50] Li *et al.*[27] conducted a large birth cohort study in which they found that infections not treated with antibiotics were more strongly associated with childhood obesity in a dose–response manner, compared with those who had not had infections. Antibiotic use was not associated with childhood obesity when compared with those who had had infections not treated with antibiotics. Just as infections may play a greater role in the onset of obesity than antibiotics, it is possible that maternal infections may also play a role in the risk of childhood overweight and obesity. Maternal infections are associated with childhood infections[28] and with childhood eczema and asthma,[51] but studies are still needed that examine the relationship between maternal infections and childhood overweight. Block *et al.*[50] found that infections appeared to cause some confounding in the relationship between antibiotics and overweight but that there was still a small significant effect of antibiotics on overweight. The authors concluded, however, that the clinical significance of antibiotics in contributing to the development of overweight was negligible at the individual level. Although it is important that antibiotic use is curbed in order to prevent the increasing morbidity and mortality caused by antibiotic resistance,[52] antibiotic reduction may not be the most effective intervention for the purpose of decreasing childhood overweight and obesity.[50,35]

Strengths of this review include the extensive search and assessments of available studies, enabling a complete overview of the existing evidence concerning the relationship between both prenatal and infant antibiotic exposure and childhood overweight/obesity. Our review contributes to increased insight into what is currently known about this relationship and calls for further well-designed studies. Some limitations include the scarcity of studies on prenatal antibiotic exposure, heterogeneity of the included studies, missing information on intra-partum antibiotics, the use of self-reported data and the lack of adjustment for confounding by infections. Differences in health care policies with regard to prescribing antibiotics and in patients with regard to treatment adherence are further issues to consider when comparing the findings across studies. Although many more studies have been conducted on infant antibiotic administration and overweight/obesity, the fact that within the last 10 years one systematic review was published in 2017 and the other three in 2018 shows that this topic is just beginning to gain more attention and this will likely increase in the coming years.

Conclusions

There is some evidence for a relationship between prenatal and infant antibiotic exposure and the onset of childhood overweight/obesity. There was a scarcity of studies on prenatal antibiotic exposure and potential confounders were often not accounted for. More well-designed studies are needed that include data on intra-partum antibiotic exposure that address important potential confounders (including maternal and childhood infections) and that use similar study measures as previous studies to increase comparability. The effects of antibiotic exposure, especially evident in certain children (i.e. exposed to multiple and broad-spectrum antibiotics, earlier postnatal exposure and male gender) merit further research.

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