

The effects of prenatal and early life antibiotic
usage on childhood overweight/obesity and
allergies

Main findings from two systematic reviews



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Background

Antibiotics: one factor disrupting the microbiome

- Decreases the diversity of bacteria in the gut
- Destroys beneficial bacterial as well as the intended pathogens
- Changes the composition of bacteria.
- Disrupts the role that bacteria play in the synthesis of vitamins, energy metabolism, absorption of nutrients, control of satiety and hunger and the gut wall permeability, leading to higher fat concentrations in the blood.
- Disrupts the developing immune system, leading to abnormal reactions to harmless microbes.

Increasing the risk of **chronic diseases**



Antibiotic exposure

- **Estimates of antibiotic use during pregnancy**
 - Denmark: 37% during pregnancy, 33% during delivery
 - Netherlands: 20,8% during pregnancy, % during delivery unknown
- **Common indications during pregnancy and delivery**
 - Urinary tract infections
 - Respiratory diseases
 - Prevention of Group B Streptococcus infection
 - Treatment/prevention of maternal/fetal infections, such as chorioamnionitis
 - Prevention of fevers associated with Caesarean Sections
 - Prevention of preterm birth



Antibiotic exposure

- **Early childhood (0-2 years)**
 - Otitis Media Acuta (55% of all episodes)
 - Upper respiratory tract infections (14% of all episodes)
- **Broad-spectrum antibiotics most common (0-2 years):**
 - Amoxicillin: 72% of antibiotic prescriptions
 - Macrolides: 13 % of antibiotic prescriptions

Study aims

Two systematic reviews

- To collect, assess and summarize the findings in studies investigating prenatal and antibiotic exposure and childhood **overweight** and **obesity**.
- To collect, assess and summarize the evidence reported by studies during the last 10 years that have investigated prenatal and infant antibiotic exposure and the relationship with childhood allergies **asthma**, **eczema** and **hay fever**

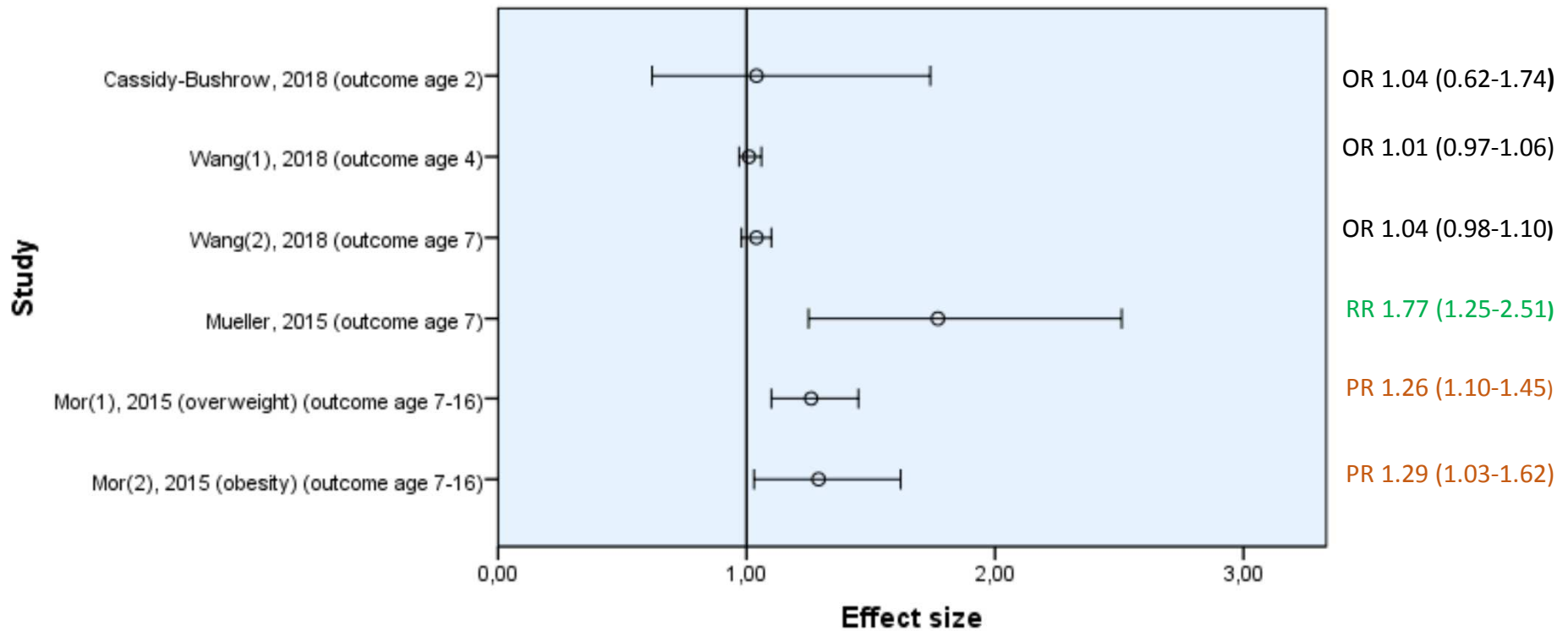
PubMed

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Main findings: 5 observational studies

Prenatal antibiotics and childhood overweight/obesity



-One study (Poulsen *et al.*, 2017) is excluded here as it only reports BMI Z-scores
 -The types of statistics used to measure effect sizes are distinguished by different colours

Main findings: 4 systematic reviews

Infant antibiotic exposure and childhood overweight/ obesity

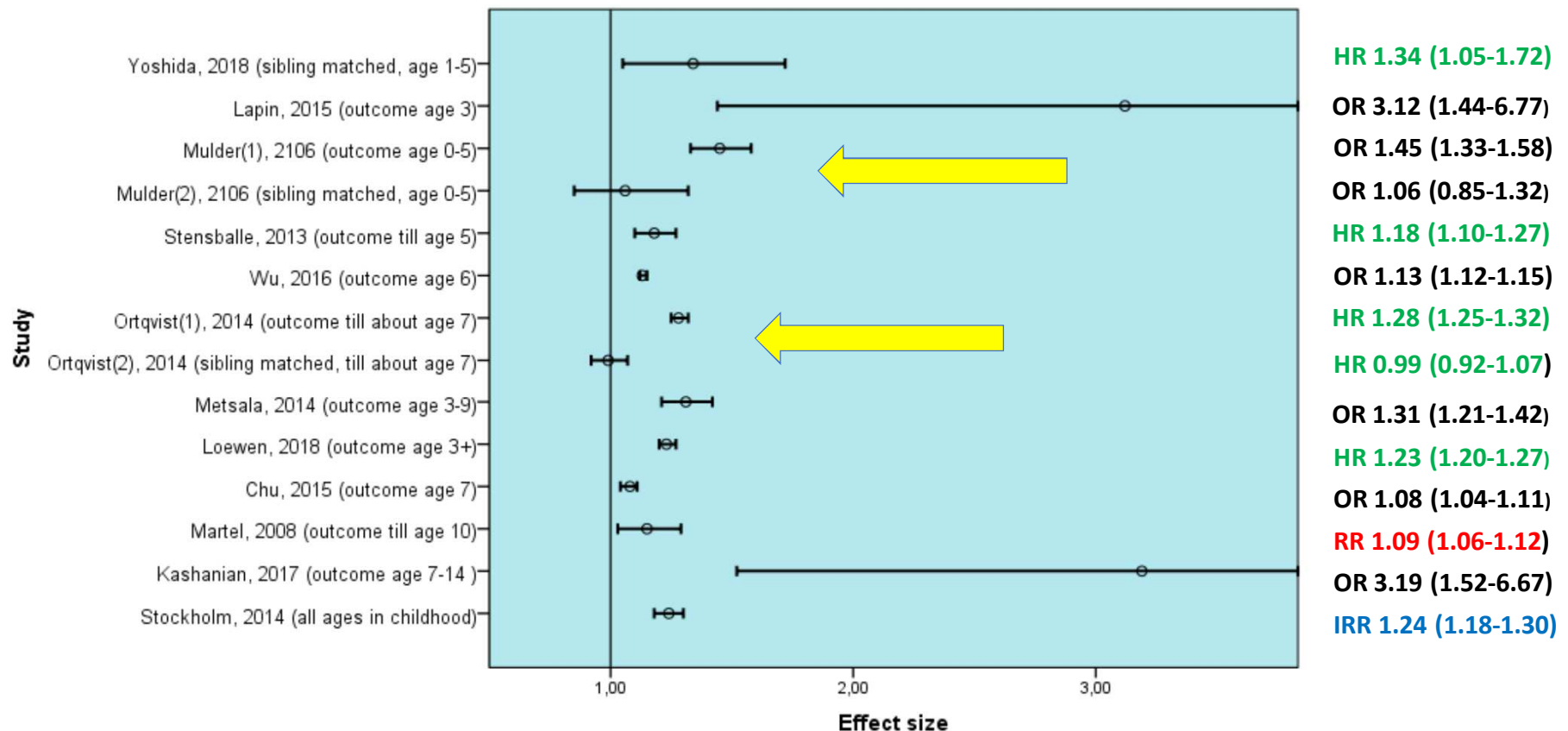
Review	Main findings	Main conclusions
1. Shao, 2017 (15 articles till Feb 2017)	Overweight: OR 1.21 (1.09-1.33) Obesity OR 1.18 (1.12-1.25)	Obvious significant dose-response relationship between antibiotic exposure in early life and childhood adiposity.
2. Rasmussen, 2018 (13 articles till March 2017)	Overweight/obesity OR 1.11 (1.02-1.20)	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. <i>Reverse causation and confounding by indication cannot be ruled out.</i>
3. Miller, 2018 (17 articles till July 2017)	OR 1.05 (1.00-1.11)	Small association between antibiotic exposure and childhood overweight and obesity in some subgroups of children <i>Studies too heterogeneous to conduct a meta-analysis and obtain meaningful summary estimates of effect.</i>
4. Partap, 2019 (13 articles till Oct 2017)	No meta-analysis, due to too much heterogeneity	No consistent and conclusive evidence of associations between early life antibiotic use and later child body mass. <i>Most studies did not appropriately account for confounding by indication for antibiotic use.</i>

General conclusions

Overweight/obesity		
<p><i>Prenatal antibiotics</i> (5 observational studies)</p>	<ul style="list-style-type: none"> • Positive trends, 2/5 publications found significant relationships • The other 3 found positive associations in certain conditions, such have multiple courses and mothers with overweight/obesity 	<ul style="list-style-type: none"> • Very little adjustments for maternal infections • 3 out of 5 gave no information on intra-partum antibiotics
<p><i>Infant antibiotics</i> (4 systematic reviews)</p>	<ul style="list-style-type: none"> • Differing opinions by the authors of the four systematic reviews • Overall, evidence of a small effect of antibiotics on overweight/ obesity. • Broad-spectrum, multiple dose antibiotics have greater effects. 	<ul style="list-style-type: none"> • Very little consideration of maternal and childhood infections. • Studies very heterogeneous. • No studies adjusted for all potential confounders

Main findings

Prenatal antibiotics and childhood asthma (n=12)

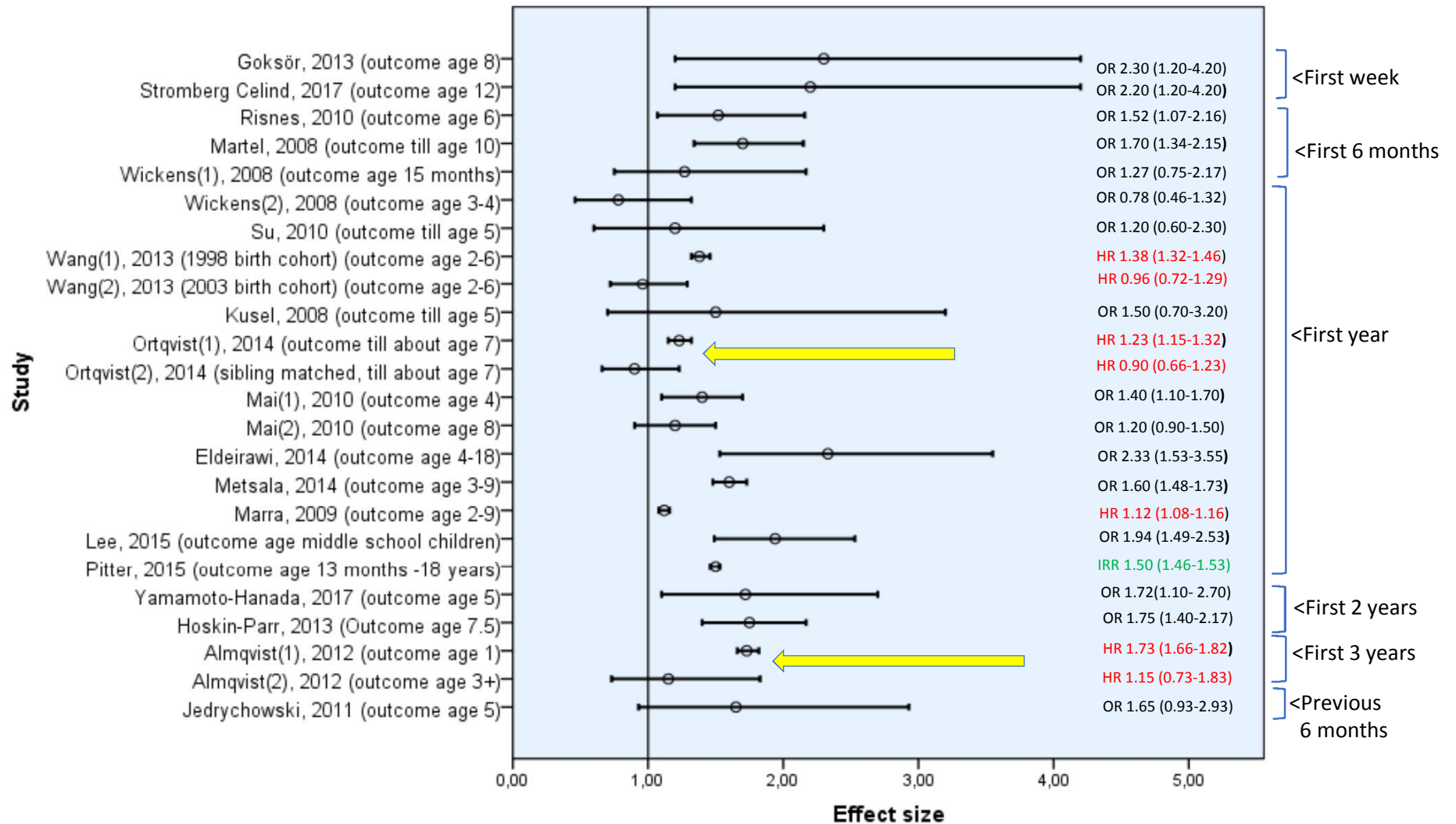


*The types of statistics used to measure effect sizes are distinguished by different colours.

Main findings

Infant antibiotics and childhood asthma

(publications having at least somewhat considered reverse causation and confounding by indication: n=19)



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General conclusions

Asthma		
<p><i>Prenatal antibiotics</i> <i>(15 observational studies)</i></p>	<ul style="list-style-type: none"> • Majority concluded there was a significant relationship • Two studies showed that maternal prenatal and postnatal antibiotic use had similar effects • One study with sibling sub-study showed insignificant effect in sibling study • Greater impact observed with broad-spectrum antibiotics, multiple doses, and younger age of onset. 	<ul style="list-style-type: none"> • Often lack of adjustment for maternal infections, delivery mode, breastfeeding and postnatal child antibiotic usage • Intra-partum antibiotics inclusion/exclusion generally not mentioned
<p><i>Infant antibiotics</i> <i>(27 observational studies)</i></p>	<ul style="list-style-type: none"> • Over half of all publications reported a significant relationship • Sibling sub-studies showing insignificance • Greater impact in antibiotics for respiratory diseases than for urinary tract infections (indicating possible confounding by indication) • Greater impact observed in broad-spectrum antibiotics, earlier antibiotic exposure, younger age of asthma onset. 	<ul style="list-style-type: none"> • Not always taken into account: infectious diseases, delivery mode, prenatal / intra-partum antibiotics • Studies generally very heterogeneous

In collaboration with

Hania Szajewska and her team in Warsaw and Winclove Probiotics, as part of **SAWANTI** (Sarphati Amsterdam/Warsaw group on **AN**tibiotic long-Term Impact)

Studies conducted as part of SAWANTI:

- ***Association between early life (prenatal and postnatal) antibiotic administration and coeliac disease: a systematic review.*** Maciej Kołodziej, Bernadeta Patro Golab, Dorota Gieruszczak-Białek, Agata Skorka, Małgorzata Pieścik-Lech, Ruth Baron, Hania Szajewska (May 2019)
- ***Early Life Exposure to Antibiotics and Autism Spectrum Disorders: A Systematic Review.*** Jan Łukasik, Bernadeta Patro Golab, Andrea Horvath, Ruth Baron, Hania Szajewska, (September 2019)
- ***The relationship of prenatal and infant antibiotic exposure with childhood overweight and obesity: a systematic review.*** Ruth Baron, Meron Taye, Isolde Besseling-van der Vaart, Joanne Ujčič-Voortman, Hania Szajewska, Jaap Seidell, Arnoud P Verhoeff (November 2019)
- ***The relationship of prenatal antibiotic exposure and infant antibiotic administration with childhood allergies: A systematic review.*** Ruth Baron, Meron Taye, Isolde Besseling-van der Vaart, Joanne Ujčič-Voortman, Hania Szajewska, Jaap Seidell, Arnoud P Verhoeff (submitted)
- **Synthesis** of all findings with first author Meron Taye. (current work)