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Review

Antibiotic exposure and adverse long-term health outcomes in children: A systematic review and meta-analysis

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SUMMARY

Background: Antibiotics are amongst the most commonly used drugs in children. In addition to inducing antibiotic resistance, antibiotic exposure has been associated with adverse long-term health outcomes.
Methods: A systematic search using PRISMA guidelines to identify original studies reporting associations between antibiotic exposure and adverse long-term health outcomes in children. Overall pooled estimates of the odds ratios (ORs) were obtained using random-effects models.
Results: We identified 160 observational studies investigating 21 outcomes in 22,103,129 children. Antibiotic exposure was associated with an increased risk of atopic dermatitis (OR 1.40, 95% confidence interval (CI) 1.30–1.52, $p < 0.01$), allergic symptoms (OR 1.93, 95%CI 1.66–2.26, $p < 0.01$), food allergies (OR 1.35, 95%CI 1.20–1.52, $p < 0.01$), allergic rhinoconjunctivitis (OR 1.66, 95%CI 1.51–1.83, $p < 0.01$), wheezing (OR 1.81, 95%CI 1.65–1.97, $p < 0.01$), asthma (OR 1.96, 95%CI 1.76–2.17, $p < 0.01$), increased weight gain or overweight (OR 1.18, 95%CI 1.11–1.26, $p < 0.01$), obesity (OR 1.21, 95%CI 1.05–1.40, $p < 0.01$), juvenile idiopathic arthritis (OR 1.74, 95%CI 1.21–2.52, $p < 0.01$), psoriasis (OR 1.75, 95%CI 1.44–2.11, $p < 0.01$), autism spectrum disorders (OR 1.19, 95%CI 1.04–1.36, $p = 0.01$) and neurodevelopment disorders (OR 1.29, 95%CI 1.09–1.53, $p < 0.01$). Dose-response effects and stronger effects with broad-spectrum antibiotic were often reported. Antibiotic exposure was not associated with an altered risk of allergic sensitisation, infantile colic, abdominal pain, inflammatory bowel disease, celiac disease, type 1 diabetes, fluorosis, and attention deficit hyperactivity disorder.
Conclusion: Although a causal association cannot be determined from these studies, the results support the meticulous application of sound antibiotic stewardship to avoid potential adverse long-term health outcomes.

Introduction

Antibiotics belong to the greatest discoveries in medicine and amongst the most life-saving medical interventions. Their efficacy and presumed safety have led to their widespread use, which sometimes is irrational or even inappropriate.[1–3] In infants and children, antibiotics are amongst to the most commonly used drugs. In many settings, more than two-thirds of children receive antibiotics before reaching the age of two years and, on average, more than half of all children receive at least one antibiotic each year with the highest rate in the second year of life.[4,5]

The reduction in the incidence of infectious diseases in many countries over the last few decades has been paralleled by a dramatic rise in the prevalence of immune-mediated diseases, including allergic diseases, inflammatory bowel diseases (IBD), rheumatological diseases and diabetes mellitus.[6–8] The 'hygiene hypothesis' proposes that decreased microbial exposure explains the rise in immune-mediated diseases.[9] It is likely that the overuse of antibiotics contributes to this.[10]

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In this systematic review and meta-analysis, we summarise studies that have investigated the association between antibiotic exposure and adverse long-term health outcomes in children.

Systematic review methods

To identify original studies investigating the association between antibiotic exposure and adverse long-term health outcomes in children and adolescents (less than 18 years of age) MEDLINE (1946 to present) was searched in April 2021 using the Ovid interface with the search terms detailed in the supplementary data. Exclusion criteria were studies in which: (i) the effect of prenatal antibiotics was investigated; (ii) the timing of antibiotic exposure was not specified; (iii) antibiotic exposure occurred after the onset of the adverse health outcome and (iv) included preterm infants without adjusting values for prematurity. References of retrieved articles were hand-searched for additional publications. The following variables were extracted from the included studies: author, country, publication year, study design, cohort size, time of antibiotic exposure, specification of antibiotic treatment, age at outcome measure, number of cases, outcome definition and key findings. Review Manager (version 5.3) was used for the calculation of the odds ratios and the meta-analyses. If studies evaluated several time points, only the latest was included in the meta-analysis. Diversity in study design and reporting, which might result in selection and reporting bias, precluded quality evaluation according to the PRISMA guidelines. The ROBINS-1 tool was used to assess risk of bias.[11]

Systematic review results

Our search identified 23,225 studies. Of these, 150 fulfilled the inclusion criteria.[12–161] An additional 10 relevant studies were identified by hand searching of references.[162–171] The selection of studies is summarised in Fig. 1. The 160 studies included in this review investigated 21 outcomes in 22,103,129 children; 159 were observational studies (23 registry-based studies, 69 cohort studies, 34 cross-sectional studies, 11 case-control studies, and 22 retrospective studies) and one was a secondary analysis of data from a randomised control trial;[45] 145 of the studies were done in industrialised countries. The number of participants in each study ranged from 50 to 9,400,000 (median 3944, mean 138,146). Exposure to antibiotics was captured through registries, medical and prescription records or parent questionnaires; studies included any course of antibiotic received, antibiotic exposure during an early-life period (e.g. first week, months or first years of life) or during a certain time before diagnosis. Outcomes were defined by validated questionnaires, diagnostic codes, parent-reported symptoms, or diagnosis, or clinical or laboratory evaluation. The results of these studies are summarised in Table 1. In addition to the overall antibiotic exposure, 17 studies investigated the effect of the number of antibiotic courses received, 17 studies compared the effect of different types of antibiotics and 41 studies both. The risk of bias summary of studies included in the review can be found in Supplementary Table 2.

Atopic dermatitis

Forty studies in 1,602,639 children (183,244 cases with one study not reporting number of cases) investigated the association between antibiotic exposure and the risk of developing atopic dermatitis, evaluated by the International Study of Allergy and Asthma in Childhood (ISAAC) questionnaire, international classification of disease (ICD) codes, parent-reported symptoms or physician's diagnosis, the Criteria by the American Academy of Dermatology, Hanifin and Rajka criteria or William's criteria (Table 1).[32,37,40,43,48–51,53,62,79,80,82,93,96,98,103,105,114,120,123,129,135,150,153–155,157,161,162,172–181] Of the 40 studies, 38 (95%) investigated the effect of antibiotic exposure in the first five years of life (36 (90%) in the first two years of life).[32,37,40,43,48–51,53,62,79,80,82,93,96,98,103,105,114,120,123,129,135,150,153,157,161,162,172–181] Overall, 26 (65%) studies reported a significantly increased incidence of atopic dermatitis in children who were exposed to antibiotics[37,40,48–51,53,62,82,93,96,103,120,123,129,150,153,157,161,172,173,175,176,179–181]; However, in two studies the incidence atopic dermatitis was higher only if exposed to two or more courses of antibiotics.[123,180] In contrast, two studies (5%) reported a decreased incidence in children who were exposed to antibiotics.[40,51] Five studies reported that the risk of atopic dermatitis increased with the number of antibiotic courses.[32,93,103,123,176] One study, however, did not find an association between the number of antibiotic courses and the risk of atopic dermatitis.[182] Four studies compared the effect of different antibiotic classes.[123,157,172,182] One study reported that the risk of atopic dermatitis increased after exposure to cephalosporins and macrolides, but not after exposure to penicillins[123]; one study after amoxicillin but not penicillin, amoxicillin/clavulanic acid, macrolides or cephalosporins,[182] one study after macrolides[157] and the last study reported an increased risk in girls after exposure to cephalosporins but a decreased risk after exposure to macrolides.[172]

Of the 40 studies, 32 (80%) provided sufficient data to be included in the meta-analysis (supplementary Fig. 1).[32,37,40,43,48,49,51,53,62,79,80,82,93,96,103,105,114,120,123,135,153,154,157,161,162,172–174,176,178,180,181] Of the 309,828 children exposed to antibiotics 51,543 (17%) developed atopic dermatitis compared to 105,587 (14%) of 766,331 children not exposed to antibiotics. The overall odds ratio (OR) for developing atopic dermatitis after antibiotic exposure was 1.40, 95% confidence interval (CI) 1.30 to 1.52, $p < 0.01$ (Fig. 2).

Allergic sensitisation

Twenty-three studies in 34,806 children (8952 cases) investigated the association between antibiotic exposure and the risk of developing allergic sensitisation diagnosed by skin prick test or serum immunoglobulin (Ig) E levels (Table 1).[24,40,43,49,60,70,79,80,82,87,93,105,116,126,135,153,175–178,181,183,184] Of the studies, 21 (91%) investigated the effect of antibiotic exposure in the first five years of life (18 (78%) in the first two years of life).[24,40,43,49,60,70,79,80,82,93,105,116,126,135,153,175–178,181,183] Four (17%) reported a significant increased incidence of allergic sensitisation in children who were exposed to antibiotics.[87,116,181,183] In contrast, one study (4%) reported a decreased incidence of allergic sensitisation in children who were exposed to antibiotics.[40] The one study which investigated if the risk of allergic sensitisation correlated with the number of antibiotic courses found no association.[176]

Of the 23 studies, 18 (78%) provided sufficient data to be included in the meta-analysis (supplementary Fig. 2).[24,40,43,49,70,79,80,82,87,93,105,116,135,153,176,178,181,183] Of the 12,502 children exposed to antibiotics 2582 (21%) developed allergic sensitisation compared to 3642 (22%) of the 16,731 children not exposed to antibiotics. Overall, the evidence did not support an association between antibiotic exposure and developing allergic sensitisation (OR 1.11, 95%CI 0.98–1.26, $p = 0.05$) (Fig. 2).

Food allergies

Fifteen studies investigated the association between antibiotic exposure and the risk of developing food allergies

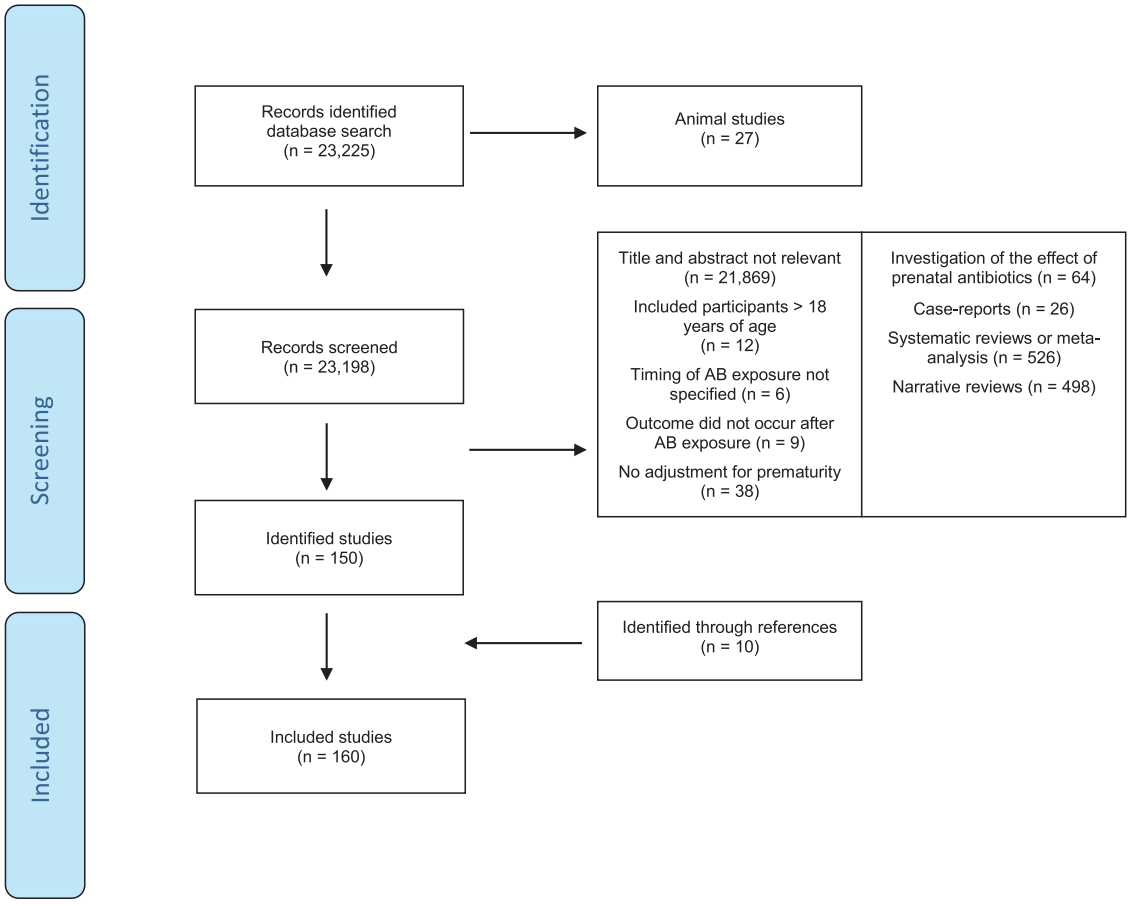
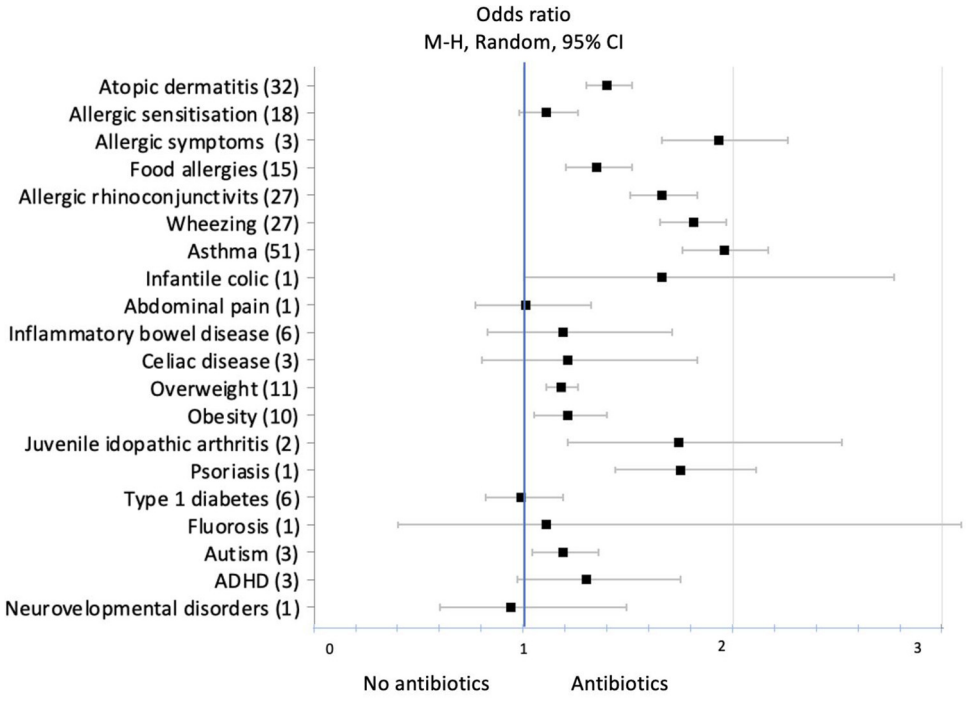


Fig. 1. Selection of studies.



CI – confidence interval H-M – Mantel-Haenszel

Fig. 2. Comparison of incidence of adverse health outcomes in children exposed and not exposed to antibiotics (number of studies in brackets).

Table 1
Summary of studies investigating the effect of antibiotic exposure on health outcomes in children. See Ref. [240]

Author Country Publication year	Study type (Level of evidence)	No of cases; cohort size No of cases in children with antibiotics; no of children with antibiotics No of cases in children without antibiotics; no of children without antibiotics	Time of antibiotic exposure (age unless otherwise specified) Antibiotic specified Evaluation of antibiotic exposure	Age at outcome measure	Outcome definition	Main findings	Factors adjusted for
Atopic dermatitis							
Aversa et al.[172] USA 2021	Multicentre prospective cohort study (2b)	297; 14,572 231; 10,220 66; 4,352	< 2 y Yes Medical records	6-11 y	ICD-9 and ICD-10 codes	Exposure to AB in first 2 y of life associated with increased risk. • **aHR 1.47 (95%CI 1.12-1.94), p<0.01** Girls • penicillins: HR 1.27 (95%CI 0.87-1.87), p=0.22 • cephalosporins: **HR 1.69 (95%CI 1.14-2.52), p=0.01** • macrolides: **HR 0.59 (95%CI 0.37-0.92), p=0.02** • sulfonamides: HR 0.98 (95%CI 0.49-1.96), p=0.95 Boys • penicillins: HR 1.40 (95%CI 0.96-2.03), p=0.08 • cephalosporins: HR 1.29 (95%CI 0.90-1.84), p=0.17 • macrolides: HR 0.83 (95%CI 0.57-1.19), p=0.30 • sulfonamides: HR 1.37 (95%CI 0.75-2.51), p=0.30	Sex, ethnicity, maternal age, education and smoking; antibiotic use during pregnancy, birth weight, delivery mode
Zou et al.[161] China 2020	Multicentre cross-sectional study (3b)	2,752; 12,667 772; 3,049 1,980; 9,618	< 1 y No Parent questionnaire	4-6 y	Questionnaire for atopic dermatitis symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.17 (95%CI 1.05-1.31), p<0.01**	Age, sex, living area, family history of atopy, breastfeeding, home decoration, pet, smoke and home dampness-related exposure

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Table 1 (*continued*)

Levin et al.[82] South-Africa 2020	Multicentre prospective cohort study (2b)	301; 1,185 182; 654 119; 531 8; 398 7; 347 1; 51	< 1 y No Parent questionnaire	12-36 m	Criteria by American Academy of Dermatology	Exposure to AB in first y of life associated with increased risk in urban cohort. • **OR 1.33 (95%CI 1.02-1.74), p=0.03*** Exposure to AB in first y of life not associated with increased risk in rural cohort. • OR 1.03 (95%CI 0.12-8.54), p=0.98*	
Rutter et al.[120] UK 2019	Multicentre cross-sectional study (3b)	15,152; 120,799 13,108*; 97,631 2,044*; 23,168	< 1 y No Parent questionnaire	6-7 y	Questionnaire for atopic dermatitis symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.41 (95%CI 1.34-1.48), p=nr**	Sex, maternal education and smoking; medication use, open fire cooking
Metzler et al.[93] Switzerland 2019	Multicentre prospective cohort study (2b)	275; 1,019 154; 419 121; 600	< 1 y No Parent questionnaire	< 6 y	Parent-reported physician's diagnosis	Exposure to AB in first y of life associated with increased risk. • **aOR 1.91 (95%CI 1.36-2.67), p<0.05** • 1 AB course: aOR 1.60 (95%CI nr), p=nr • 2 AB courses: aOR 2.06 (95%CI nr), p=nr • ≥ 3 AB courses: aOR 7.25 (95%CI nr), p=nr	Sex, family history of atopy, number of siblings, living area, smoking and pet exposure during pregnancy; delivery mode, duration of breastfeeding, pet exposure
Gao et al.[51] China 2019	Single-centre prospective cohort study (2b)	226; 903 26; 184 200; 719	< 1 y No Parent questionnaire	12 m	Parent-reported atopic dermatitis symptoms	Exposure to AB in first y of life associated with decreased risk. • **aOR 0.44 (95%CI 0.28-0.70), p<0.01**	Sex, family history of atopy, antibiotic use during pregnancy, season of birth, egg and milk consumption
Ho et al.[62] Taiwan 2019	Multicentre cross-sectional study (3b)	2,625; 23,908 562; 3,691 2,063; 20,217	< 1 y No Parent questionnaire	6-8 y	Questionnaire for atopic dermatitis symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.37 (95%CI 1.22-1.53), p<0.01**	Sex, number of siblings, number of LRTIs, duration of breastfeeding, timing of solid food introduction, pet and home dampness-related exposure

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Table 1 (*continued*)

Norbäck et al.[103] China 2019	Multicentre retrospective cohort study (2b)	9,573; 39,782 7,497; 29,303 2,076; 10,479	< 1 y No Parent questionnaire	3-6 y	Parent-reported physician's diagnosis	Exposure to AB in first y of life associated with increased risk. • **aOR 1.20 (95%CI 1.11-1.30), p<0.01** • 1 AB course: **aOR 1.15 (95%CI 1.07-1.24), p<0.01** • > 1 AB courses: **aOR 1.45 (95%CI 1.36-1.56), p<0.01**	Living area, temperature in each city, time spend outdoors, air pollution
Oosterloo et al.[105] Netherlands 2018	Multicentre prospective cohort study (2b)	156; 436 57; 151 99; 285	< 1 w No Parent questionnaire	0-1 y	Parent-reported atopic dermatitis symptoms	Exposure to AB in first w of life not associated with increased risk. • aOR 1.09 (95%CI 0.70-1.70), p=0.70	Family history of atopy, parental education, day care, number of siblings, smoking during pregnancy, delivery mode, duration of breastfeeding, household smoking
Mitre et al.[96] USA 2018	Multicentre retrospective cohort study (2b)	112,608; 792,130 21,638; 131,708 90,970; 660,422	< 6 m No Registry	1-6 y	ICD-9-CM codes	Exposure to AB in first 6 m of life associated with increased risk. • **aHR 1.18 (95%CI 1.16-1.19), p=nr**	Sex, prematurity, delivery mode, medication (incl. anti-reflux medication) use
Singh et al.[129] India 2018	Multicentre cross-sectional study (3b)	1,249; 44,928 nr; nr nr; nr	< 1 y No Parent questionnaire	6-7 y	Questionnaire for atopic dermatitis symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **OR 1.80 (95%CI 1.60-2.00), p<0.01**	
Yamamoto-Hanada et al.[157] Japan 2017	Multicentre prospective cohort study (2b)	194; 902 107; 436 87; 466	< 2 y Yes Parent questionnaire	5 y	Questionnaire for atopic dermatitis symptoms (ISAAC) plus medical records	Exposure to AB in first 2 y of life associated with increased risk. • **aOR 1.40 (95%CI 1.01-1.94), p=0.04** • penicillins: aOR 1.41 (95%CI 0.82-2.43), p=0.22 • cephem: aOR 1.37 (95%CI 0.94-1.99), p=0.10 • macrolides: **aOR 1.58 (95%CI 1.07-2.33), p=0.02**	Sex, maternal age, BMI education and history of atopy; parity, smoking during pregnancy, gestational age, delivery mode, number of LRTIs, day care
Park et al.[174] Korea 2016	Multicentre cross-sectional study (3b)	1,424; 4,003 607; 1585* 817; 2418* 981; 4,112 288; 1090* 693; 3022*	< 1 y No Parent questionnaire	6-7 y 12-13 y	Questionnaire for atopic dermatitis symptoms (ISAAC)	Exposure to AB in first y of life not associated with increased risk. • aOR 1.09 (95%CI 0.88-1.39), p=0.70 Exposure to AB in first y of life not associated with increased risk. • aOR 1.04 (95%CI 0.86-1.34), p=0.70	Age, sex, family history of atopy, living area, atopy

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Table 1 (*continued*)

Taylor-Robinson et al.[173] UK 2016	Multicentre prospective cohort study (2b)	3,489; 12,917 1,909; 5,678 1,580; 7,239	< 1 y No Registry	5 y	Questionnaire for atopic dermatitis symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.28 (95%CI 1.16-1.42), p<0.01**	Sex, ethnicity, maternal age, BMI, education and history of atopy; maternal smoking and alcohol consumption during pregnancy; day care, number of siblings, birth weight, delivery mode, breastfeeding, timing of solid food and cow's milk introduction, smoke and grime exposure
Loo et al.[175] Singapore 2015	Multicentre prospective cohort study (2b)	43; 792 nr; nr nr; nr	< 6 m No Parent questionnaire	6 m-1 y	Parents-reported physician's diagnosis	Exposure to AB in first 6 m of life not associated with increased risk. • aOR 3.19 (95%CI 0.72-14.11), p=0.13	Sex, sibling history of atopy, living area, age of child at outcome
		47; 792 nr; nr nr; nr		1-1.5 y		Exposure to AB in first 6 m of life associated with increased risk. • **aOR 3.11 (95%CI 1.10-8.76), p=0.03**	
Hoskin-Parr et al.[176] UK 2013	Single-centre prospective cohort study (2b)	994; 5,780 494*; 2,659 500*; 3,121	< 2 y No Parent questionnaire	7.5 y (mean)	Parents-reported physician's diagnosis	Exposure to AB in first 2 y of life associated with increased risk. • **aOR 1.20 (95%CI 1.02-1.41), p=nr** • 1 AB course: aOR 1.05 (95%CI 0.85-1.29), p=nr • 2 AB courses: aOR 1.23 (95%CI 1.00-1.51), p=nr • 3 AB courses: aOR 1.17 (95%CI 0.93-1.47), p=nr • ≥ 4 AB courses: aOR 1.41 (95%CI 1.14-1.74), p=nr	Age, sex, maternal age and education; parental marital status, home ownership status, difficulty in paying for food, smoking and disinfectant use during pregnancy, gestational age, birth weight, delivery mode, age of child at outcome, breastfeeding, time spend outdoors, pet exposure

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Table 1 (*continued*)

Wang et al.[150] Taiwan 2013	Multicentre prospective cohort study (2b)	19,015; 263,620 nr; 15,663 nr; 247,957	< 1 y Yes Medical records	2-6 y	ICD-9-CM codes	Exposure to AB in first y of life associated with increased risk. • **aHR 1.61 (95%CI 1.53-1.70), p<0.05** Results according to antibiotic class nr	Living area, socioeconomic status, healthcare use
Sandini et al.[177] Finland 2011	Single-centre prospective cohort study (2b)	270; 925 nr; nr nr; nr	< 6 m No Parent questionnaire	2 y	William's criteria	Exposure to AB in first 6 m of life not associated with increased risk. • OR 1.18 (95%CI 0.77-1.81), p=0.44	
		368; 891 nr; nr nr; nr		5 y		Exposure to AB in first 6 m of life not associated with increased risk. • OR 1.20 (95%CI 0.79-1.81), p=0.39	
Schmitt et al.[123] Germany 2010	Multicentre prospective cohort study (2b)	44; 370 24; 155 20; 215	< 1 y Yes Registry	2 y	ICD-10 codes plus prescription records	Exposure to AB in first y of life associated with increased risk, significant only for ≥ 2 AB courses. • OR 1.79 (95%CI 0.95-3.37), p=0.07* • 1 AB course: RR 1.45 (95%CI 0.76-2.75), p=nr • ≥ 2 AB courses: **RR 2.11 (95%CI 1.05-4.22), p=nr** • penicillins: RR 0.88 (95%CI 0.37-2.12), p=nr • cephalosporins: **RR 1.93 (95%CI 1.07-3.49), p=nr** • macrolides: **RR 2.15 (95%CI 1.18-3.91), p=nr**	
Su et al.[135] USA 2010	Single-centre prospective cohort study (2b)	134; 424 49; 136 85; 288	< 9 m No Parent questionnaire	1-5 y	Parent-reported physician's diagnosis	Exposure to AB in first 9 m of life not associated with increased risk. • OR 1.35 (95%CI 0.87-2.07), p=0.18*	
Dom et al.[40] Belgium 2010	Multicentre prospective cohort study (2b)	243; 670 192; 564 51; 106	< 4 y No Parent questionnaire	< 4 y	Questionnaire for atopic dermatitis symptoms (ISAAC)	Exposure to AB in first 4 y of life associated with decreased risk. • **OR 0.56 (95%CI 0.37-0.85), p<0.01*** Exposure to AB in first y of life not associated with decreased risk. • aOR 0.61 (95%CI 0.36-1.01), p=0.05 Exposure to AB in second to fourth y of life with decreased risk. • **aOR 0.11 (95%CI 0.05-0.23), p<0.01**	Sex, maternal age, family history of atopy, day care, number of siblings, parental education, smoking and pet exposure during pregnancy, birth weight, number of LRTIs, breastfeeding, household smoking, pet exposure

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Table 1 (*continued*)

Mai et al.[178] Sweden 2010	Single-centre prospective cohort study (2b)	663; 3,306 318; 1,420 345; 1,886	< 1 y No Parent questionnaire	4 y	Questionnaire for atopic dermatitis symptoms (BAMSE based on ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.30 (95%CI 1.10-1.50), p=nr**	Sex, maternal age and smoking; family history of atopy, number of siblings, breastfeeding
		523; 3,306 255; 1,420 268; 1,886		8 y		Exposure to AB in first y of life associated with increased risk. • **aOR 1.30 (95%CI 1.10-1.60), p=nr**	
Garcia-Marcos et al.[53] Spain 2010	Multicentre retrospective case-control study (3b)	922; 13,325 589; 6,831 333; 6,494	< 1 y No Parent questionnaire	6-7 y	Questionnaire for atopic dermatitis symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.66 (95%CI 1.43-1.92), p<0.01**	Age, sex, number of siblings, living area, maternal education and smoking; pet and traffic exposure
Karimi et al.[162] Iran 2009	Multicentre cross-sectional study (3b)	90; 1,476 63; 952* 27; 524*	< 1 y No nr	6-7 y	Questionnaire for atopic dermatitis symptoms (ISAAC)	Exposure to AB in first y of life not associated with increased risk. • OR 1.30 (95%CI 0.79-2.13), p=0.20	
Foliaki et al.[50] Sweden 2009	Multicentre retrospective cross-sectional study (3b)	nr; 193,412 nr; 135,775 nr; 57,637	< 1 y No Parent questionnaire	6-7 y	Questionnaire for atopic dermatitis symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.58 (95%CI 1.33-1.51), p=nr**	Sex, language, living area, income

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Table 1 (*continued*)

Wickens et al.[153] New Zealand 2008	Multicentre prospective cohort study (2b)	398; 1,064 52*; 148 346*; 916	< 3 m No Parent questionnaire	15 m	Questionnaire for atopic dermatitis symptoms (ISAAC)	Exposure to AB in first 3 m of life not associated with increased risk. • aOR 0.84 (95%CI 0.57-1.22), p=0.35	Number of LRTIs
		305; 1,011 242*; 722 63*; 289	< 15 m	4 y		Exposure to AB in first 15 m of life associated with increased risk. • **aOR 1.75 (95% CI, 1.03-2.96), p=0.04**	
Kusel et al.[80] Australia 2008	Multicentre prospective cohort study (2b)	62; 198 37*; 107 25*; 91	< 1 y Yes Parent questionnaire	0-5 y	Hanifin and Rajka criteria	Exposure to AB in first y of life not associated with increased risk. • aOR 1.50 (95%CI 0.70-3.30), p=nr Results according to antibiotic class nr	Sex, day care, number of GP visits, pet exposure
Kummeling et al.[79] Netherlands 2007	Multicentre prospective cohort study (2b)	817; 2,462 145; 489 672; 1,973	< 6 m No Parent questionnaire	< 2 y	Questionnaire for atopic dermatitis symptoms (ISAAC)	Exposure to AB in first 6 m not associated with increased risk. • aOR 0.94 (95%CI 0.75-1.18), p=nr	Sex, family history of atopy, day care, number of siblings, delivery mode, vaccination status, fever, breastfeeding, pet and smoke exposure
Mullooly et al.[98] USA 2007	Single-centre retrospective case-control study (3b)	58; 844 nr; nr nr; nr	< 2 y No Medical records	10.3 y (mean)	Parent-reported physician's diagnosis	Exposure to AB in first 2 y of life not associated with increased risk. • aOR 1.03 (95%CI 0.96-1.10), p=nr	Sex, ethnicity, maternal age, birth weight, age of child at time of outcome, breastfeeding, household smoking
Floistrup et al.[49] Netherlands, Austria, Germany, Sweden, Switzerland 2006	Multicentre cross-sectional study (3b)	520; 4,606 126*; 788 394*; 3,818	< 1 y No Parent questionnaire	7-11 y	Parent-reported physician's diagnosis	Exposure to AB in first y of life associated with increased risk. • **aOR 1.63 (95%CI 1.22-2.17), p=nr**	Age, sex, family history of atopy, number of siblings, country, parental education, measles infection, vaccination status, medication use, smoking during pregnancy, diet, household smoking, pet exposure

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Purvis et al.[114] New Zealand 2005	Multicentric, prospective case-control study (3b)	87; 550 57; 369 30; 181	< 1 y No Parent questionnaire	3.5-4 y	Questionnaire for atopic dermatitis symptoms (ISAAC) plus serum IgE (environmental allergens)	Exposure to AB in first y of life not associated with increased risk. • OR 1.18 (95%CI, 0.61-2.26), p=0.62	
Cohet et al.[37] New Zealand 2004	Single-centre retrospective case-control study (3b)	1,549; 3,927 1,130; 2,684 419; 1,243	< 1 y No Parent questionnaire	6-7 y	Questionnaire for atopic dermatitis symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **OR 1.40 (95%CI 1.21-1.62), p=nr**	
Celedon et al.[32] USA 2002	Multicentre prospective cohort study (2b)	22; 448 16; 302 6; 146	< 1 y No Parent questionnaire	5 y	Parent-reported physician's diagnosis	Exposure to AB in first y of life not associated with increased risk. • 1 AB course: aOR 0.90 (95%CI 0.30-3.40), p=nr • ≥ 2 AB courses: aOR 1.10 (95%CI 0.40-3.10), p=nr	Sex, family history of atopy, income
Bohme et al.[180] Sweden 2002	Multicentre prospective cohort study (2b)	952; 3,786 ≥ 2 AB courses: 450; 1,586 502; 2,200	1-2 y No Parent questionnaire	2 y	Questionnaire for atopic dermatitis symptoms (BAMSE)	Exposure to ≥ 2 AB courses in first 2 y of life associated with increased risk. • **aRP 1.29 (95%CI 1.07-1.56), p=nr**	Sex, maternal age and smoking; family history of atopy, parental education, gestational age, age of child at outcome, breastfeeding duration
McKeever et al.[182] UK 2002	Single-centre prospective cohort study (2b)	3,580; 19,133 nr; 12,497 nr; 6,636	< 1 y Yes Medical records	< 11 y 2.2 y (mean)	Oxford Medical Information System (OXMIS), ICD-8 or Read codes	Exposure to AB in first y of life associated with increased risk. • 1 AB course: **aHR 1.22 (95%CI 1.12-1.34), p=nr** • 2 AB courses: **aHR 1.21 (95%CI 1.09-1.35), p=nr** • 3 AB courses: **aHR 1.22 (95%CI 1.08-1.38), p=nr** • 4 AB courses: aHR 1.11 (95%CI 0.95-1.28), p=nr • > 4 AB courses: aHR 1.01 (95%CI 0.88-1.17), p=nr	Number of GP visits

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						• penicillin: aHR 1.07 (95%CI 0.97-1.18), p=nr • amoxicillin: **aHR 1.09 (95%CI 1.01-1.17), p=nr** • amoxicillin/clavulanic acid: aHR 1.16 (95%CI 0.98-1.38), p=nr • cephalosporins: aHR 0.90 (95%CI 0.80-1.02), p=nr • macrolides: aHR 0.96 (95%CI 0.89-1.04), p=nr	
Wjst et al.[155] Germany 2001	Multicentre cross-sectional study (3b)	768; 2,512 nr; 2,025 nr; 487	< 5-14 y No Medical records	5-14 y	Questionnaire for atopic dermatitis symptoms (ISAAC)	Exposure to AB between the fifth and fourteenth y of life not associated with increased risk. • aOR 1.30 (95%CI 0.80-2.20), p=0.27	Age, sex, family history of atopy, season, parental education
Droste et al.[43] Belgium 2000	Multicentre retrospective cross-sectional study (3b)	233; 1,180 85; 375 148; 805	< 1 y No Parent questionnaire	7-8 y	Questionnaire for atopic dermatitis symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk in high-risk children. • **aOR 1.30 (95%CI 1.00-1.80), p=0.05**	Sex, family history of atopy, number of siblings, living area, smoking during pregnancy, smoke exposure
Von Mutius et al.[181] Germany 1999	Single-centre cross-sectional study (3b)	812; 5,006 673; 3,904 139; 1,102	< 3 y No Medical records	5-7 y	Questionnaire for atopic dermatitis symptoms (ISAAC)	Exposure to AB in first 3 y of life associated with increased risk. • **OR 1.44 (95%CI 1.19-1.76), p<0.01***	
		865; 5,267 701; 4006 164; 1261		9-11 y		Exposure to AB in first 3 y of life associated with increased risk. • **OR 1.42 (95%CI 1.18-1.70), p<0.01***	
Wickens et al.[154] New Zealand 1999	Multicentre retrospective cross-sectional study (3b)	125; 447 98; 334 27; 113	< 10 y No Parent questionnaire	5-10 y	Questionnaire for atopic dermatitis symptoms (ISAAC)	Exposure to AB in first 10 y of life not associated with increased risk. • aOR 1.23 (95%CI 0.71-2.13), p=nr	Age, sex, ethnicity, family history of atopy, household size, parental smoking
Farooqi et al.[48] UK 1998	Single-centre retrospective cohort study (2b)	367; 1,855 287*; 1,237 80*; 618	< 2 y Yes Medical records	6-12 y	Physician's diagnosis	Exposure to AB in first 2 y of life associated with increased risk. • **OR 2.04 (95%CI 1.53-2.73), p<0.01** Results according to antibiotic class nr	

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Allergic sensitisation							
Levin et al.[82] South-Africa 2020	Multicentre prospective cohort study (2b)	107; 1,185 64; 654 43; 531	< 1 y No Parent questionnaire	12-36 m	SPT (food and inhalant allergens)	Exposure to AB in first y of life not associated with increased risk. • OR 1.23 (95%CI 0.82-1.85), p=0.31*	
		11; 398 11; 347 0; 51				Exposure to AB in first y of life not associated with increased risk in rural cohort. • OR 3.52 (95%CI 0.20-60.65), p=0.39*	
Metzler et al.[93] Switzerland 2019	Multicentre prospective cohort study (2b)	388; 1,019 167; 419 221; 600	< 1 y No Parent questionnaire	< 6 y	Serum IgE (seasonal, perennial and food allergens)	Exposure to AB in first y of life not associated with increased risk. • aOR 1.06 (95%CI 0.70-1.60), p=nr	Sex, family history of atopy, number of siblings, living area, smoking and pet exposure during pregnancy; delivery mode, duration of breastfeeding, pet exposure
Oosterloo et al.[105] Netherlands 2018	Multicentre prospective cohort study (2b)	18; 205 9; 77 9; 128	< 1 w No Parent questionnaire	0-1 y	Serum IgE (food and inhalant allergens)	Exposure to AB in first w of life not associated with increased risk. • aOR 3.26 (95%CI 0.95-11.13), p=0.06	Family history of atopy, parental education, day care, number of siblings, smoking during pregnancy, delivery mode, duration of breastfeeding, household smoking
Batool et al.[183] Canada 2016	Multicentre prospective cohort study (2b)	141; 576 63; 205 78; 371	< 1 y No Parent questionnaire	1 y	SPT (food and inhalant allergens)	Exposure to AB in first y of life associated with increased risk. • **OR 1.67 (95%CI 1-13-2.46), p<0.01***	
Azad et al.[24] Canada 2015	Multicentre prospective cohort study (2b)	12; 166 6; 78 6; 88	< 3 m No Medical records	1 y	SPT (food allergens)	Exposure to AB in first 3 m of life not associated with increased risk. • OR 1.14 (95%CI 0.35-3.69), p=0.83*	
		12; 166 9; 105 3; 61	< 1 y No Medical records			Exposure to AB in first y of life not associated with increased risk. • OR 1.81 (95%CI 0.47-6.97), p=0.39*	

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Loo et al.[175] Singapore 2015	Multicentre prospective cohort study (2b)	94; 696 nr; nr nr; nr	< 6 m No Parent questionnaire	1.5 y	SPT (food and inhalant allergens)	Exposure to AB in first 6 m of life not associated with increased risk. • aOR 11.44 (95%CI 0.50-260.29), p=0.13	Sex, living area, family history of atopy, age of child at time of outcome
Semic-Jusufagic et al.[126] UK 2014	Multicentre prospective cohort study (2b)	209; 800 nr; 564 nr; 236	< 1 y No Parent questionnaire	1-11 y	SPT (food and inhalant allergens)	Exposure to AB in first y of life not associated with increased risk. • HR 1.02 (95%CI 0.60-1.78), p=0.92	
Hoskin-Parr et al.[176] UK 2013	Single-centre prospective cohort study (2b)	830; 5,780 386*; 2,659 444*; 3,121	< 2 y No Parent questionnaire	7.5 y (mean)	SPT (inhalant allergens)	Exposure to AB in first 2 y of life not associated with increased risk. • aOR 1.02 (95%CI 0.85-1.22), p=nr • 1 AB course: aOR 1.00 (95%CI 0.80-1.25), p=nr • 2 AB courses: aOR 1.10 (95%CI 0.89-1.39), p=nr • 3 AB courses: aOR 0.96 (95%CI 0.74-1.24), p=nr • ≥ 4 AB courses: aOR 1.00 (95%CI 0.79-1.27), p=nr	Age, sex, maternal age and education; parental marital status, home ownership status, degree of difficulty in paying for food, smoking during pregnancy, disinfectant use during pregnancy, gestational age, birth weight, delivery mode, age of child at outcome, breastfeeding, time spend outdoors, pet exposure

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Risnes et al.[116] USA 2011	Multicentric prospective cohort study (2b)	151; 1,401 71*; 464 80*; 937	< 6 m No Parent questionnaire	6 y	SPT (food and inhalant allergens)	Exposure to AB in first 6 m of life associated with increased risk. • **aOR 1.59 (95% CI, 1.10-2.28), p=nr**	Maternal age, family history of atopy, number of LRTIs
Sandini et al.[177] Finland 2011	Single-centre prospective cohort study (2b)	271; 916 nr; nr nr; nr 367; 889 nr; nr nr; nr	< 6 m No Parent questionnaire	2 y 5 y	SPT or serum IgE (food and inhalant allergens)	Exposure to AB in first 6 m of life not associated with increased risk. • OR 1.22 (95%CI 0.79-1.88), p=0.37 Exposure to AB in first 6 m of life not associated with increased risk. • OR 0.82 (95%CI 0.54-1.25), p=0.35	
Dom et al.[40] Belgium 2010	Multicentre prospective cohort study (2b)	160; 450 121; 384 39; 66	< 4 y No Parent questionnaire	< 4 y	Serum IgE (food and inhalant allergens)	Exposure to AB before first 4 y of life associated with decreased risk. • **OR 0.32 (95%CI 0.19-0.54), p<0.01***	Sex, maternal age, family history of atopy, day care, number of siblings, parental education, smoking and pet exposure during pregnancy, birth weight, number of LRTIs, breastfeeding, household smoking, pet exposure
Mai et al.[178] Sweden 2010	Single-centre prospective cohort study (2b)	579; 3,306 244; 1,420 335; 1,886 828; 3,306 358; 1,420 470; 1,886	< 1 y No Parent questionnaire	4 y 8 y	Serum IgE (food and inhalant allergens)	Exposure to AB in first y of life not associated with increased risk. • aOR 0.90 (95%CI 0.70-1.10), p=nr Exposure to AB in first y of life not associated with increased risk. • aOR 1.00 (95%CI 0.80-1.20), p=nr	Sex, maternal age and smoking; family history of atopy, number of siblings, breastfeeding
Su et al.[135] USA 2010	Single-centre prospective cohort study (2b)	202; 398 65; 136 137; 262	< 9 m No Parent questionnaire	1-5 y	Serum IgE (food and inhalant allergens)	Exposure to AB in first 9 m of life not associated with increased risk. • OR 0.84 (95%CI 0.55-1.26), p=0.39*	

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Kusel et al.[80] Australia 2008	Multicentre prospective cohort study (2b)	67; 198 36*; 107 31*; 91	< 1 y Yes Parent questionnaire	0-5 y	SPT plus serum IgE (food and inhalant allergens)	Exposure to AB in first y of life not associated with increased risk. • aOR 1.00 (95%CI 0.50-2.10), p=nr Results according to antibiotic class nr	Sex, day care, number of GP visits, pet exposure
Wickens et al.[153] New Zealand 2008	Multicentre prospective cohort study (2b)	249; 1,064 44*; 148 205*; 916	< 3 m No Parent questionnaire	15 m	SPT (food and inhalant allergens)	Exposure to AB before 3 m of life not associated with increased risk. • aOR 1.36 (95% CI, 0.91-2.05), p=0.14	Number of LRTIs
Harris et al.[60] UK 2007	Single-centre prospective cohort study (2b)	104; 490 27; nr 77; nr	< 5 y No Medical records	8 y	SPT (inhalant allergens)	Exposure to AB in first 5 y of life not associated with increased risk. • aOR 1.00 (95%CI 0.97-1.03), p=0.86	Family history of atopy, birth order, smoke exposure
Majkowska-Wojciechowska et al.[87] Poland 2007	Multicentre prospective cohort study (2b)	128; 201 8*; 10 120*; 191	nr No Parent questionnaire	12-16 y	SPT	Early-life exposure to AB associated with increased risk. • **OR 2.12 (95%CI 1.16-3.85), p=0.02**	
Kummeling et al.[79] Netherlands 2007	Multicentre prospective cohort study (2b)	223; 2,462 44; 489 179; 1,973	< 6 m No Parent questionnaire	2 y	Serum IgE (food and inhalant allergens)	Exposure to AB in first 6 m of life not associated with increased risk. • aOR 1.32 (95%CI 0.86-2.02), p=nr	Sex, family history of atopy, day care, number of siblings, delivery mode, vaccination status, fever, breastfeeding, pet and smoke exposure

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Floistrup et al.[49] Netherlands, Austria, Germany, Sweden, Switzerland 2006	Multicentre cross-sectional study (3b)	1,487; 4,606 264*; 788 1,223*; 3,818	< 1 y No Parent questionnaire	7-11 y	Serum IgE (food and inhalant allergens)	Exposure to AB in first y of life not associated with increased risk. • aOR 0.91 (95%CI 0.60-1.37), p=nr	Age, sex, family history of atopy, number of siblings, country, parental education, measles infection, vaccination status, medication use, smoking during pregnancy, diet, parental smoking, pet exposure
Johnson et al.[70] USA 2005	Multicentre prospective cohort study (2b)	157; 448 83*; 221 74*; 227	< 6 m No Medical records	6-7 y	Clinical evaluation plus SPT	Exposure to AB in first 6 m of life not associated with increased risk. • aOR 1.48 (95%CI 0.94-2.34), p=0.09	Family history of atopy, number of LRTIs, duration of breastfeeding, pet exposure
Wjst et al.[155] Germany 2001	Multicentre cross-sectional study (3b)	1,944; 2,512 nr; 2,025 nr; 487	< 5-14 y No Medical records	5-14 y	SPT (food and inhalant allergens)	Exposure to AB in first y of life not associated with increased risk. • aOR 0.90 (95%CI 0.60-1.40), p=0.71	Age, sex, family history of atopy, season, parental education
Droste et al.[43] Belgium 2000	Multicentre cross-sectional study (3b)	130; 660 45; 210 85; 450	< 1 y No Parent questionnaire	7-8 y	SPT (inhalant allergens)	Exposure to AB in first y of life not associated with increased risk in high-risk children. • aOR 1.10 (95%CI 0.70-1.70), p=0.10	Sex, family history of atopy, number of siblings, living area, smoking during pregnancy, smoke exposure
Von Mutius et al.[181] Germany 1999	Single-centre cross-sectional study (3b)	222; 5,006 168; 3,904 54; 1,102 946; 5,267 745; 4,006 201; 1,261	< 3 y No Medical records	5-7 y 9-11 y	Serum IgE (inhalant allergens) plus SPT	Exposure to AB in first 3 y of life not associated with increased risk. • OR 0.87 (95%CI 0.64-1.19), p=0.40* Exposure to AB in first 3 y of life associated with increased risk. • **OR 1.20 (95%CI 1.02-1.43), p=0.03***	

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Food allergies							
Aversa et al.[172] USA 2021	Multicentre prospective cohort study (2b)	261; 14,572 201; 10,220 60; 4,352	< 2 y Yes Medical records	6-11 y	ICD-9 and ICD-10 codes	Exposure to AB in first 2 y of life not associated with increased risk. • aHR 1.33 (95%CI 0.99-1.77), p=0.05 Girls • penicillins: HR 0.74 (95%CI 0.47-1.15), p=0.18 • cephalosporins: **HR 2.73 (95%CI 1.74-4.28), p<0.01** • macrolides: HR 1.00 (95%CI 0.62-1.59), p=0.99 • sulfonamides: HR 1.27 (95%CI 0.65-2.49), p=0.49 Boys • penicillins: HR 1.06 (95%CI 0.73-1.53), p=0.77 • cephalosporins: **HR 1.96 (95%CI 1.39-2.76), p<0.01** • macrolides: HR 0.99 (95%CI 0.69-1.41), p=0.94 • sulfonamides: HR 0.67 (95%CI 0.31-1.43), p=0.30	Sex, ethnicity, maternal age, education and smoking; antibiotic use during pregnancy, birth weight, delivery mode,
Zou et al.[161] China 2020	Multicentre cross-sectional study (3b)	1,938; 12,667 560; 3,049 1,378; 9,618	< 1 y No Parent questionnaire	4-6 y	Questionnaire for allergic symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.29 (95%CI 1.13-1.46), p<0.01**	Age, sex, living area, family history of atopy, breastfeeding, home decoration, pet, smoke and home dampness-related exposure
Levin et al.[82] South-Africa 2020	Multicentre prospective cohort study (2b)	27; 1,185 18; 654 9; 531 2; 398 2; 347 0; 51	< 1 y No Parent questionnaire	12-36 m	Questionnaire for allergic symptoms (based on ISAAC)	Exposure to AB in first y of life not associated with increased risk in urban cohort. • OR 1.64 (95%CI 0.73-3.68), p=0.23* Exposure to AB in first y of life not associated with increased risk in rural cohort. • OR 0.75 (95%CI 0.04-15.75), p=0.19*	
Metzler et al.[93] Switzerland 2019	Multicentre prospective cohort study (2b)	75; 1,019 37; 419 38; 600	< 1 y No Parent questionnaire	< 6 y	Questionnaire for allergic symptoms (based on ISAAC) plus parent-reported physician's diagnosis	Exposure to AB in first y of life not associated with increased risk. • aOR 1.47 (95%CI 0.73-2.98), p=nr	Sex, family history of atopy, number of siblings, living area, smoking during pregnancy, pet exposure during pregnancy, delivery mode, duration of breastfeeding, pet exposure

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Gao et al.[51] China 2019	Single-centre prospective cohort study (2b)	200; 903 43; 201 157; 702	< 1 y No Parent questionnaire	12 m	Parent-reported	Exposure to AB in first y of life not associated with increased risk. • OR 0.94 (95%CI 0.65-1.38), p=0.77*	Sex, family history of atopy, antibiotic use during pregnancy, season of birth, egg and milk consumption
Li et al.[185] USA 2019	Multicentre prospective cohort study (2b)	14,812; 1,001,294 9,193; 500,647 5,619; 500,647	< 1 y No Registry	< 4 y	ICD-9-CM codes	Exposure to AB in first y of life associated with increased risk. • **aHR 1.40 (95%CI 1.34-1.45), p=nr**	Day care, living area, prematurity, birth weight, delivery mode, neonatal intensive-care unit admission, State Children's Health Insurance Program, atopy
Mitre et al.[96] USA 2018	Multicentre retrospective cohort study (2b)	24,514; 792,130 4,753; 131,708 19,761; 660,422	< 6 m No Registry	1-6 y	ICD-9-CM codes	Exposure to AB in first 6 m of life associated with increased risk. • **aHR 1.14 (95%CI 1.10-1.18), p=nr**	Sex, prematurity, delivery mode, medication (incl. anti-reflux medication) use
Hirsch et al.[61] USA 2017	Multicentre case-control study (3b)	484; 2,904 210; 1,074 274; 1,830	>1-2 m before diagnosis Yes Medical records	< 7 y	Cow's milk allergy ICD-9 codes plus medical or prescription records	Exposure to AB until 2 m before diagnosis associated with increased risk. • **aOR 1.58 (95%CI 1.24-2.02), p=nr** • ≤ 2 AB courses: **aOR 1.49 (95%CI 1.15-1.96), p=nr** • ≥ 3 AB courses: **aOR 1.78 (95%CI 1.28-2.48), p=nr** • penicillins: **aOR 1.58 (95%CI 1.24-2.02), p=nr** • cephalosporins: **aOR 1.40 (95%CI 1.02-1.93), p=nr** • macrolides: **aOR 1.68 (95%CI 1.19-2.37), p=nr**	Ethnicity, healthcare use
		598; 3,588 445; 2,496 153; 1,092			Non-milk food allergy ICD-9 codes plus medical or prescription records	Exposure to AB until 2 m before diagnosis associated with increased risk. • **aOR 1.49 (95%CI 1.18-1.87), p=nr** • ≤ 2 AB courses: **aOR 1.38 (95%CI 1.08-1.77), p=nr** • ≥ 3 AB courses: **aOR 1.65 (95%CI 1.27-2.14), p=nr** • penicillins: **aOR 1.29 (95%CI 1.04-1.59), p=nr** • cephalosporins: **aOR 1.57 (95%CI 1.29-1.93), p=nr** • macrolides: **aOR 1.58 (95%CI 1.28-1.96), p=nr**	

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Batool et al.[183] Canada 2016	Multicentre prospective cohort study (2b)	143; 818 62; 285 81; 533	< 1 y No Parent questionnaire	1 y	Parent-reported food allergies or SPT	Exposure to AB in first y of life associated with increased risk. • **OR 1.55 (95%CI 1.07-2.24), p=0.02***	
Love et al.[163] USA 2016	Multicentre retrospective case-control study (3b)	1,504; 7,499 722; 3,324 782; 4,175	< 1 y Yes Prescription records	0-3 y	ICD-9-CM codes	Exposure to AB in first y of life associated with increased risk. • **aOR 1.21 (95%CI 1.06-1.39), p<0.01** • penicillins: **aOR 1.19 (95%CI 1.04-1.36), p=0.01** • cephalosporins: **aOR 1.50 (95%CI 1.27-1.77), p<0.01** • macrolides: **aOR 1.36 (95%CI 1.13-1.63), p<0.01** • sulfonamides: **aOR 1.54 (95%CI 1.19-2.01), p<0.01**	Maternal age and smoking, pre-pregnancy diabetes, living area, smoking during pregnancy, gestational age, delivery mode, atopy, breastfeeding,
Metsälä et al.[91] Finland 2013	Multicentre case-control study (3b)	533; 15,672 162*; 3,292 371*; 12,380	< 1 m before diagnosis Yes Registry	1 m-8 y	Cow's milk allergy ICD-10 codes plus SPT plus serum IgE	Exposure to AB within 1 m before diagnosis associated with increased risk. • **aOR 1.71 (95%CI 1.59-1.84), p=nr** • penicillin: **aOR 1.97 (95%CI 1.50-2.58), p=nr** • amoxicillin: **aOR 1.39 (95%CI 1.29-1.51), p=nr** • cephalosporins: **aOR 2.43 (95%CI 2.14-2.77), p=nr** • macrolides: **aOR 1.65 (95%CI 1.49-1.82), p=nr** • trimethoprim/sulfamethoxazole: **aOR 1.60 (95%CI 1.27-2.02), p=nr**	Maternal age, parity, maternal smoking during pregnancy, birth weight, delivery mode
Dowhower Karpa et al.[42] USA	Single-centre retrospective case-control study (4)	99; 291 16; 40 83; 251	< 1 m No Medical	0-18 y	ICD-9-CM codes plus serum IgE or SPT or physician's	Early exposure to AB not associated with increased risk. • OR 1.35 (95%CI 0.68-2.68), p=0.39	

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Raciborski et al.[115] Poland 2012	Multicentre retrospective cohort study (2b)	307; 1,330 211; 820 96; 510	< 1 y No Parent questionnaire	6-8 y	Questionnaire for allergic symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **OR 1.49 (95%CI 1.14-1.96), p<0.01*** • 1 AB course: OR 1.23 (95%CI nr), p=0.22 • 2-3 AB courses: OR 1.30 (95%CI nr), p=0.18 • > 3 AB courses: **OR 1.52 (95%CI nr), p=0.05**	
		307; 1,321 273; 1,145 34; 176	1-3 y No Parent questionnaire			Exposure to AB in first to third y of life not associated with increased risk. • OR 1.31 (95%CI 0.88-1.95), p=0.19 • 1-2 AB courses: OR 1.12 (95%CI nr), p=0.62 • 3-4 AB courses: OR 1.32 (95%CI nr), p=0.23 • > 4 AB courses: OR 1.32 (95%CI nr), p=0.24	
Mai et al.[178] Sweden 2010	Single-centre prospective cohort study (2b)	354; 3,306 181; 1,420 173; 1,886	< 1 y No Parent questionnaire	4 y	Questionnaire for allergic symptoms (BAMSE based on ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.40 (95%CI 1.10-1.70), p=nr**	Sex, maternal age and smoking; family history of atopy, number of siblings, breastfeeding,
		436; 3,306 206; 1,420 230; 1,886		8 y		Exposure to AB in first y of life not associated with increased risk. • aOR 1.20 (95%CI 0.90-1.40), p=nr	
Eggesbo et al.[46] Norway 2003	Single-centre retrospective cohort study (2b)	32; 2,759 12; 963 20; 1,796	< 6 m No Parent questionnaire	2.5 y	Parent-reported immediate reaction plus serum IgE	Exposure to AB in first 6 m of life not associated with increased risk. • aOR 1.50 (95% CI, 0.60-3.70), p=0.40	Maternal age, education and smoking; number of siblings, restricted growth in pregnancy, pregnancy complications, gestational age, birth weight
Allergic rhinoconjunctivitis							
Aversa et al.[172] USA 2021	Multicentre prospective cohort study (2b)	971; 14,572 760; 10,220 211; 4,352	< 2 y Yes Medical records	6-11 y	ICD-9 and ICD-10 codes	Exposure to AB in first 2 y of life associated with increased risk. • **aHR 1.36 (95%CI 1.17-1.59), p<0.01**	Sex, ethnicity, maternal age, education and smoking; antibiotic use during pregnancy, birth weight, delivery mode,

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						Girls • penicillins: HR 1.15 (95%CI 0.91-1.46), p=0.25 • cephalosporins: **HR 1.83 (95%CI 1.46-2.30), p<0.01** • macrolides: HR 1.11 (95%CI 0.88-1.40), p=0.36 • sulfonamides: HR 1.16 (95%CI 0.81-1.66), p=0.41 Boys • penicillins: HR 1.16 (95%CI 0.95-1.41), p=0.15 • cephalosporins: **HR 1.29 (95%CI 1.07-1.55), p<0.01** • macrolides: **HR 1.39 (95%CI 1.16-1.66), p<0.01** • sulfonamides: HR 1.10 (95%CI 0.80-1.52), p=0.56	
Zou et al.[161] China 2020	Multicentre cross-sectional study (3b)	1,579; 12,667 479; 3,049 1,100; 9,618	< 1 y No Parent questionnaire	4-6 y	Questionnaire for allergic rhinitis symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.23 (95%CI 1.07-1.41), p<0.01**	Age, sex, living area, family history of atopy, breastfeeding, home decoration, pet, smoke and home dampness-related exposure
Levin et al.[82] South-Africa 2020	Multicentre prospective cohort study (2b)	295; 1,185 187; 654 108; 531	< 1 y No Parent questionnaire	12-36 m	Questionnaire for allergic rhinitis symptoms (based on ISAAC)	Exposure to AB in first y of life associated with increased risk in urban cohort. • **OR 1.57 (95%CI 1.20-2.06), p<0.01***	
		13; 398 12; 347 1; 51				Exposure to AB in first y of life not associated with increased risk in rural cohort. • OR 1.79 (95%CI 0.23-14.07), p=0.58*	
Chinratanapisit et al.[35] Thailand 2019	Multicentre cross-sectional study (3b)	462; 3,074 237; 1,138 225; 1,936	< 1 y No Parent questionnaire	6-7 y	Questionnaire for allergic rhinitis symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **OR 2.00 (95%CI 1.64-2.44), p<0.01***	Age, sex, family history of atopy, number of siblings, migration, birth weight, BMI, medication use, parental smoking, diet, pet, farm animal, air pollution, cooking fuels, and traffic exposure
Ni et al.[102] USA 2019	Single-centre retrospective cohort study (4)	233; 2,398 130*; 1,060 103*; 1,338	< 1 y Yes Medical records	1-10 y	ICD-9 and ICD-10 codes	Exposure to AB in first y of life not associated with increased risk. • aOR 1.41 (95%CI 0.48-4.14), p=0.53 Results according to antibiotic class nr	Age, sex, ethnicity, socioeconomic status, prematurity, birth weight, delivery mode, neonatal intensive-care unit admission
		215; 2,398 198*; 1,755 17*; 643	< 10 y Yes Medical records			Exposure to AB in first 10 y of life associated with increased risk. • **aOR 2.43 (95%CI 1.43-4.11), p<0.01** Results according to antibiotic class nr	

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Norbäck et al.[103] China 2019	Multicentre retrospective cohort study (2b)	3,463; 39,782 3,000; 29,303 463; 10,479	< 1 y No Parent questionnaire	3-6 y	Parent-reported physician's diagnosis	Exposure to AB in first y of life associated with increased risk. • **aOR 1.77 (95%CI 1.54-2.03), p<0.01** • 1 AB course: **aOR 1.19 (95%CI 1.06-1.34), p<0.01** • > 1 AB courses: **aOR 1.51 (95%CI 1.36-1.68), p<0.01**	Living area, time spend outdoors, air pollution, temperature in each city
Metzler et al.[93] Switzerland 2019	Multicentre prospective cohort study (2b)	59; 1,019 21; 419 38; 600	< 1 y No Parent questionnaire	< 6 y	Questionnaire for allergic symptoms (based on ISAAC) plus parent-reported physician's diagnosis	Exposure to AB in first y of life not associated with increased risk. • aOR 0.70 (95%CI 0.33-1.51), p=nr	Sex, family history of atopy, number of siblings, living area, smoking during and pet exposure during pregnancy; delivery mode, duration of breastfeeding, pet exposure
Mitre et al.[96] USA 2018	Multicentre retrospective cohort study (2b)	24,585; 792,130 5,047; 131,708 19,538; 660,422	< 6 m No Registry	1-6 y	Allergic conjunctivitis ICD-9-CM codes	Exposure to AB in first 6 m of life associated with increased risk. • **aHR 1.42 (95%CI 1.34-1.50), p=nr**	Sex, prematurity, delivery mode, medication (incl. anti-reflux medication) use
		248,232; 792,130 52,135; 131,708 196,097; 660,422			Allergic rhinitis ICD-9-CM codes	Exposure to AB in first 6 m of life associated with increased risk. • **aHR 1.75 (95%CI 1.72-1.78), p=nr**	

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Singh et al.[129] India 2018	Multicentre cross-sectional study (3b)	1,753; 44,928 nr; nr nr; nr	< 1 y No Parent questionnaire	6-7 y	Questionnaire for allergic rhinoconjunc-tivitis symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **OR 1.90 (95%CI 1.70-2.20), p<0.01**	
		5,100; 44,928 nr; nr nr; nr			Questionnaire for allergic rhinitis symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **OR 1.90 (95%CI 1.70-2.00), p<0.01**	
Han et al.[59] Argentina 2017	Multicentre cross-sectional study (3b)	207; 1,517 155; 921 52; 596	< 1 y No Parent questionnaire	6-7 y	Questionnaire for allergic rhinoconjunc-tivitis symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.90 (95%CI 1.30-2.70), p<0.01**	Number of LRTIs, medication use
Yamamoto-Hanada et al.[157] Japan 2017	Multicentre prospective cohort study (2b)	96; 902 59; 436 37; 466	< 2 y Yes Parent questionnaire	5 y	Questionnaire for allergic rhinitis (ISAAC) symptoms plus medical records	Exposure to AB in first 2 y of life associated with increased risk. • **aOR 1.65 (95%CI 1.05-2.58), p=0.03** • penicillins: aOR 0.58 (95%CI 0.22-1.51), p=0.26 • cephem: **aOR 1.82 (95%CI 1.12-2.93), p=0.02** • macrolides: aOR 1.50 (95%CI 0.902.49), p=0.12	Sex, maternal age, BMI, education and history of atopy; parity, day care, , smoking during pregnancy, gestational age, delivery mode, number of LRTIs
Wang et al.[186] China 2016	Multicentre cross-sectional study (3b)	1,624; 13,335 nr; nr nr; nr	< 1 y No Parent questionnaire	4-6 y	Questionnaire for allergic rhinitis (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.23 (95%CI 1.09–1.40), p=nr**	Age, sex, family history of atopy
Yang et al.[158] Korea 2014	Multicentre cross-sectional study (3b)	1,768; 6,435 1,258; 1,947 2,629; 4,488	< 1 y No Parent questionnaire	15 y	Questionnaire for allergic rhinitis symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.25 (95%CI 1.04-1.50), p=0.02**	Age, sex, study centre, family history of atopy, income, BMI

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Alm et al.[16] Sweden 2014	Multicentre prospective cohort study (2b)	564; 4,051 40*; 187 524*; 3,864	< 1 w No Parent questionnaire	8 y	Questionnaire for allergic rhinitis symptoms (ISAAC and BAMSE)	Exposure to AB in first w of life associated with increased risk. • **aOR 1.75 (95%CI 1.03-2.97), p=nr**	Sex, maternal age, family history of atopy, living area, paternal education, maternal medication during pregnancy, weight for gestational age, atopy, diet, pacifier use, time spend outdoors, pet exposure
Tamay et al.[187] Turkey 2014	Multicentre prospective cohort study (2b)	803; 9,875 nr; nr nr; nr	< 1 y No Parent questionnaire	6-7 y	Questionnaire for allergic rhinitis symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.41 (95%CI 1.15-1.73), p<0.05**	Number of LRTIs, perianal redness, adenotonsillectomy, medication use, pet exposure, environmental factors
Hoskin-Parr et al.[176] UK 2013	Single-centre prospective cohort study (2b)	503; 5,780 260*; 2,659 243*; 3,121	< 2 y No Parent questionnaire	7.5 y (mean)	Parents-reported physician's diagnosis	Exposure to AB in first 2 y of life associated with increased risk. • **aOR 1.28 (95%CI 1.03-1.60), p=nr** • 1 AB course: aOR 1.17 (95%CI 0.88-1.54), p=nr • 2 AB courses: aOR 1.21 (95%CI 0.90-1.61), p=nr • 3 AB courses: aOR 1.18 (95%CI 0.86-1.61), p=nr • ≥ 4 AB courses: aOR 1.60 (95%CI 1.21-2.10), p=nr	Age, sex, maternal age and education; parental marital status, home ownership status, degree of difficulty in paying for food, smoking during pregnancy, disinfectant use during pregnancy, gestational age, birth weight, delivery mode, age of child at outcome, breastfeeding, time spend outdoors, pet exposure
Muc et al.[97] Portugal 2013	Multicentre cross-sectional study (3b)	14; 1,037 5*; 237 9*; 800	< 1 y No Parent questionnaire	6-9 y	Questionnaire for allergic rhinitis symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.84 (95%CI 1.30-2.59), p<0.01**	Age, sex, prematurity, atopy

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Wang et al.[150] Taiwan 2013	Multicentre prospective cohort study (2b)	82,292; 263,620 nr; 15,663 nr; 247,957	< 1 y Yes Medical records	2-6 y	ICD-9-CM codes	Exposure to AB in first y of life associated with increased risk. • **aHR 1.41 (95%CI 1.35-1.47), p<0.05** Results according to antibiotic class nr	Sex, living area, socioeconomic status, healthcare use
Kim et al.[74] Korea 2012	Multicentre cross-sectional study (3b)	1,550; 4,436 748*; 1,528 802*; 2,908	< 1 y No Parent questionnaire	9.5 y (mean)	Questionnaire for allergic rhinitis symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.95 (95%CI 1.61-2.36), p<0.01** Strongest risk of children with atopic parents • **aOR 6.00 (95%CI 4.63-7.80), p=nr**	Age, sex, study centre, family history of atopy, maternal education, BMI, smoke exposure
Peñaranda et al.[110] Colombia 2012	Multicentre cross-sectional study (3b)	588; 3,256 401; nr 163; nr	< 1 y No Parent questionnaire	6-7 y	Questionnaire for allergic rhinitis symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.30 (1.10-1.70), p=0.01**	Maternal education, delivery mode, atopy, medication use, household smoking
Sandini et al.[177] Finland 2011	Single-centre prospective cohort study (2b)	177; 891 nr; nr nr; nr	< 6 m No Parent questionnaire	5 y	Parent-reported allergic rhinitis symptoms	Exposure to AB in first 6 m of life not associated with increased risk. • OR 0.92 (95%CI 0.54-1.56), p=0.75	
Mai et al.[178] Sweden 2010	Single-centre prospective cohort study (2b)	369; 3,306 176; 1,420 193; 1,886 447; 3,306 202; 1,420 245; 1,886	< 1 y No Parent questionnaire	4 y 8 y	Questionnaire for allergic rhinitis symptoms (BAMSE based on ISAAC)	Exposure to AB in first y of life not associated with increased risk. • aOR 1.20 (95%CI 0.90-1.50), p=nr Exposure to AB in first y of life not associated with increased risk. • aOR 1.10 (95%CI 0.90-1.30), p=nr	Sex, maternal age and smoking; family history of atopy, number of siblings, breastfeeding,
Sultesz et al.[188] Hungary 2010	Single-centre case-control study (3b)	883; 3,322 473; 1,495 410; 1,827	< 1 y No Parent questionnaire	6-12 y	Questionnaire for allergic rhinitis symptoms (based on ISAAC)	Exposure to AB in first y of life associated with increased risk. • **OR 1.60 (95%CI 1.37-1.87), p<0.01**	

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Foliaki et al.[50] Sweden 2009	Multicentre retrospective cross-sectional study (3b)	nr; 193,412 nr; 135,775 nr; 57,637	< 1 y No Parent questionnaire	6-7 y	Questionnaire for rhinoconjunc-tivitis (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.56 (95%CI 1.46-1.66), p=nr**	Sex, language, living area, income
Karimi et al.[162] Iran 2009	Multicentre cross-sectional study (3b)	195; 1,476 134; 958* 61; 518*	< 1 y No nr	6-7 y	Questionnaire for allergic rhinitis symptoms (ISAAC)	Exposure to AB in first y of life not associated with increased risk. • OR 1.22 (95%CI 0.87-1.72), p=0.20	
Harris et al.[60] UK 2007	Single-centre prospective cohort study (2b)	124; 523 43; nr 81; nr	< 5 y No Medical records	8 y	Questionnaire for allergic rhinitis symptoms (ISAAC)	Exposure to AB in first 5 y of life associated with increased risk. • **aOR 1.06 (95%CI 1.03-1.09), p<0.01**	Family history of atopy, birth order, smoke exposure
Mullooly et al.[98] USA 2007	Single-centre case-control study (3b)	660; 844 nr; nr nr; nr	< 2 y No Medical records	10.3 y (mean)	Parent-reported physician's diagnosis	Exposure to AB in first 2 y of life not associated with increased risk. • aOR 1.03 (95%CI 0.99-1.08), p=nr	Sex, ethnicity, maternal age, birth weight, age of child at time of outcome, breastfeeding, household smoking
Tamay et al.[189] Turkey 2007	Multicentre prospective cohort study (2b)	671; 2,500 430; nr 241; nr	< 1 y No Parent questionnaire	6-12 y	Questionnaire for allergic rhinitis symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.26 (1.01-1.57), p=nr**	Family history of atopy, number of LRTIs and sinusitis, atopy, adenotonsillectomy, perianal redness, medication use, pet, home-dampness and diesel truck exposure
Floistrup et al.[49] Netherlands, Austria, Germany, Sweden, Switzerland 2006	Multicentre cross-sectional study (3b)	216; 4,606 67*; 788 149*; 3,818	< 1 y No Parent questionnaire	7-11 y	Parent-reported physician's diagnosis	Exposure to AB in first y of life associated with increased risk. • **aOR 1.97 (95%CI 1.26-3.08), p=nr**	Age, sex, family history of atopy, number of siblings, country, parental education, measles infection, vaccination status, medication use, smoking during pregnancy, diet, household smoking, pet exposure

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Thomsen et al.[190] Denmark 2006	Single-centre case-control study (4)	44; 470 12*; 152 32*; 318	< 2 y No Parent questionnaire	7-17 y	Parent-reported physician's diagnosis	Exposure to AB in first 2 y of life not associated with increased risk. • OR 0.77 (95%CI 0.38-1.53), p=0.45*
Cohet et al.[37] New Zealand 2004	Single-centre case-control study (3b)	699; 3,927 534; 2,684 165; 1,243	< 1 y No Parent questionnaire	6-7 y	Questionnaire for allergic rhinitis symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **OR 1.52 (95%CI 1.25-1.85), p=nr**
Bremner et al.[29] UK 2003	Multicentre nested case-control study (3b)	2,902; 40,183 nr; nr nr; nr	< 3 y Yes Medical records	5.1 y (mean)	Read codes	Exposure to AB in first 3 y of life associated with increased risk. • AB first y: **OR 1.15 (95%CI, 1.03-1.29), p=0.02** • AB in second y: **OR 1.29 (95%CI, 1.15-1.46), p<0.01** • AB in third y: **OR 1.32 (95%CI, 1.17-1.48), p<0.01** Results according to antibiotic class nr
		4,196; 76,310 nr; nr nr; nr	< 1 y Yes Medical records	4.6 y (mean)	Oxford Medical Information System (OXMIS) or Read codes	Exposure to AB in first y of life not associated with increased risk. • AB first y: OR 1.08 (95%CI, 0.98-1.20), p=0.13 • 1 AB course: **aOR 1.11 (95%CI 1.02-1.22), p=0.02** • 2 AB courses: **aOR 1.26 (95%CI 1.14-1.41), p<0.01** • ≥ 3 AB courses: **aOR 1.36 (95%CI 1.23-1.50), p<0.01**

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						• penicillins: aOR 0.97 (95%CI 0.92-1.03), p=0.35 • cephalosporins: aOR 0.95 (95%CI 0.86-1.06), p=0.34 • macrolides: aOR 0.97 (95%CI 0.91-1.04), p=0.46 • trimethoprim/sulfamethoxazole: aOR 0.92 (95%CI 0.82-1.02), p=0.12	
			1-2 y Yes Medical records			Exposure to AB in second y of life associated with increased risk. • **OR 1.40 (95%CI, 1.26-1.56), p<0.01** Results according to antibiotic class nr	
			2-3 y Yes Medical records			Exposure to AB in third y of life associated with increased risk. • **OR 1.59 (95%CI, 1.44-1.75), p<0.01** Results according to antibiotic class nr	
Celedon et al.[32] USA 2002	Multicentre prospective cohort study (2b)	45; 448 30; 302 15; 146	< 1 y No Parent questionnaire	5 y	Parent-reported physician's diagnosis	Exposure to AB in first y of life not associated with increased risk. • OR 0.96 (95%CI 0.50-1.85), p=0.91* • 1 AB course: aOR 0.90 (95%CI 0.40-2.20), p=nr • ≥ 2 AB courses: aOR 0.70 (95%CI 0.30-1.50), p=nr	Sex, family history of atopy, income
McKeever et al.[182] UK 2002	Single-centre prospective cohort study (2b)	2,948; 23,604 nr; 15,775 nr; 7,829	< 1 y Yes Medical records	< 11 y 3.5 (mean)	Oxford Medical Information System (OXMIS), ICD-8 or Read codes	Exposure to AB in first y of life not associated with increased risk. • 1 AB course: aHR 1.14 (95%CI 0.94-1.38), p=nr • 2 AB courses: aHR 1.13 (95%CI 0.92-1.40), p=nr • 3 AB courses: aHR 0.95 (95%CI 0.74-1.22), p=nr • 4 AB courses: aHR 1.29 (95%CI 0.99-1.69), p=nr • > 4 AB courses: aHR 1.14 (95%CI 0.88-1.47), p=nr • penicillin: aHR 1.05 (95%CI 0.87-1.26), p=nr • amoxicillin: aHR 1.05 (95%CI 0.91-1.21), p=nr • amoxicillin/clavulanic acid: aHR 0.94 (95%CI 0.67-1.32) p=nr • cephalosporins: aHR 1.01 (95%CI 0.81-1.26), p=nr • macrolides: aHR 1.09 (95%CI 0.94-1.27), p=nr	Number of GP visits

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Wjst et al.[155] Germany 2001	Multicentre cross-sectional study (3b)	180; 2,512 nr; 2,025 nr; 487	< 5-14 y No Medical records	5-14 y	Questionnaire for allergic rhinitis symptoms (ISAAC)	Exposure to AB in first y of life not associated with increased risk. • aOR 2.30 (95%CI 0.80-6.50), p=0.13	Age, sex, family history of atopy, season, parental education
Droste et al.[43] Belgium 2000	Multicentre cross-sectional study (3b)	67; 1,180 34; 375 33; 805	< 1 y No Parent questionnaire	7-8 y	Questionnaire for allergic rhinitis symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk in high-risk children. • **aOR 2.30 (95%CI 1.30-3.80) p<0.01**	Sex, family history of atopy, number of siblings, living area, smoking during pregnancy, smoke exposure
Ponsonby et al.[112] Australia 1999	Multicentre prospective cohort study (2b)	162; 864 24; 117 138; 747	< 1 m No Parent questionnaire	2.1 y (mean)	Questionnaire for allergic rhinitis symptoms (ISAAC)	Exposure to AB in first m of life not associated with increased risk. • aRR 0.95 (95%CI 0.62-1.44), p=nr	Age, prematurity, birth weight, smoking family history of atopy, breastfeeding, household size, gas heater in living room
Von Mutius et al.[181] Germany 1999	Single-centre cross-sectional study (3b)	222; 5,006 179; 3,904 43; 1,102 487; 5,267 403; 4,006 84; 1,261	< 3 y No Medical records	5-7 y 9-11 y	Questionnaire for allergic rhinitis symptoms (ISAAC)	Exposure to AB in first 3 y of life not associated with increased risk. • OR 1.18 (95%CI 0.84-1.66), p=0.33* Exposure to AB in first 3 y of life associated with increased risk. • **OR 1.57 (95%CI 1.23-2.00), p<0.01***	
Wickens et al.[154] New Zealand 1999	Multicentre retrospective cross-sectional study (3b)	81; 447 70; 334 11; 113	< 10 y No Parent questionnaire	5-10 y	Questionnaire for allergic rhinitis symptoms (ISAAC)	Exposure to AB in first 10 y of life not associated with increased risk. • aOR 1.99 (95%CI 0.93-4.26), p=nr	Age, sex, ethnicity, family history of atopy, household size, parental smoking
Farooqi et al.[48] UK 1998	Single-centre retrospective cohort study (2b)	484; 1,855 374*; 1,237 110*; 618	< 2 y Yes Medical records	6-12 y	Physician's diagnosis of seasonal nasal or ocular irritation	Exposure to AB in first 2 y of life associated with increased risk. • **OR 2.04 (95%CI 1.59-2.62), p<0.01** Results according to antibiotic class nr	

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Wheezing							
Zou et al.[161] China 2020	Multicentre cross-sectional study (3b)	3,584; 12,667 1,082; 3,049 2,502; 9,618	< 1 y No Parent questionnaire	4-6 y	Questionnaire for wheezing symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.44 (95%CI 1.30-1.60), p<0.01**	Age, sex, living area, family history of atopy, breastfeeding, home decoration, pet, smoke and home dampness-related exposure
Norbäck et al.[103] China 2019	Multicentre retrospective cohort study (2b)	7,831; 39,782 6,442; 29,303 1,389; 10,479	< 1 y No Parent questionnaire	3-6 y	Parent-reported physician's diagnosis	Exposure to AB in first y of life associated with increased risk. • **aOR 1.66 (95%CI 1.52-1.82), p<0.01** • 1 AB course: **aOR 1.24 (95%CI 1.14-1.34), p<0.01** • > 1 AB courses: **aOR 1.57 (95%CI 1.46-1.69), p<0.01**	Living city, time spend outdoors, air pollution, temperature in each city
Oosterloo et al.[105] Netherlands 2018	Multicentre prospective cohort study (2b)	149; 436 62; 151 87; 285	< 1 w No Parent questionnaire	0-1 y	Parent-reported wheezing	Exposure to AB in first w of life not associated with increased risk. • aOR 1.56 (95%CI 0.99-2.46), p=0.06	Family history of atopy, parental education, day care, number of siblings, smoking during pregnancy, delivery mode, duration of breastfeeding, household smoking
Yamamoto-Hanada et al.[157] Japan 2017	Multicentre prospective cohort study (2b)	148; 902 81; 436 67; 466	< 2 y Yes Parent questionnaire	5 y	Questionnaire for wheezing symptoms (ISAAC) plus medical records	Exposure to AB in first 2 y of life not associated with increased risk. • aOR 1.24 (95%CI 0.86-1.78), p=0.26 • penicillins: aOR 1.16 (95%CI 0.61-2.18), p=0.65 • cephem: aOR 1.39 (95%CI 0.92-2.09), p=0.12 • macrolides: aOR 1.04 (95%CI 0.66-1.64), p=0.86	Sex, maternal age, BMI, education, history of atopy; parity, day care, smoking during pregnancy, gestational age, delivery mode, number of LRTIs
Han et al.[59] Argentina 2017	Multicentre cross-sectional study (3b)	224; 1,517 175; 921 49; 596	< 1 y No Parent questionnaire	6-7 y	Questionnaire for wheezing symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.80 (95%CI 1.30-2.60), p<0.01**	Number of LRTIs, paracetamol use

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Eldeirawi et al.[191] USA 2015	Multicentre cross-sectional study (3b)	107; 1,789 63; 803 44; 986	< 1 y No Parent questionnaire	1 y	Questionnaire for wheezing (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.64 (95% CI, 1.53-3.55), p=0.04** • 1-2 AB courses: aOR 1.24 (95%CI 0.73-2.12), p=42 • ≥ 3 AB courses: **aOR 2.47 (95%CI 1.39-4.38), p<0.01**	Age, sex, country of birth, family history of atopy, having a regular doctor or clinic, number of ear infections
Sun et al.[137] China 2015	Multicentre prospective cohort study (2b)	29; 606 nr; 142 nr; 464	< 3 y Yes Parent questionnaire	6 m-3 y	Questionnaire for wheezing symptoms (ISAAC)	Exposure to AB in first 3 y of life associated with increased risk in children with high atopic risk factors. • **aRR 1.09 (95%CI 1.05-1.13), p<0.05** • penicillin: aRR 1.00 (95%CI 0.94-1.05), p=nr • ampicillin: aRR 0.99 (95%CI 0.94-1.03), p=nr • cephalosporins: aRR 1.02 (95%CI 1.00-1.05), p=nr • macrolides: **aRR 1.09 (95%CI 1.05-1.13), p<0.05** • trimethoprim: aRR 0.98 (95%CI 0.88-1.09), p=nr • broad-spectrum AB: aRR 1.02 (95%CI 0.98-1.06), p=nr	Family history of atopy, country, maternal education, birth order
Lapin et al.[164] USA 2014	Multicentre prospective cohort study (2b)	65; 295 nr; 162 nr; 133	< 1 y No nr	2-3 y	Parent-reported wheezing	Exposure to AB in first y of life associated with increased risk in high-risk children. • **aOR 1.29 (95%CI 1.07-1.55), p=nr**	Ethnicity, smoking during pregnancy, antibiotic and medication use during pregnancy, maternal asthma, birth weight, breastfeeding, household smoking
Ong et al.[104] Australia 2014	Multicentre retrospective cohort study (2b)	5,460; 62,576 3,190* 26,693 2,270*; 35,883	< 1 y No Registry	< 3 y	ICD-9 codes	Exposure to AB in first y of life associated with increased risk. • **OR 2.00 (95%CI 1.90-2.20), p<0.01**	
Semic-Jusufagic et al.[126] UK 2014	Multicentre prospective cohort study (2b)	199; 684 nr; nr nr; nr	< 1 y No Parent questionnaire	1-11 y	Parent-reported plus medical records	Exposure to AB in first y of life associated with increased risk. • **OR 1.91 (95%CI, 1.29-2.83), p<0.01**	

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Muc et al.[97] Portugal 2013	Multicentre cross-sectional study (3b)	357; 1,037 117*; 237 240*; 800	< 1 y No Parent questionnaire	6-9 y	Questionnaire for wheezing symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 2.33 (95%CI 1.70-3.18), p<0.01**	Age, sex, prematurity, atopy
Raciborski et al.[115] Poland 2012	Multicentre retrospective cohort study (2b)	197; 1,330 150; 820 47; 510	< 1 y No Parent questionnaire	6-8 y	Questionnaire for wheezing symptoms (ISAAC and ECRHS II)	Exposure to AB in first y of life associated with increased risk. • **OR 2.21 (95%CI 1.56-3.12), p<0.01*** • 1 AB course: OR 1.12 (95%CI nr), p=0.61 • 2-3 AB courses: **OR 1.93 (95%CI nr), p<0.01** • > 3 AB courses: **OR 4.68 (95%CI 2.60-12.01), p<0.01**	
		197; 1,321 185; 1,145 12; 176	1-3 y No Parent questionnaire			Exposure to AB in first to third y of life associated with increased risk. • **OR 2.63 (95%CI 1.44-4.83), p<0.01*** • 1-2 AB courses: OR 1.41 (95%CI nr), p=0.31 • 3-4 AB courses: **OR 1.89 (95%CI nr), p=0.06** • > 4 AB courses: **OR 4.73 (95%CI 1.41-15.90), p<0.01**	
Kwon et al.[165] Korea 2011	Multicentre cross-sectional study (3b)	442; 3,765 nr; nr nr; nr	< 1 y No Parent questionnaire	9.5 y (mean)	Questionnaire for wheezing (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.88 (95%CI 1.35-2.62), p<0.01**	Age, sex, parental asthma, maternal education and BMI; smoke exposure
Rusconi et al.[119] Italy	Multicentre cross-sectional study (3b)	1,598; 16,933 1,114; 5,863 484; 11,070	< 1 y No	< 2 y	Early transient wheezing Questionnaire for wheezing (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 3.76 (95%CI 3.31-4.27), p=nr**	Age, sex, study centre, person who completed the questionnaire, maternal age, family history of atopy, day care, number of siblings,

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Table 1 (*continued*)

2011		910; 16,933	Parent questionnaire	< 4-5 y	Persistent wheezing Questionnaire for wheezing (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 3.06 (95%CI 2.60-3.60), p=nr**	sharing a bedroom, parental education, smoking during pregnancy, prematurity, season, breastfeeding, dampness-related exposure
		596; 5,345 314; 11,588					
		1,011; 16,933		4-5 until 6-7 y	Late-onset wheezing Questionnaire for wheezing (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.18 (95%CI 1.02-1.38), p=nr**	
		412; 5,161 599; 11,772					
Goksor et al.[56] Sweden 2011	Multicentre prospective cohort study (2b)	245; 4,495 26; 203 219; 4,292	< 1 w No Parent questionnaire	4.5 y	Questionnaire for wheezing symptoms (ISAAC and BAMSE)	Exposure to AB in first w of life associated with increased risk. • **aOR 2.20 (95%CI 1.30-3.80), p<0.05**	Prematurity, delivery mode
Dom et al.[40] Belgium 2010	Multicentre prospective cohort study (2b)	235; 667 210; 586 25; 81	< 4 y No Parent questionnaire	6 m-4 y	Questionnaire for wheezing symptoms (ISAAC)	Exposure to AB before first y of life not associated with increased risk. • OR 1.25 (95%CI 0.76-2.06), p=0.38*	Sex, maternal age, family history of atopy, day care, number of siblings, parental education, smoking during pregnancy, pet exposure during pregnancy, birth weight, number of LRTIs, breastfeeding, household smoking, pet exposure
Mai et al.[178] Sweden 2010	Single-centre prospective cohort study (2b)	482; 3,306 254; 1,420 228; 1,886	< 1 y No Parent questionnaire	4 y	Questionnaire for wheezing symptoms (BAMSE based on ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.40 (95%CI 1.20-1.80), p=nr** • ≥ 2 AB courses: **aOR 1.60 (95%CI 1.10-2.20), p<0.01**	Sex, maternal age and smoking; family history of atopy, number of siblings, breastfeeding
		330; 3,306		8 y		Exposure to AB in first y of life associated with increased risk.	
		170; 1,420 160; 1,886				• **aOR 1.40 (95%CI 1.10-1.70), p=nr**	

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Karimi et al.[162] Iran 2009	Multicentre cross-sectional study (3b)	141; 1,476 95; 953* 46; 523*	< 1 y No nr	6-7 y	Questionnaire for wheezing symptoms (ISAAC)	Exposure to AB in first y of life not associated with increased risk. • OR 1.13 (95%CI 0.77-1.67), p=0.50	
Mitchell et al.[95] New Zealand 2009	Multicentre cross-sectional study (3b)	2,315; 10,423 1,764; 6,476 551; 3,947	< 1 y No Parent questionnaire	6-7 y	Questionnaire for wheezing symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.78 (95%CI 1.56-2.04), p<0.01**	Sex, ethnicity, country of birth, number of siblings, socioeconomic status, medication use, maternal smoking
Alm et al.[15] Sweden 2008	Multicentre prospective cohort study (2b)	994, 4,921 67; 219 927; 4,702	< 1 m No Parent questionnaire	1 y	Questionnaire for wheezing (BAMSE study)	Exposure to AB in first m of life associated with increased risk. • **aOR 1.60 (95%CI 1.00–2.50), p=0.04**	Sex, prematurity, neonatal intensive-care unit admission, smoking during pregnancy, family history of atopy, light sleep at 12 months, breastfeeding, pacifier use
Kusel et al.[80] Australia 2008	Multicentre prospective cohort study (2b)	56; 198 34*; 107 22*; 91	< 1 y Yes Parent questionnaire	0-5 y	Parent-reported current wheeze	Exposure to AB in first y of life not associated with increased risk. • aOR 1.00 (95%CI 0.50-2.20), p=nr Results according to antibiotic class nr	Sex, day care, number of GP visits, pet exposure
Simon et al.[192] USA 2008	Multicentre prospective cohort study (2b)	117; 239 67; 142 50; 97	< 6 m No Medical records	1-4 y	Parent-reported	Exposure to AB in first 6 m of life associated with increased risk. • **aRR 1.60 (95%CI 1.00-2.60), p=0.05**	Sex, family history of atopy, day care, birth order, fever, breastfeeding, pet exposure
Verhulst et al.[193] Belgium 2008	Multicentre prospective cohort study (2b)	36; 154 25*; 76 11*; 78	< 1 y No Parent questionnaire	1 y	Questionnaire for wheezing (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **OR 2.94 (95%CI 1.59-5.43), p<0.01**	

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Harris et al.[bu] UK 2007	Single-centre prospective cohort study (2b)	79; 523 30; nr 49; nr	< 5 y No Medical records	8 y	Questionnaire for wheezing (ISAAC)	Exposure to AB in first 5 y of life associated with increased risk. • **aOR 1.07 (95%CI 1.03-1.10), p<0.01**	Family history of atopy, birth order, smoke exposure
Sharma et al.[166] India 2007	Multicentre prospective cohort study (2b)	300; 8,470 147*; 3,260 153*; 5,210	5-13 y No Parent questionnaire	6-14 y	Questionnaire for wheezing (ISAAC)	Exposure to AB in infancy associated with increased risk. • **OR 1.60 (95%CI 1.10-2.10), p<0.01**	
Kummeling et al.[79] Netherlands 2007	Multicentre prospective cohort study (2b)	265; 2,462 93; 489 172; 1,973	< 6 m No Parent questionnaire	2 y	Questionnaire for wheezing symptoms (ISAAC)	Exposure to AB in first 6 m of life associated with increased risk. • **aOR 2.65 (95%CI, 1.95-3.60), p=nr**	Sex, family history of atopy, day care, number of siblings, delivery mode, vaccination status, fever, breastfeeding, pet and smoke exposure
Floistrup et al.[49] Netherlands, Austria, Germany, Sweden, Switzerland 2006	Multicentre cross-sectional study (3b)	396; 4,606 113*; 788 283*; 3,818	< 1 y No Parent questionnaire	7-11 y	Parent-reported physician's diagnosis	Exposure to AB in first y of life associated with increased risk. • **aOR 2.05 (95%CI 1.48-2.85), p=nr**	Age, sex, family history of atopy, number of siblings, country, parental education, measles infection, vaccination status, medication use, smoking during pregnancy, diet, household smoking, pet exposure
Ahn et al.[13] Korea 2005	Multicentre cross-sectional study (3b)	1,352; 25,787 480*; 6,273 872*; 19,514	< 1 y No Parent questionnaire	7-12 y	Questionnaire for wheezing symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.52 (95%CI 1.32-1.75), p<0.01** • 1-2 AB courses: **aOR 1.31 (95%CI 1.11-1.56), p<0.01** • 3-4 AB courses: aOR 1.23 (95%CI 0.94-1.61), p=nr	Episodes of fever or acute gastroenteritis

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Awasthi et al.[194] India 2004	Multicentre cross-sectional study (3b)	188; 1,492 46; 142 142; 1,350	< 1 y No Parent questionnaire	6-7 y	Questionnaire for wheezing symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 3.06 (95%CI 1.92-4.88), p=nr**	Maternal education, diet, exercise
Cohet et al.[37] New Zealand 2004	Single-centre case-control study (3b)	938; 3,927 738; 2,684 200; 1,243	< 1 y No Parent questionnaire	6-7 y	Questionnaire for wheezing symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **OR 1.78 (95%CI 1.49-2.14), p=nr**	
Wjst et al.[155] Germany 2001	Multicentre cross-sectional study (3b)	562; 2,512 171; 2,025 391; 487	< 5-14 y No Parent questionnaire	5-14 y	Questionnaire for wheezing symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.90 (95%CI 1.20-3.30), p=0.01**	Age, sex, family history of atopy, season, parental education
Wickens et al.[154] New Zealand 1999	Multicentre retrospective cross-sectional study (3b)	138; 447 117; 334 21; 113	< 10 y No Parent questionnaire	5-10 y	Questionnaire for wheezing symptoms (ISAAC)	Exposure to AB in first 10 y of life associated with increased risk. • **aOR 1.86 (95%CI 1.06-3.26), p=nr**	Age, sex, ethnicity, family history of atopy, household size, parental smoking
Asthma							
Aversa et al.[172] USA 2021	Multicentre prospective cohort study (2b)	1,176; 14,572 964; 10,220 212; 4,352	< 2 y Yes Medical records	6-11 y	ICD-9 and ICD-10 codes	Exposure to AB in first 2 y of life associated with increased risk. • **aHR 1.90 (95%CI 1.63-2.20), p<0.01**	Sex, ethnicity, maternal age and education, antibiotic use during pregnancy, birth weight, delivery mode, maternal smoking

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						Girls • penicillins: **HR 1.50 (95%CI 1.21-1.87), p<0.01** • cephalosporins: **HR 1.39 (95%CI 1.13-1.71), p<0.01** • macrolides: **HR 1.33 (95%CI 1.08-1.62), p<0.01** • sulfonamides: HR 1.27 (95%CI 0.93-1.74), p=0.13 Boys • penicillins: **HR 1.35 (95%CI 1.12-1.62), p<0.01** • cephalosporins: **HR 1.29 (95%CI 1.09-1.53), p<0.01** • macrolides: **HR 1.34 (95%CI 1.14-1.58), p<0.01** • sulfonamides: HR 0.92 (95%CI 0.66-1.27), p=0.60	
Neto et al.[101] Brazil 2020	Multicentre cross-sectional study (3b)	339; 850 180*; 368 159*; 482	< 6 m No Parent questionnaire	9-12 y	Questionnaire for asthma symptoms (ISAAC)	Exposure to AB in first 6 m of life associated with increased risk. • **aOR 1.57 (95%CI 1.13-2.17), p<0.01**	Maternal asthma, shared bedroom, number of LRTIs, atopy, medication use, pet exposure
Donovan et al.[41] USA 2020	Single-centre retrospective cohort study (4)	20,984; 152,622 18,233; 120,973 2,751; 31,649	< 1 y Yes Medical records	4.5-6 y	ICD-9-CM codes plus prescription records	Exposure to AB in first y of life associated with increased risk. • **aOR 1.88 (95%CI 1.80-1.96), p=nr** Results according to antibiotic class nr	Age, sex, ethnicity, maternal age and education; household size, living area, marital status, smoking during pregnancy, gestational age, birth weight, season of birth, delivery mode, medication use, pet exposure
Levin et al.[82] South Africa 2020	Multicentre prospective cohort study (2b)	106; 1,185 83; 654 23; 531 4; 398 4; 347 0; 51	< 1 y No Parent questionnaire	12-36 m	Questionnaire for asthma symptoms (based on ISAAC)	Exposure to AB in first y of life associated with increased risk in urban cohort. • **OR 3.21 (95%CI 1.99-5.17), p<0.01*** Exposure to AB in first y of life not associated with increased risk in rural cohort. • OR 1.35 (95%CI 0.07-25.43), p=0.84*	

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Patrick et al.[109] Canada 2020	Multicentre prospective cohort study (2b)	118; 1,947 29; 289 89; 1,658	< 1 y Yes Registry	5 y	Questionnaire for asthma symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 2.15 (95%CI 1.37-3.39), p<0.01** • 1 AB course: **aOR 1.93 (95%CI 1.15-3.26), p=0.01** • 2 AB courses: aOR 2.66 (95%CI 0.99-7.18), p=0.05 • ≥ 3 AB courses: **aOR 3.25 (95%CI 1.05-10.08), p=0.04** Results according to antibiotic class nr	Sex, ethnicity, study centre, family history of atopy, number of siblings, birth weight, season of birth, delivery mode, breastfeeding, smoke and environmental nitrogen dioxide exposure
Zou et al.[161] China 2020	Multicentre cross-sectional study (3b)	1,285; 12,667 412; 3,049 873; 9,618	< 1 y No Parent questionnaire	4-6 y	Questionnaire for asthma symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.38 (95%CI 1.19-1.61), p<0.01**	Age, sex, living area, family history of atopy, breastfeeding, home decoration, pet, smoke and home dampness-related exposure
Ni et al.[102] USA 2019	Single-centre retrospective cohort study (4)	177; 2,398 128*; 1,060 49*; 1,338	< 1 y Yes Medical records	1-10 y	ICD-9 and ICD-10 codes	Exposure to AB in first y of life associated with increased risk. • **aOR 2.66 (95%CI 1.11-6.40), p=0.03** Results according to antibiotic class nr	Age, sex, ethnicity, socioeconomic status, prematurity, birth weight, delivery mode, neonatal intensive-care unit admission
		253; 2,398 211*; 1,755 42*; 643	< 10 y Yes Medical records			Exposure to AB in first 10 y of life associated with increased risk. • **aOR 3.54 (95%CI 1.99-6.30), p<0.01** Results according to antibiotic class nr	
Metzler et al.[93] Switzerland 2019	Multicentre prospective cohort study (2b)	73; 1,019 35; 419 38; 600	< 1 y No Parent questionnaire	< 6 y	Questionnaire for asthma symptoms (based on ISAAC) plus parent-reported physician's diagnosis	Exposure to AB in first y of life associated with increased risk. • **aOR 1.65 (95%CI 0.95-2.86), p<0.05**	Sex, family history of atopy, number of siblings, living area, smoking during pregnancy, pet exposure during pregnancy, delivery mode, duration of breastfeeding, pet exposure

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Norbäck et al.[103] China 2019	Multicentre retrospective cohort study (2b)	2,936; 39,782 2,586; 29,303 250; 10,479	< 1 y No Parent questionnaire	3-6 y	Parent-reported physician's diagnosis	Exposure to AB in first y of life associated with increased risk. • **aOR 2.03 (95%CI 1.72-2.40), p<0.01** • 1 AB course: **aOR 1.26 (95%CI 1.11-1.44), p<0.01** • > 1 AB courses: **aOR 2.08 (95%CI 1.87-2.33), p<0.01**	Living area, time spend outdoors, air pollution, temperature in each city
Soto-Martinez et al.[132] Costa Rica 2019	Multicentre cross-sectional study (3b)	595; 2,689 380; 1,290 215; 1,399	< 1 y No Parent questionnaire	6-13 y	Questionnaire for asthma symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.20 (95%CI 1.01-1.43), p=0.04**	Atopy, dry cough, medication use, traffic exposure
Chen et al.[34] Taiwan 2018	Multicentre case-control study (3b)	2,082; 4,164 1,849; 3,512 233; 652	< 5 y before diagnosis Yes Registry	2-18 y	ICD-9-CM codes plus prescription records (ATC codes)	Exposure to AB in 5 y before diagnosis associated with increased risk. • **aOR 2.10 (95%CI 1.75-2.52), p<0.01** • low-dose: **aOR 1.64 (95%CI 1.35-2.01), p<0.01** • moderate-dose: **aOR 2.23 (95%CI 1.81-2.74), p<0.01** • high-dose: **aOR 3.33 (95%CI 2.67-4.15), p<0.01** • penicillins: **aOR 1.77 (95%CI 1.43-2.20), p<0.01** • cephalosporins: **aOR 1.67 (95%CI 1.32-2.11), p<0.01** • macrolides: **aOR 2.02 (95%CI 1.48-2.76), p<0.01**	Age, sex, living area, comorbidities, medication use
Mitre et al.[96] USA 2018	Multicentre retrospective cohort study (2b)	111,792; 792,130 27,488; 131,708 84,304; 660,422	< 6 m No Registry	1-6 y	ICD-9-CM codes	Exposure to AB in first 6 m of life associated with increased risk. • **aHR 2.09 (95%CI 2.05-2.13), p=nr**	Sex, prematurity, delivery mode, medication (incl. anti-reflux medication) use
Strömberg et al.[134] Sweden 2018	Multicentre prospective cohort study (2b)	233; 3,637 19; 152 214; 3,485	< 1 w No Parent questionnaire	12 y	Atopic asthma Questionnaire for asthma symptoms (ISAAC and BAMSE)	Exposure to AB in first w of life associated with increased risk. • **aOR 2.20 (95%CI 1.20-4.20), p<0.05**	Family history of atopy, prematurity, weight for gestational age, delivery mode
					Non-atopic asthma Questionnaire for asthma symptoms (ISAAC and BAMSE)	Exposure to AB in first w of life not associated with increased risk. • aOR 1.40 (95%CI 0.50-3.40), p=nr	

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Yoshida et al.[195] Japan 2018	Multicentre retrospective cohort study (2b)	3,633; 83,470 2,517; 46,562 1,116; 36,908	< 1 y Yes Registry	1-3 y	ICD-10 codes plus prescription records	Exposure to AB in first y of life associated with increased risk. • **aHR 2.43 (95%CI 2.20-2.69), p=nr** • 1-2 AB courses: **aHR 1.89 (95%CI 1.69-2.11), p=nr** • 3-4 AB courses: **aHR 2.93 (95%CI 2.58-3.33), p=nr** • > 5 AB courses: **aHR 4.66 (95%CI 4.04-5.36), p=nr** • penicillins: **aHR 1.39 (95%CI 1.26-1.53), p=nr** • cephalosporins: **aHR 1.55 (95%CI 1.41-1.70), p=nr** • macrolides: **aHR 2.00 (95%CI 1.83-2.20), p=nr**	Sex
				3-6 y		Exposure to AB in first y of life associated with increased risk. • **aHR 1.23 (95%CI 1.11-1.36), p=nr** • 1-2 AB courses: **aHR 1.15 (95%CI 1.03-1.29), p=nr** • 3-4 AB courses: **aHR 1.28 (95%CI 1.11-1.48), p=nr** • > 5 AB courses: **aHR 1.53 (95%CI 1.28-1.83), p=nr** • penicillins: **aHR 0.87 (95%CI 0.76-0.98), p=nr** • cephalosporins: **aHR 1.20 (95%CI 1.08-1.33), p=nr** • macrolides: **aHR 1.17 (95%CI 1.05-1.31), p=nr**	
Ahmadizar et al.[12] Netherlands Scotland 2017	Multicentre prospective cohort study (2b)	74; 891 28*; 260 46*; 631	< 6 m No Parent questionnaire	9-10 y	Parent-reported physician's diagnosis	Exposure to AB in first 6 m of life not associated with increased risk. • aOR 1.50 (95%CI 0.91-2.46), p=nr	Sex, family history of asthma
		448, 3,960 414*; 3,178 34*; 782	< 3 y No Parent questionnaire	10 y		Exposure to AB in first 3 y of life associated with increased risk. • **aOR 2.84 (95%CI 1.70-4.75), p=nr**	Sex, family history of atopy

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Han et al.[59] Argentina 2017	Multicentre cross-sectional study (3b)	58; 1,517 44; 921 14; 596	< 1 y No Parent questionnaire	6-7 y	Questionnaire for asthma symptoms (ISAAC)	Exposure to AB in first y of life not associated with increased risk. • aOR 1.30 (95%CI 0.60-2.60), p=nr	Number of LRTIs, medication use
Yamamoto-Hanada et al.[157] Japan 2017	Multicentre prospective cohort study (2b)	95; 902 58; 436 37; 466	< 2 y Yes Parent questionnaire	5 y	Questionnaire for asthma symptoms (ISAAC) plus medical records	Exposure to AB in first 2 y of life associated with increased risk. • **aOR 1.72 (95%CI 1.10-2.70), p=0.02** • penicillins: aOR 1.21 (95%CI 0.58-2.56), p=0.61 • cephem: **aOR 1.97 (95%CI 1.23-3.16), p<0.01** • macrolides: aOR 1.46 (95%CI 0.88-2.44), p=0.15	Sex, maternal age, BMI, education, maternal and history of atopy, parity, day care, smoking during pregnancy, gestational age, delivery mode, number of LRTIs,
Wu et al.[156] USA 2016	Multicentric prospective cohort study (2b)	18,087; 136,098 13,740*; 99,054 4,347*; 37,044	< 1 y No Medical records	4.5-6 y	ICD-9-CM codes	Exposure to AB in first y of life associated with increased risk. • **aOR 1.16 (95% CI, 1.15-1.18), p=nr**	Sex, ethnicity, maternal age, education, and asthma; number of siblings, smoking during pregnancy, gestational age, neonatal intensive-care unit admission, birth weight, delivery mode, number of LRTIs, comorbidities, healthcare use
Korpela et al.[75] Finland 2016	Multicentre case-control study (3b)	16*; 148 9*; 32 7*; 116	< 2 y Yes Registry	2-7 y	Parent-reported physician's diagnosis	Exposure to AB in first 2 y of life associated with increased risk. • macrolides: **OR 6.11 (95%CI 1.53-26.58), p<0.01**	
Pitter et al.[111] Italy 2016	Multicentre retrospective cohort study (2b)	34,957; 143,163 16,406; 54,685 18,551; 88,478	< 1 y Yes Registry	13 m-18 y	ICD-9 codes plus prescription records (ATC codes)	Exposure to AB in first y associated with increased risk. • **aIRR 1.50 (95%CI 1.46-1.53), p<0.05**	Age, sex, maternal age, and education; gestational age, birth weight, hospital admissions for infections

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						• penicillins: **aIRR 1.43 (95%CI 1.40-1.46), p<0.05** • cephalosporins: **aIRR 1.36 (95%CI 1.32-1.40), p<0.05** • macrolides: **aIRR 1.57 (95%CI 1.52-1.63), p<0.05** • 1-2 AB courses: **aIRR 1.41 (95%CI 1.38-1.44), p<0.01** • 3-4 AB courses: **aIRR 1.84 (95%CI 1.77-1.92), p<0.01** • ≥ 5 AB courses: **aIRR 2.13 (95%CI 2.00-2.28), p<0.01**	
Krenz-Niedbala et al.[77] Poland 2015	Multicentre cross-sectional study (3b)	130; 1,277 59*; 433 71*; 844	< 1 y No Parent questionnaire	8 y	Questionnaire for asthma symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **OR 1.71 (95%CI 1.29-2.26) p=nr**	
Metsälä et al.[92] Finland 2015	Multicentre case-control study (3b)	1,419; 6,690 1,212; 5,352 207; 1,338	< 6 m before diagnosis Yes Registry	3-10 y	ICD-10 codes plus prescription records (ATC codes)	Exposure to AB 6 m before diagnosis associated with increased risk. • **aOR 1.60 (95%CI 1.48-1.73), p<0.05** • penicillin: **aOR 1.33 (95%CI 1.21-1.47), p=nr** • amoxicillin: **aOR 2.35 (95%CI 2.10-2.63), p=nr** • cephalosporins: **aOR 1.91 (95%CI 1.76-2.07), p=nr** • macrolides: **aOR 2.74 (95%CI 2.50-2.99), p=nr** • trimethoprim/sulfamethoxazole: **aOR 1.98 (95%CI 1.80-2.18), p=nr**	Parity, maternal asthma, gestational age
Lee et al.[169] Korea 2015	Multicentre cross-sectional study (3b)	459; 6,161 189; 1,865 270; 4,296	< 1 y No Parent questionnaire	13.9 y (mean)	Questionnaire for asthma symptoms (based on ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.94 (95%CI 1.49-2.53) p=nr**	Age, sex, family history of atopy, income, BMI, smoke exposure
Eldeirawi et al.[191] USA 2015	Multicentre cross-sectional study (3b)	133; 1,786 92; 799 41; 987	< 1 y No Parent questionnaire	1 y	Parent-reported physician's diagnosis	Exposure to AB in first y of life associated with increased risk. • **aOR 2.33 (95% CI, 1.53-3.55), p<0.01** • 1-2 AB courses: **aOR 1.81 (95%CI 1.13-2.88), p=0.01** • ≥ 3 AB courses: **aOR 3.43 (95%CI 2.06-5.73), p<0.01**	Age, sex, country of birth, family history of atopy, having a regular doctor or clinic, number of ear infections

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Khalkhali et al.[168] Iran 2014	Single-centre prospective case-control study (3b)	157; 361 120; 230 47; 131	< 1 y No Parent questionnaire	2-8 y	Global Initiative for Asthma (GINA) criteria	Exposure to AB in first y of life associated with increased risk. • **aOR 1.91 (95%CI 1.27-2.88), p=0.03**	Family history of atopy, prematurity, delivery mode, birth order
Lapin et al.[164] USA 2014	Multicentre prospective cohort study (2b)	44; 295 nr; 162 nr; 133	< 1 y No nr	3 y	Parent-reported physician's diagnosis	Exposure to AB in first y of life associated with increased risk in high-risk children. • **aOR 1.58 (95%CI 1.27-1.96), p=nr**	Ethnicity, smoking during pregnancy, antibiotic and medication use during pregnancy, maternal asthma, birth weight, breastfeeding, household smoking
Ong et al.[104] Australia 2014	Multicentre retrospective cohort study (2b)	5,946; 62,576 3,162*; 26,693 2,784*; 35,883 6,418; 62,576 2,875*; 26,693 3,543*; 35,883	< 1 y No Registry	< 3 y > 3 y	ICD-9 codes	Exposure to AB in first y of life associated with increased risk. • **OR 1.60 (95%CI 1.50-1.70), p<0.01** Exposure to AB in first y of life not associated with increased risk. • OR 1.10 (95%CI 1.00-1.10), p=0.10	
Semic-Jusufagic et al.[126] UK 2014	Multicentre prospective cohort study (2b)	529; 800 nr; 564 nr; 236	< 1 y No Parent questionnaire	1-11 y	Parent-reported plus medical records	Exposure to AB in first y of life associated with increased risk. • **HR 2.26 (95%CI 1.03-4.94), p=0.04**	
Örtqvist et al.[196] Sweden 2014	Multicentre prospective cohort study (2b)	29,753; 493,785 25,306; 305,938 4,447; 187,847	< 2 y Yes Registry	< 5 y > 2 y	ICD-10 codes or prescription records (ATC codes)	Exposure to AB in first 2 y of life associated with increased risk. • **aHR 2.03 (95%CI 1.93-2.12), p=nr** Results according to antibiotic class nr	Sex, maternal country of birth and age; parity, parental marital status, parental education, antibiotic use during pregnancy, gestational age, birth weight,

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							delivery mode, respiratory diagnosis (respiratory distress, congenital pneumonia, neonatal aspiration syndromes, interstitial emphysema, pulmonary haemorrhage, chronic respiratory disease)
Goksor et al.[55] Sweden 2013	Multicentre prospective cohort study (2b)	231; 4,051 19; 187 212; 3,864	< 1 w No Parent questionnaire	8 y	Questionnaire for asthma symptoms (ISAAC and BAMSE)	Exposure to AB in first w of life associated with increased risk. • **aOR 2.30 (95%CI 1.20-4.20), p<0.05**	Family history of atopy, prematurity, weight for gestational age, delivery mode
Hoskin-Parr et al.[176] UK 2013	Single-centre prospective cohort study (2b)	630; 5,780 367*; 2,659 263*; 3,121	< 2 y No Parent questionnaire	7.5 y (mean)	Parents-reported physician's diagnosis	Exposure to AB in first 2 y of life associated with increased risk. • **aOR 1.75 (95%CI 1.40-2.17), p=nr** • 1 AB course: aOR 1.11 (95%CI 0.84-1.48), p=nr • **2 AB courses: aOR 1.50 (95%CI 1.14-1.98), p=nr** • **3 AB courses: aOR 1.79 (95%CI 1.34-2.40), p=nr** • **≥ 4 AB courses: aOR 2.82 (95%CI 2.19-3.63), p=nr**	Age, sex, maternal age and education; parental marital status, home ownership status, degree of difficulty in paying for food, smoking during pregnancy, disinfectant use during pregnancy, gestational age, birth weight, delivery mode, age of child at outcome, breastfeeding, time spend outdoors, pet exposure
Muc et al.[97] Portugal 2013	Multicentre cross-sectional study (3b)	106; 1,037 38*; 237 68*; 800	< 1 y No Parent questionnaire	6-9 y	Questionnaire for asthma symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.96 (95%CI 1.25-3.08), p<0.01**	Age, sex, prematurity, atopy
Wang et al.[150] Taiwan 2013	Multicentre prospective cohort study (2b)	57,328; 263,620 nr; 15,663 nr; 247,957	< 1 y Yes Medical records	2-6 y	ICD-9-CM codes	Exposure to AB in first y of life associated with increased risk. • **aHR 1.38 (95%CI 1.32-1.46), p<0.05** Results according to antibiotic class nr	Sex, living area, socioeconomic status, healthcare use

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Almqvist et al.[197] Sweden 2012	Multicentre prospective cohort study (2b)	nr; 9,400,000 95,628; 211,192 nr; 9,188,808	< 3 y Yes Registry	<1 y	Prescription records (ATC codes)	Exposure to AB in first 3 y of life associated with increased risk. • **HR 2.20 (95%CI 2.12-2.28), p=nr** • 1-2 AB courses: **HR 1.72 (95%CI 1.45-2.05), p=nr** • 3-5 AB courses: **HR 1.25 (95%CI 1.86-2.72), p=nr** • ≥ 6 AB courses: **HR 2.36 (95%CI 1.76-3.16), p=nr** • narrow-spectrum: **HR 1.60 (95%CI 1.35-1.91), p=nr** • broad-spectrum: **HR 2.04 (95%CI 1.71-2.42), p=nr** Results according to antibiotic class nr
				1 y		• **HR 1.73 (95%CI 1.66-1.82), p=nr** • 1-2 AB courses: **HR 1.37 (95%CI 1.16-1.61), p=nr** • 3-5 AB courses: **HR 2.03 (95%CI 1.72-2.40), p=nr** • ≥ 6 AB courses: **HR 2.50 (95%CI 2.09-3.01), p=nr** • narrow-spectrum: **HR 1.28 (95%CI 1.09-1.50), p=nr** • broad-spectrum: **HR 1.83 (95%CI 1.56-2.15), p=nr** Results according to antibiotic class nr
				2 y		• **HR 1.29 (95%CI 1.15-1.45), p=nr** • 1-2 AB courses: HR 0.85 (95%CI 0.53-1.36), p=nr • 3-5 AB courses: HR 1.26 (95%CI 0.78-2.02), p=nr • ≥ 6 AB courses: **HR 1.77 (95%CI 1.10-2.86), p=nr** • narrow-spectrum: HR 0.96 (95%CI 0.65-1.41), p=nr • broad-spectrum: HR 1.38 (95%CI 0.94-2.04), p=nr Results according to antibiotic class nr
				≥ 3 y		• HR 1.15 (95%CI 0.73-1.83), p=nr Results according to antibiotic class nr

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Raciborski et al.[115] Poland 2012	Multicentre retrospective cohort study (2b)	63; 1,330 52; 820 11; 510	< 1 y No Parent questionnaire	6-8 y	Questionnaire for asthma symptoms (ISAAC and ECRHS II)	Exposure in first y of life associated with increased risk when ≥ 2 AB courses. • 1 AB course: OR 1.54 (95%CI nr), p=0.30 • 2 AB courses: **OR 2.55 (95%CI nr), p=0.02** • > 3 AB courses: **OR 5.59 (95%CI 2.6-12.01), p<0.01**	
		63; 1,321 60; 1,145 3; 176	1-3 y No Parent questionnaire			Exposure in second and third y of life associated with increased risk when > 4 AB courses. • 1-2 AB courses: OR 1.42 (95%CI nr), p=0.59 • 3-4 AB courses: OR 2.87 (95%CI nr), p=0.09 • > 4 AB courses: **OR 4.73 (95%CI 1.41-15.90), p<0.01**	
Jedrychowski et al.[69] USA 2011	Multicentre prospective cohort study (2b)	29; 310 26*; 244 3*; 66	< 2 y Yes Parent questionnaire	5 y	Parent-reported physician's diagnosis	Exposure to AB in first 5 y of life associated with increased risk. • **aOR 2.08 (95%CI 1.32-3.28), p=nr** • penicillins: aOR 1.49 (95%CI 0.89-2.49), p=nr • cephalosporins: **aOR 2.45 (95%CI 1.49-4.02), p=nr** • macrolides: **aOR 2.14 (95%CI 1.16-3.95), p=nr**	Age, maternal atopy and education, parity, smoke exposure
Risnes et al.[116] USA 2011	Multicentric prospective cohort study (2b)	164; 1,401 65; 464 99; 937	< 6 m No Parent questionnaire	6 y	ICD-9 codes	Exposure to AB in first 6 m of life associated with increased risk. • **aOR 1.52 (95% CI, 1.07-2.16), p=nr** • 1 AB course: aOR 1.40 (95%CI 0.90-2.15), p=nr • ≥ 2 AB courses: aOR 1.72 (95%CI 1.11-2.65), p=0.01	Maternal age, family history of asthma, income, number of LRTIs
Sandini et al.[177] Finland 2011	Single-centre prospective cohort study (2b)	121; 891 nr; nr nr; nr	< 6 m No Parent questionnaire	5 y	Parent-reported physician's diagnosis	Exposure to AB in first 6 m of life not associated with increased risk. • OR 0.90 (95%CI 0.41-1.98), p=0.79	

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Yeh et al.[159] Taiwan 2011	Multicentre cross-sectional study (3b)	566; 2,037 nr; nr nr; nr	< 1 y No Parent questionnaire	3-6 y	Questionnaire for asthma symptoms (ISAAC) plus parent-reported physician's diagnosis	Exposure to AB in first y of life associated with increased risk. • **OR 2.35 (95%CI 1.52-3.66), p<0.01**	
Su et al.[135] USA 2010	Multicentre prospective cohort study (2b)	50; 424 22; 136 28; 288	< 9 m No Parent questionnaire	1-5 y	Parent-reported physician's diagnosis (questionnaire for respiratory symptoms)	Exposure to AB in first 9 m of life associated with increased risk. • **aOR 1.50 (95%CI 1.10-2.10), p=0.02** Exposure to AB in first 9 m of life not associated with increased risk after adjustment for number of illness visits. • aOR 1.20 (95%CI 0.60-2.30), p=0.70	Number of illness visits
Mai et al.[178] Sweden 2010	Single-centre prospective cohort study (2b)	228; 3,306 125; 1,420 103; 1,886	< 1 y No Parent questionnaire	4 y	Questionnaire for asthma symptoms (BAMSE based on ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.50 (95%CI 1.10-2.00), p=nr** • ≥ 2 AB courses: **aOR 1.90 (95%CI 1.20-3.00), p<0.01**	Sex, maternal age and smoking; family history of atopy, number of siblings, breastfeeding
		210; 3,306 104; 1,420 106; 1,886		8 y		Exposure to AB in first y of life not associated with increased risk. • aOR 1.20 (95%CI 0.90-1.60), p=nr	
Foliaki et al.[50] Sweden 2009	Multicentre retrospective cross-sectional study (3b)	nr; 193,412 nr; 135,775 nr; 57,637	< 1 y No Parent questionnaire	6-7 y	Questionnaire for asthma symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.94 (95%CI 1.83-2.06), p=nr**	Sex, language, living area, income
Karimi et al.[162] Iran 2009	Multicentre cross-sectional study (3b)	49; 1,476 39; 950* 10; 526*	< 1 y No nr	6-7 y	Questionnaire for asthma symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **OR 2.21 (95%CI 1.05-4.80), p=0.02**	

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Martel et al.[88] Canada 2009	Multicentre prospective case-control study (3b)	5,226; 109,746 2,057; 29,509 3,169; 80,237	< 6 m No Registry	< 10 y	ICD-9 codes	Exposure to AB in first 6 m of life associated with increased risk. • **aOR 1.70 (95%CI 1.34-2.15), p=nr**	Maternal asthma
Garcia et al.[52] Colombia 2008	Multicentre cross-sectional study (3b)	175; 641 nr; 420 nr; 221	< 1 y No Parent questionnaire	6-7 y	Questionnaire for asthma symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.90 (95%CI 1.40-2.50), p<0.01**	Maternal and medication use; time spent watching television per day, pet exposure
Wickens et al.[153] New Zealand 2008	Multicentre prospective cohort study (2b)	119; 1,064 29*; 148 90*; 916	< 3 m No Parent questionnaire	15 m	Questionnaire for asthma symptoms (ISAAC)	Exposure to AB in first 3 m of life not associated with increased risk after adjustment for chest infections. • aOR 1.58 (95% CI, 0.96-2.60), p=0.07	Number of LRTIs
		168; 1,011 128*; 722 40*; 289	< 15 m No Parent questionnaire	4 y		Exposure to AB in first 15 m of life not associated with increased risk. • aOR 0.98 (95%CI 0.60-1.59), p=0.92	
Kusel et al.[80] Australia 2008	Multicentre prospective cohort study (2b)	37; 198 24*; 107 13*; 91	< 1 y Yes Parent questionnaire	0-5 y	Parent-reported current asthma	Exposure to AB in first y of life not associated with increased risk. • aOR 0.90 (95%CI 0.40-2.30), p=nr Results according to antibiotic class nr	Sex, day care, number of GP visits, pet exposure
		57; 198 39*; 107 18*; 91			Parent-reported physician's diagnosis	Exposure to AB in first y of life not associated with increased risk. • aOR 1.50 (95%CI 0.70-3.20), p=nr Results according to antibiotic class nr	

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Kozyrskyj et al.[76] Canada 2007	Multicentre prospective cohort study (2b)	787; 13,116 nr; 8,525 nr; 4,591	< 1 y Yes Registry	7 y	≥ 1 physician visits or hospitalizations for asthma or 2 prescriptions for asthma	Exposure to AB in first y of life associated with increased risk. • **aOR 1.86 (95%CI 1.02-3.37), p=nr** • 1-2 AB courses: **aOR 1.21 (95%CI 1.011.46), p=nr** • 3-4 AB courses: **aOR 1.30 (95%CI 1.04-1.63), p=nr** • > 4 AB courses: **aOR 1.46 (95%CI 1.14-1.88), p=nr** Results according to antibiotic class nr	Sex, maternal history of asthma, living area, number of siblings, number of LRTIs, healthcare use
Mullooly et al.[98] USA 2007	Single-centre case-control study (3b)	383; 844 nr; nr nr; nr	< 2 y No Medical records	10.3 y (mean)	Parent-reported physician's diagnosis	Exposure to AB in first 2 y of life not associated with increased risk. • aOR 1.02 (95%CI 0.98-1.06), p=nr	Sex, ethnicity, maternal age, birth weight, age of child at outcome, breastfeeding, household smoking
Del-Rio-Navarro et al.[39] Mexico 2006	Multicentre cross-sectional study (3b)	794; 4,106 601*; 2,583 193*; 1,523 Boys: 451; 2,098 342*; 1,364 109*; 734 Girls: 343; 2,008 259*; 1,219 84*; 789	< 1 y No Parent questionnaire	6-7 y	Questionnaire for asthma symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **OR 2.09 (95%CI 1.75-2.49), p<0.01** Exposure to AB in first y of life associated with increased risk boys. • **OR 1.92 (95%CI 1.41-2.62), p<0.01** Exposure to AB in first y of life associated with increased risk in girls. • **OR 2.27 (95%CI 1.49-3.44), p<0.01**	

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Floistrup et al.[49] Netherlands, Austria, Germany, Sweden, Switzerland 2006	Multicentre cross-sectional study (3b)	419; 4,606 161*; 788 258*; 3,818	< 1 y No Parent questionnaire	7-11 y	Parent-reported physician's diagnosis	Exposure to AB in first y of life associated with increased risk. • **aOR 2.79 (95%CI 2.03-3.83), p=nr**	Age, sex, family history of atopy, number of siblings, country, parental education, measles infection, vaccination status, medication use, smoking during pregnancy, diet, household smoking, pet exposure
Ahn et al.[13] Korea 2005	Multicentre cross-sectional study (3b)	2,354; 25,787 976*; 6,273 1,378*; 19,514	< 1 y No Parent questionnaire	7-12 y	Questionnaire for asthma symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **aOR 1.86 (95%CI 1.67-2.08), p<0.01** • 1-2 AB courses: **aOR 1.54 (95%CI 1.35-1.76), p<0.01** • 3-4 AB courses: **aOR 1.79 (95%CI 1.47-2.18), p<0.01** • ≥ 5 AB courses: **aOR 2.53 (95%CI 2.10-3.06), p<0.01**	Episodes of fever or acute gastroenteritis
Celedon et al.[198] USA 2004	Multicentre prospective cohort study (2b)	323; 4,408 280; 3,292 43; 1,116	< 1 y Yes Prescription records	1-2 y	ICD-9 codes	Exposure to AB in first y of life associated with increased risk. • **OR 2.32 (95%CI 1.67-3.22), p<0.01*** • 1-2 AB courses: **aOR 1.90 (95%CI 1.30-2.70), p<0.01** • 3-4 AB courses: aOR 1.60 (95%CI 1.10-2.40), p=0.03 • > 4 AB courses: **aOR 2.10 (95%CI 1.50-3.20), p<0.01** Results according to antibiotic class nr	Number of respiratory tract infections
		314; 4,178 241; 3,092 73; 1,086		2-5 y		Exposure to AB in first y of life not associated with increased risk. • OR 1.17 (95%CI 0.89-1.54), p=0.25 • 1-2 AB courses: aOR 1.10 (95%CI 0.80-1.40), p=0.72 • 3-4 AB courses: aOR 1.30 (95%CI 0.90-1.80), p=0.14 • > 4 AB courses: aOR 1.00 (95%CI 0.70-1.40), p=0.87 Results according to antibiotic class nr	
Cohet et al.[37] New Zealand 2004	Single-centre case-control study (3b)	1,277; 3,927 1,020; 2,684 257; 1,243	< 1 y No Parent questionnaire	6-7 y	Questionnaire for asthma symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk. • **OR 2.10 (95%CI 1.79-2.48), p=nr**	

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Celedon et al.[32] USA 2002	Multicentre prospective cohort study (2b)	38; 448 24; 314 14; 134	< 1 y No Parent questionnaire	5 y	Parent-reported physician's diagnosis (telephone questionnaire)	Exposure to AB in first y of life not associated with increased risk. • OR 0.71 (95%CI 0.35-1.42), p=0.33 • 1 AB course: aOR 0.50 (95%CI 0.20-1.40), p=nr • ≥ 2 AB courses: aOR 0.90 (0.40-1.80), p=nr	Sex, family history of atopy, income
McKeever et al.[182] UK 2002	Single-centre prospective cohort study (2b)	915; 21,129 nr; 13,497 nr; 7,632	< 1 y Yes Medical records	2.2 y (mean)	Oxford Medical Information System (OXMIS), ICD-8 or Read codes	Exposure to AB in first y of life associated with increased risk. • 1 AB course: **aHR 1.26 (95%CI 1.13-1.40), p=nr** • 2 AB courses: **aHR 1.46 (95%CI 1.30-1.65), p=nr** • 3 AB courses: **aHR 1.76 (95%CI 1.56-2.13), p=nr** • 4 AB courses: **aHR 1.82 (95%CI 1.56-2.13), p=nr** • > 4 AB courses: **aHR 1.99 (95%CI 1.72-2.31), p=nr** • penicillin: aHR 0.99 (95%CI 0.89-1.10), p=nr • amoxicillin: **aHR 1.25 (95%CI 1.16-1.36), p=nr** • amoxicillin/clavulanic acid: **aHR 1.43 (95%CI 1.19-1.72), p=nr** • cephalosporins: **aHR 1.44 (95%CI 1.28-1.63), p=nr** • macrolides: **aHR 1.41 (95%CI 1.30-1.53), p=nr**	Number of GP visits
Illi et al.[167] Germany 2001	Multicentre prospective cohort study (2b)	57; 937 22; 338 35; 599	< 3 y No Parent questionnaire	0-7 y	Parent-reported physician's diagnosis	Exposure to AB in first 3 y of life not associated with increased risk. • aOR 1.08 (95%CI 0.59-1.99), p=nr	High risk of atopy at birth (elevated cord blood IgE or family history of atopy), parental education and smoking
Wjst et al.[155] Germany 2001	Multicentre cross-sectional study (3b)	37; 2,512 nr; 2,025 nr; 487	< 5-14 y No Medical records	5-14 y	Questionnaire for asthma symptoms (ISAAC)	Exposure to AB in first y of life not associated with increased risk. • aOR 0.90 (95%CI 0.60-1.40), p=0.71	Age, sex, family history of atopy, season, parental education

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Droste et al.[43] Belgium 2000	Multicentre cross-sectional study (3b)	55; 1,206 27; 384 28; 822	< 1 y No Parent questionnaire	7-8 y	Questionnaire for asthma symptoms (ISAAC)	Exposure to AB in first y of life associated with increased risk in high-risk children. • **aOR 1.70 (95%CI 1.00-3.10), p<0.01**	Sex, family history of atopy, number of siblings, living area, smoking during pregnancy, smoke exposure
Ponsonby et al.[112] Australia 1999	Multicentre prospective cohort study (2b)	276; 856 40; 114 236; 742	< 1 m No Parent questionnaire	2.1 y (mean)	Questionnaire for asthma symptoms (ISAAC)	Exposure to AB in first m of life not associated with increased risk. • aRR 1.04 (95%CI 0.78-1.37), p=nr	Age, family history of asthma, household size, prematurity, birth weight, age of child at time of outcome, breastfeeding, maternal smoking, household smoking, gas heater in living room
Von Mutius et al.[181] Germany 1999	Single-centre cross-sectional study (3b)	374; 5,006 340; 3,904 34; 1,102	< 3 y No Medical records	5-7 y	Questionnaire for asthma symptoms (ISAAC)	Exposure to AB in first 3 y of life associated with increased risk. • **aOR 1.64 (95%CI 1.26-2.13), p=nr** • ≥ 6 AB courses: aOR 7.95 (95%CI 6.02-10.50), p=nr	Family history of atopy, number of siblings, parental education, study area, school grade
		461; 5,267 397; 4,006 64; 1,261		9-11 y		Exposure to AB in first 3 y of life associated with increased risk. • **OR 2.06 (95%CI 1.57-2.70), p<0.01***	
Wickens et al.[154] New Zealand 1999	Multicentre retrospective cross-sectional study (3b)	71; 447 65; 334 6; 113	< 10 y No Parent questionnaire	5-10 y	Questionnaire for asthma symptoms (ISAAC)	Exposure to AB in first 10 y of life associated with increased risk. • **aOR 2.74 (95%CI 1.10-6.85), p=nr** • 1-2 AB courses: aOR 2.27 (95%CI 1.14-4.51), p=nr • ≥ 3 AB courses: aOR 4.02 (95%CI 1.57-10.31), p=nr	Age, sex, ethnicity, family history of atopy, household size, parental smoking
Farooqi et al.[48] UK 1998	Single-centre retrospective cohort study (2b)	484; 1,855 402*; 1,237 82*; 618	< 2 y Yes Medical records	6-12 y	Recurrent episodes of wheeze > 2 y of life	Exposure to AB in first 2 y of life associated with increased risk. • **OR 3.19 (95%CI 2.43-4.18), p<0.01** Results according to antibiotic class nr	

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Allergic symptoms							
Levin et al.[82] South-Africa 2020	Multicentre prospective cohort study (2b)	528; 1,185 326; 654 202; 531 23; 398 21; 347 2; 51	< 1 y No Parent questionnaire	12-36 m	Questionnaire for allergic symptoms (based on ISAAC)	Exposure to AB in first y of life associated with increased risk in urban cohort. • **OR 1.62 (95%CI 1.28-2.04), p<0.01*** Exposure to AB in first y of life not associated with increased risk in rural cohort. • OR 1.58 (95%CI 0.36-6.94), p=0.55*	
Hirsch et al.[61] USA 2017	Multicentre case-control study (3b)	3,652; 21,912 3,145; 16,967 507; 4,945	1-2 m before diagnosis Yes Medical records	< 7 y	ICD-9 codes plus medical or prescription records for milk allergy, non-milk food allergies and other unspecified allergies incl. allergic rhinitis	Exposure to AB in 2 m before diagnosis associated with increased risk. • **aOR 2.32 (95%CI 2.07-2.59), p=nr** • 1-2 AB courses: **aOR 1.69 (95%CI 1.50-1.92), p=nr** • ≥ 3 AB courses: **aOR 3.07 (95%CI 2.72-3.46), p=nr** • penicillins: **aOR 2.28 (95%CI 2.06-2.53), p=nr** • cephalosporins: **aOR 1.70 (95%CI 1.57-1.83), p=nr** • macrolides: **aOR 1.98 (95%CI 1.83-2.15), p=nr**	Ethnicity, healthcare use
Batool et al.[183] Canada 2016	Multicentre prospective cohort study (2b)	360; 818 163; 285 197; 533	< 1 y No Parent questionnaire	1 y	Parent-reported allergic symptoms (atopic dermatitis, allergic rhinitis, wheezing or asthma)	Exposure to AB in first y of life associated with increased risk. • **OR 2.28 (95%CI 1.70-3.6), p<0.01***	
Sandini et al.[177] Finland 2011	Single-centre prospective cohort study (2b)	308; 925 nr; nr nr; nr 479; 891 nr; nr nr; nr	< 6 m No Parent questionnaire	2 y 5 y	Parent-reported allergic symptoms (atopic dermatitis, food allergy, allergic rhinitis, asthma)	Exposure to AB in first 6 m of life not associated with increased risk. • OR 1.25 (95%CI 0.82-1.90), p=0.30 Exposure to AB in first 6 m of life not associated with increased risk. • OR 1.26 (95%CI 0.83-1.92), p=0.27	

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Infantile colic							
Oosterloo et al.[105] Netherlands 2018	Multicentre prospective cohort study (2b)	74; 436 33; 151 41; 285	< 1 w No Parent questionnaire	0-1 y	Parent-reported	Exposure to AB in first w of life not associated with increased risk. • aOR 1.66 (95%CI 1.00-2.77), p=0.05	Family history of atopy, parental education, day care, number of siblings, smoking during pregnancy, delivery mode, duration of breastfeeding, household smoking
Abdominal pain							
Uusijarvi *et al.*[144] Sweden 2014	Multicentre prospective cohort study (2b)	231; 2,654 87; 861 144; 1,793	< 2 y Yes Parent questionnaire	11-14 y	Questionnaire for abdominal pain and GI disorders (QPGS-RIII)	Exposure to AB in first 2 y of life not associated with increased risk abdominal pain. • aOR 1.37 (95%CI 0.94-1.99), p=nr Results according to antibiotic class nr	Sex, asthma at 12 years of age
		245; 2,732 94; 1,045 151; 1,687	9-12 y Yes Parent questionnaire			Exposure to AB between 9 and 12 y of life not associated with increased risk. • 1 AB course: aOR 0.88 (95%CI 0.61-1.25), p=nr • 2 AB courses: aOR 0.76 (95%CI 0.44-1.31), p=nr • ≥ 3 AB courses: aOR 1.18 (95%CI 0.71-1.98), p=nr • penicillin: aOR 1.04 (95%CI 0.76-1.43), p=nr • amoxicillin: aOR 1.27 (95%CI 0.76-2.11), p=nr • flucloxacillin: aOR 0.80 (95%CI 0.46-1.41), p=nr • erythromycin: aOR 1.01 (95%CI 0.53-1.94), p=nr • cefadroxil: aOR 0.65 (95%CI 0.28-1.53), p=nr • tetracycline: aOR 1.75 (95%CI 0.71-4.31), p=nr	
Inflammatory bowel disease							
Canova et al.[30] Italy 2020	Multicentre retrospective case-control study (3b)	70; 770 33; 353 37; 417	< 1 y No Registry	< 18 y	ICD-9-CM codes	Exposure to AB in first 12 m of life not associated with increased risk. • aOR 1.07 (95%CI 0.64-1.80), p=nr Exposure to AB for ≥ 4 AB courses associated with increased risk. • first 6 m: **aOR 6.34 (95%CI 1.68-24.02), p=0.01** • first 12 m: **aOR 2.91 (95%CI 1.31-6.45), p=0.01**	Age, sex, maternal age and education; parity, number of siblings, gestational age, birth weight, Apgar scores, season of birth, gastrointestinal infections

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Table 1 (*continued*)

Örtqvist et al.[106] Sweden 2019	Multicentre prospective cohort study (2b)	51; 827,239 43; 539,809 8; 287,430	< 1 y before diagnosis Yes Registry	< 6 y	ICD-10 codes	Exposure to AB in 12 m before diagnosis associated with increased risk. • **OR 2.86 (95%CI 1.35-6.09), p<0.01*** • aHR 1.11 (95%CI 0.57-2.15), p=nr • 1 AB course: aHR 0.73 (95%CI 0.28-1.89), p=nr • 2 AB courses: aHR 1.85 (95%CI 0.80-4.30), p=nr • ≥ 3 AB courses: aHR 1.12 (95%CI 0.47-2.65), p=nr • penicillin: aHR 1.25 (95%CI 0.70-2.26), p=nr	Parental country of birth, education and history of IBD; mode of delivery, gastroenteritis
Kronman et al.[78] UK 2012	Multicentre retrospective cohort study (2b)	748; 1,072,426 436; 618,663 312; 453,763	< 1 y Yes Registry	< 17 y	Read codes	Exposure to AB in first y of life associated with increased risk. • **aHR 5.51 (95%CI 1.66-18.28), p<0.01** • 1-2 AB courses: **aHR 3.13 (95%CI 1.54-6.36), p<0.01** • > 2 AB courses: **aHR 5.15 (95%CI 2.36-11.25), p<0.01** • penicillins: **aHR 5.26 (95%CI 1.60-17.25), p<0.01** • cephalosporins: **aHR 1.58 (95%CI 1.21-2.05), p<0.01** • macrolides: aHR 1.21 (95%CI 0.96-1.51), p=0.10 • sulfonamides: aHR 1.31 (95%CI 0.98-1.74), p=0.07 • metronidazole: **aHR 337.78 (95%CI 37.42-3,048.96), p<0.01** • fluoroquinolones: **aHR 3.70 (95%CI 2.25-6.08), p<0.01** • tetracyclines: aHR 1.05 (95%CI 0.65-1.69), p=0.85	Sex, chronic granulomatous disease, primary sclerosing cholangitis, socioeconomic deprivation, family history of IBD
Virta et al.[148] Finland 2012	Multicentric case-control study (3b)	595; 2,975 359; 1,576 236; 1,399	< 1 y Yes Registry	1-16 y	ICD-10 plus endoscopy and histologic verification	Exposure to AB in first y of life associated with increased risk. • **OR 1.45 (95%CI, 1.21-1.75), p<0.01** Results according to antibiotic class nr	Additional chronic diseases

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Table 1 (*continued*)

		Crohn's disease: 233; 1,165 152; 613 81; 552				Exposure to AB in first y of life associated with increased risk of Crohn's disease. • **aOR 1.87 (95%CI 1.37-2.56), p=nr** • 1 AB course: aOR 1.32 (95%CI 0.92-1.88), p=nr • 2 AB courses: **aOR 1.98 (95%CI 1.22-3.20), p=nr** • ≥ 3 AB courses: aOR 1.42 (95%CI 0.87-2.33), p=nr • 3 cephalosporin courses: **aOR 2.82 (95%CI 1.65-4.81), p=nr** Results according to antibiotic class nr	
		Ulcerative colitis: 362; 1,810 207; 963 155; 847				Exposure to AB in first y of life not associated with increased risk of ulcerative colitis. • aOR 1.18 (95%CI, 0.92-1.52), p=nr • 1 AB course: aOR 0.98 (95%CI 0.72-1.34), p=nr • 2 AB courses: aOR 1.45 (95%CI 0.98-2.16), p=nr • ≥ 3 AB courses: aOR 1.26 (95%CI 0.87-1.82), p=nr Results according to antibiotic class nr	
Hviid et al.[68] Denmark 2011	Multicentre prospective cohort study (2b)	117; 577,627 84; 489,946 33; 87,681	< 10 y Yes Registry	< 10 y	ICD-10 codes	Exposure to AB in first y of life associated with increased risk. • **aRR 1.84 (95% CI 1.08-3.15), p=nr** Results according to antibiotic class nr Strongest association for AB < 3 m before diagnosis and risk of Crohn's disease. • aRR **4.43 (95% CI 1.88-10.44), p=nr** • narrow-spectrum penicillins: **aRR 2.92 (95%CI 1.22-6.97), p=nr** • broad-spectrum penicillins: **aRR 3.13 (95%CI 1.33-7.40), p=nr** • macrolides: aRR 0.97 (95%CI 0.13-7.14), p=nr	Age, season

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Shaw et al.[127] Canada 2010	Multicentre case-control study (3b)	36; 396 21; 160 15; 236	< 1 y No Registry	< 12 y	ICD-9-CM and ICD-10-CA codes	Exposure to AB in first y of life associated with increased risk. • **aOR 2.91 (95%CI 1.21-6.97), p=0.02**	Age, sex, living area
Celiac disease							
Aversa et al.[172] USA 2021	Multicentre prospective cohort study (2b)	45; 14,572 40; 10,220 5; 4,352	< 2 y Yes Medical records	6-11 y	ICD-9 and ICD-10 codes	Exposure to AB in first 2 y of life associated with increased risk. • **aHR 2.89 (95%CI 1.14-7.35), p=0.03** Girls • penicillins: **HR 6.74 (95%CI 1.56-29.23), p=0.01** • cephalosporins: HR 0.49 (95%CI 0.16-1.50), p=0.21 • macrolides: HR 1.26 (95%CI 0.53-3.03), p=0.60 • sulfonamides: HR 0.57 (95%CI 0.07-4.28), p=0.58 Boys • penicillins: HR 1.61 (95%CI 0.51-5.12), p=0.42 • cephalosporins: HR 1.53 (95%CI 0.59-3.95), p=0.38 • macrolides: HR 1.08 (95%CI 0.42-2.79), p=0.87 • sulfonamides: HR 1.42 (95%CI 0.32-6.34), p=0.65	Sex, ethnicity, maternal age and education; antibiotic use during pregnancy, birth weight, delivery mode, maternal smoking
Dydensborg et al.[44] Denmark Norway 2019	Multicentre prospective cohort study (2b)	3,346; 1,706,113 1,012; 550,746 2,334; 1,155,367	< 1 y No Registry	11.6 y (mean Denmark) 5.4 y (mean Norway)	ICD-10 codes	Exposure to AB in first y of life associated with increased risk. • **aOR 1.26 (95%CI 1.16-1.36), p=nr**	Maternal age, BMI, country of birth, autoimmune diseases and education; parity, smoking during pregnancy, gestational age, weight for gestational age, birth weight, season of birth

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Kemppainen et al.[73] USA 2017	Multicentre prospective cohort study (2b)	783; 6,558 nr; nr nr; nr	3 m-4 y Yes Medical records	2-4 y	Islet or tissue transglutaminase autoantibodies	Exposure to AB in first 4 y of life not associated with increased risk. • aHR 1.00 (95%CI 0.98-1.02), p=nr • penicillin: aHR 1.03 (95%CI 0.92-1.09), p=nr • amoxicillin: aHR 0.99 (95%CI 0.96-1.02), p=nr • cephalosporins: aHR 1.01 (95%CI 0.94-1.09), p=nr • macrolides: aHR 0.99 (95%CI 0.91-1.08), p=nr	Sex, HLA genotype, family history of type 1 diabetes or celiac disease, country, antibiotic use during pregnancy, season of birth, delivery mode, probiotic use, breastfeeding
Myleus et al.[199] Sweden 2012	Multicentric case-control study (3b)	373; 954 97; 231 276; 723	< 6 m No Parent questionnaire	< 2 y	Small intestinal biopsy or diagnostic criteria of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition	Exposure to AB in first 6 m of life not associated with increased risk. • OR 1.20 (95%CI 0.87-1.60), p=0.27	
Increased weight gain and overweight							
Aversa et al.[172] USA 2021	Multicentre prospective cohort study (2b)	4,856; 14,572 3,637; 10,220 1,219; 4,352	< 2 y Yes Medical records	6-11 y	BMI ≥ 85th percentile	Exposure to AB in first 2 y of life associated with increased risk of overweight. • **aHR 1.22 (95%CI 1.14-1.30), p<0.01** Girls • penicillins: **HR 1.11 (95%CI 1.02-1.22), p=0.02** • cephalosporins: HR 1.10 (95%CI 1.00-1.22), p=0.06 • macrolides: **HR 1.16 (95%CI 1.05-1.28), p<0.01** • sulfonamides: HR 1.11 (95%CI 0.94-1.31), p=0.23 Boys • penicillins: **HR 1.13 (95%CI 1.03-1.24), p<0.01** • cephalosporins: **HR 1.11 (95%CI 1.01-1.22) p=0.03** • macrolides: **HR 1.11 (95%CI 1.01-1.21), p=0.03** • sulfonamides: **HR 1.20 (95%CI 1.01-1.41), p=0.03**	Sex, ethnicity, maternal age, education and smoking; antibiotic use during pregnancy, birth weight, delivery mode
Chelimo et al.[33] New Zealand 2020	Multicentre prospective cohort study (2b)	1,051; 5,128 1,010; 4,886 41; 242	< 2 y Yes Registry	4.5 y	BMI	Exposure to AB in first 2 y of life not associated with increased risk of d overweight. • OR 1.22 (95%CI 0.87-1.71), p=0.25* • < 1 y of age: aOR: 1.21 (95%CI 0.81-1.81), p=0.36 • > 1 y of age: aOR: 1.18 (95%CI 0.79-1.78), p=0.42	Sex, ethnicity, maternal age, parity, pre-pregnancy weight, socioeconomic status, school grade, alcohol and antibiotic use during pregnancy, birth weight,

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						• 1-3 AB courses: aOR 0.95 (95%CI 0.63-1.46), p=0.83 • 4-6 AB courses: aOR 1.36 (95%CI 0.90-2.07), p=0.15 • 7-9 AB courses: aOR 1.38 (95%CI 0.90-2.13), p=0.14 • > 9 AB courses: aOR 1.23 (95%CI 0.81-1.86), p=0.34 • penicillins: aOR 0.95 (95%CI 0.67-1.34), p=0.77 • macrolides: aOR 1.16 (95%CI 0.94-1.43), p=0.17 • cephalosporins: aOR 1.19 (95%CI 0.97-1.47), p=0.10 • trimethoprim/sulfamethoxazole: aOR 1.05 (95%CI 0.85-1.30), p=0.64	season of birth, delivery mode, birth order, anti-reflux medication use, breastfeeding, diet, sleep duration, time spent watching television, DVDs, or videos
Dawson-Hahn et al.[200] USA 2019	Multicentre retrospective cohort study (2b)	65; 586 39*; 355 25*; 231	< 1 y No Parent questionnaire	6 y	BMI z-score	Exposure to AB in first y of life associated with increased risk of overweight. • **OR 1.03 (95%CI 1.01-1.05), p=nr** (from[240]) • BMI z-score: +0.17 (95%CI 0.09-0.25), p=nr	
Kamphorst et al.[71] Netherlands 2019	Multicentre prospective cohort study (2b)	nr, 436 nr; 151 nr 285	< 1 y Yes Parent questionnaire	1 y	Weight	Exposure to AB in first y of life associated with increased risk of increased weight gain. • **weight gain of 76 g after every AB course, p=0.03** Results according to antibiotic class nr	
Sejersen et al.[170] Denmark 2019	Multicentre prospective cohort study (2b)	nr; 661 nr; 306 nr; 355	< 1 y Yes Parent questionnaire	6 y	BMI z-score	Exposure to AB in first y of life not associated with increased risk of overweight. • BMI z-score: -0.06 (95%CI -0.17-0.06), p=0.33	
		nr; 467 nr; 216 nr; 251		3.5 y	Fat percentage with dual-energy X-ray absorptiometry	Exposure to AB in first y of life not associated with increased risk of increased fat percentage. • difference in fat percentage: 0.85% (95%CI -1.84-3.55), p=0.53 Results according to antibiotic class nr	

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		nr; 500 nr; 221 nr; 279		6 y		Exposure to AB in first y of life not associated with increased risk of increased fat percentage. • difference in fat percentage: 0.60% (95%CI -0.21-1.41), p=0.15 Results according to antibiotic class nr	
Smith-Brown et al.[131] Australia 2019	Single-centre cross-sectional study (3b)	11; 50 nr, 11 nr; 39	< 1 m No Parent questionnaire	6-24 m	BMI z-score plus bioelectrical impedance analysis	Exposure to AB in first m of life associated with increased risk of increased BMI z-score and body fat. • BMI z-score: **+1.17 (p<0.01) (mean increase 1.1 vs mean of 0.025)** • bioelectrical impedance analysis**: +3.5% (p<0.01)**	
Block et al.[27] USA 2018	Multicentre retrospective cohort study (2b)	45,295; 310,947 27,225; 180,739 18,070; 130,208	< 2 y Yes Registry	5 y	BMI z-score (≥ 85th percentile)	Exposure to AB in first 2 y of life associated with increased risk of overweight. • **aOR 1.05 (95%CI 1.03-1.07), p=nr** Results according to antibiotic class nr	Age, sex, prematurity, ethnicity, asthma, corticosteroid use, number of infections
Poulsen et al.[201] USA 2017	Multicentre retrospective cohort study (2b)	nr; 8,793 nr; 7,224 nr; 1,569	< 3 y Yes Medical records	3 y	BMI z-score	Exposure to AB in first 3 y of life associated with increased risk of increased BMI. • **OR 1.17 (95%CI 1.06-1.29), p=nr** (from[240]) • 1 AB course: BMI z-score + 0.04 (95%CI -0.04-0.11), p=0.39 • 2-3 AB courses: BMI z-score +0.02 (95%CI -0.05-0.09), p=0.58 • 4-5 AB courses: BMI z-score +0.09 (95%CI 0.01-0.17), p=0.03 • 6-8 AB courses: BMI z-score +0.11 (95%CI 0.03-0.20), p<0.01 • ≥ 9 AB courses: BMI z-score +0.175 (95%CI 0.09-0.26), p<0.01 • ≥ 4 courses of penicillins: BMI z-score +0.08 (95%CI 0.01-0.15), p=0.08 • ≥ 3 courses of cephalosporins: BMI z-score +0.11 (95%CI 0.03-0.29), p=0.02 • ≥ 2 courses of macrolides: BMI z-score +0.10 (95%CI 0.01-0.19), p=0.04	

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Rogawski et al.[202] 8 countries 2017	Multicentre prospective cohort study (2b)	nr; 1,954 nr; 1,284 nr; 670	< 6 m Yes Parent questionnaire	2 y	Weight-for-age (WAZ) z-score	Exposure to AB in first 6 m of life associated with increased risk of increased weight gain. • **OR 1.23 (95%CI 1.04-1.45), p=nr** (from[240]) • WAZ difference: +0.03 (95%CI 0.00-0.05), p=ns • penicillins, WAZ difference: +0.09 (95%CI -0.02-0.19), p=ns • cephalosporins, WAZ difference: +0.03 (95%CI -0.09-0.16), p=ns • metronidazole, WAZ difference: +0.14 (95%CI -0.01-0.29), p=ns • macrolides, WAZ difference: +0.09 (95%CI -0.03-0.21), p=ns • sulfonamides, WAZ difference: +0.03 (95%CI -0.09-0.15), p=ns • fluoroquinolones, WAZ difference: +0.08 (95%CI -0.14-0.30), p=ns	
Korpela et al.[75] Finland 2016	Multicentre prospective case-control study (3b)	28; 148 nr; 32 nr; 116	< 2 y Yes Registry	2-7 y	BMI z-score	Exposure to AB in first 2 y of life not associated with increased risk of overweight. Results according to antibiotic class nr	
Mbakwa et al.[89] Netherlands 2016	Multicentre prospective cohort study (2b)	135; 979 90*; 613 45*; 366	< 1 y Yes Parent questionnaire	1 y	BMI z-score	Exposure to AB in first y of life not associated with increased risk of overweight. • OR 1.23 (95%CI 0.84-1.80), p=0.30* • 1 AB course: aOR 1.09 (95%CI 0.76-1.57), p=0.64 • 2-3 AB courses: aOR 1.13 (95%CI 0.79-1.63), p=0.51 • ≥ 4 AB courses: aOR 1.03 (95%CI 0.66-1.60), p=0.89 • narrow-spectrum penicillins: aOR 0.95 (95%CI 0.68-1.34), p=0.79 • broad-spectrum penicillins: aOR 1.00 (95%CI 0.57-1.76), p=0.99 • macrolides: aOR 1.29 (95%CI 0.89-1.86), p=0.18	Age, sex, maternal education, weight and pregnancy weight gain, household size, gestational diabetes, gestational hypertension, smoking during pregnancy, gestational age, birth weight, delivery mode, breastfeeding duration, diet, child's physical activity

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Schwartz et al.[124] USA 2016	Multicentre prospective cohort study (2b)	79,752; 142,824 54,802*; 97,120 24,950*; 45,704	< 1 y before each BMI Yes Registry	3-18 y	BMI	Exposure to AB 1 y before BMI measure associated with increased risk of weight gain. • **OR 1.08 (95%CI 1.06-1.10), p=nr** (from[240]) Strongest association with macrolides: BMI +0.43 Results according to antibiotic class nr	
Gerber et al.[54] USA 2016	Multicentre retrospective cohort study (2b)	nr; 38,522 nr; 5,287 nr; 33,235	< 6 m Yes Registry	< 8 y	Weight	Exposure to AB in first 6 m of life not associated with increased weight gain. • OR* 1.02 (95%CI 0.86-1.20), p=nr (from[240]) • weight gain difference: +0.07% (95%CI -0.10-1.50), p=0.07 • narrow-spectrum: +0.40% (95%CI -0.60-1.30), p=0.45 • broad-spectrum: -0.30% (95%CI -2.10-1.50), p=0.72 • macrolides: +2.20% (95%CI -1.20-5.70), p=0.20	
			< 2 y Yes Registry			Exposure to AB in first 2 y of life associated with increased risk of weight gain. • **weight gain difference: +2.10% (95%CI 0.80-3.30), p<0.01** • narrow-spectrum: +1.90% (95%CI 0.50-3.20), p<0.01 • broad-spectrum: +2.20% (95%CI 0.70-3.80), p<0.01 • macrolides: +2.40% (95%CI 0.60-4.20), p<0.01	
Saari et al.[121] Finland 2015	Multicentre prospective cohort study (2b)	2,094; 12,062 1,673; 9,236 421; 2826	< 2 y Yes Registry	2-3 y	BMI z-score	Exposure to AB in first 2 y of life associated with increased risk of overweight. • **OR 1.26 (95%CI 1.12-1.42), p<0.01***	
		Boys: 1,376; 6,114				Exposure to AB in first 2 y of life associated with increased risk of overweight.	Birth weight, birth length, delivery mode,

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		1,121; 4,828 255; 1,286				• **OR 1.26 (95%CI 1.04-1.49), p<0.01** • 1 AB course: aOR 1.16 (95% CI, 0.92-1.48), p=nr • 2-3 AB courses: **aOR 1.28 (95%CI 1.04-1.59), p<0.05** • ≥ 4 AB courses: **aOR 1.27 (95%CI 1.04-1.55), p<0.05** Strongest effects in boys, exposures before < 6 m of life • < 6 m: **aOR 1.34 (95%CI 1.06-1.66), p<0.05** • 1 penicillin course: aOR 1.13 (95%CI 0.90-1.41), p=ns • 1 cephalosporin course: **aOR 1.39 (95%CI 1.10-1.76), p<0.05** • 1 macrolide course: aOR 1.20 (95%CI 0.96-1.49), p=ns • ≥ 2 macrolide courses: **aOR 1.47 (95%CI 1.16-1.86), p<0.05**	smoking during pregnancy, parental relationship
		Girls: 718; 5,948 552; 4,408 166; 1,540				Exposure to AB in first 2 y of life not associated with increased risk of overweight. • 1 AB course: aOR 1.03 (95% CI, 0.81-1.32), p=nr • 2-3 AB courses: aOR 1.14 (95%CI 0.91-1.42), p=nr • ≥ 4 AB courses: aOR 1.19 (95%CI 0.96-1.48), p=nr • 1 penicillin course: aOR 1.11 (95%CI 0.89-1.40), p=ns • 1 cephalosporin course: aOR 1.05 (95%CI 0.80-1.38), p=ns • 1 macrolide course: aOR 0.94 (95%CI 0.94-1.50), p=ns	Birth weight, delivery mode, smoking during pregnancy
Azad et al.[23] Canada 2014	Single-centre, retrospective nested case-control study (3b)	181; 616 144; 438 37; 178	< 1 y Yes Medical records	9 y	BMI (> 85th percentile)	Exposure to AB in first y of life associated with increased risk of overweight. • **aOR 1.74 (95%CI 1.04-2.94), p=nr** • girls: aOR 1.20 (95%CI 0.53-2.70), p=nr • **boys: aOR 2.19 (95%CI 1.06-4.54), p=nr** Results according to antibiotic class nr	Maternal asthma and overweight; number of siblings, income, birth weight, asthma, breastfeeding, diet, child's physical activity, smoke exposure
		121; 431 97; 299 24; 132		12 y		Exposure to AB in first y of life associated with increased risk of overweight. • **aOR 2.56 (95%CI 1.36-4.79), p=nr** • girls: aOR 1.13 (95%CI 0.46-2.81), p=nr • **boys: aOR 5.35 (95%CI 1.94-14.72), p=nr** Results according to antibiotic class nr	

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Trasande et al.[143] USA 2013	Single-centre prospective cohort study (2b)	1,700; 8,881 1,322*; 6,598 378*; 2,283	< 6 m No Parent questionnaire	38 m	BMI z-score	Exposure to AB in first 6 m of life associated with increased risk of overweight. • **aOR 1.22 (95%CI nr), p<0.05**	Ethnicity, parity, parental education, BMI and socioeconomic status; smoking during pregnancy, birth weight, breastfeeding, diet, timing of solid food introduction, sleep duration, time watching television and in car
		1,700; 8,881 1,274*; 6,598 426*; 2,283	< 6-14 m No Parent questionnaire			Exposure to AB in at 6 to 14 m of life not associated with increased risk of overweight. • aOR 1.04 (95%CI nr), p=0.63	
		1,700; 8,881 1,317*; 6,598 383*; 2,283	< 15-23 m No Parent questionnaire			Exposure to AB at 15 to 23 m of life not associated with increased risk of overweight. • aOR 1.24 (95%CI nr), p=0.09	
		1,962; 8,881 1,467*; 6,598 495*; 2,283	< 6 m No Parent questionnaire	7 y		Exposure to AB in first 6 m of life not associated with increased risk of overweight. • aOR 1.03 (95%CI nr), p=0.78	
		1,962; 8,881 1,442*; 6,598 520*; 2,283	< 6-14 m No Parent questionnaire			Exposure to AB in at 6 to 14 m of life not associated with increased risk of overweight. • aOR 0.95 (95%CI nr), p=0.58	
		1,962; 8,881 1,464*; 6,598 498*; 2,283	< 15-23 m No Parent questionnaire			Exposure to AB at 15 to 23 m of life not associated with increased risk of overweight. • aOR 1.02 (95%CI nr), p=0.87	

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Ajslev et al.[14] Denmark 2011	Multicentre prospective cohort study (2b)	2,333; 22,368 197*; 1,628 2,136*; 20,740	< 6 m No Parent questionnaire	7 y	BMI	Exposure to AB in first 6 m of life not associated with increased risk of overweight. • aOR 1.04 (95%CI 0.79-1.37), p<0.78	Sex, maternal age, BMI, and smoking; weight gain during pregnancy, parity, paternal BMI, socioeconomic status, birth weight, delivery mode, breastfeeding,
Obesity							
Aversa et al.[172] USA 2021	Multicentre prospective cohort study (2b)	2,567; 14,572 1,932; 10,220 635; 4,352	< 2 y Yes Medical records	6-11 y	BMI ≥ 95th percentile	Exposure to AB in first 2 y of life associated with increased risk. • **aHR 1.20 (95%CI 1.10-1.32), p<0.01** Girls • penicillins: HR 1.05 (95%CI 0.92-1.19), p=0.50 • cephalosporins: **HR 1.17 (95%CI 1.02-1.35), p=0.03** • macrolides: HR 1.08 (95%CI 0.94-1.24), p=0.26 • sulfonamides: HR 1.15 (95%CI 0.92-1.45), p=0.22 Boys • penicillins: **HR 1.15 (95%CI 1.02-1.31), p=0.02** • cephalosporins: HR 1.08 (95%CI 0.96-1.22), p=0.22 • macrolides: **HR 1.15 (95%CI 1.02-1.29), p=0.02** • sulfonamides: HR 1.11 (95%CI 0.89-1.39), p=0.34	Sex, ethnicity, maternal age, education and smoking; antibiotic use during pregnancy, birth weight, delivery mode
Chelimo et al.[33] New Zealand 2020	Multicentre prospective cohort study (2b)	437; 5,128 428; 4,886 9; 242	< 2 y Yes Registry	4.5 y	BMI	Exposure to AB in first 2 y of life not associated with increased risk, expect trimethoprim/sulfamethoxazole • penicillins: aOR 0.95 (95%CI 0.51-1.78), p=0.87 • cephalosporins: aOR 1.11 (95%CI 0.97-1.47), p=0.52 • macrolides: aOR 1.24 (95%CI 0.94-1.43), p=0.19 • trimethoprim/sulfamethoxazole: **aOR 1.60 (95%CI 1.18-2.17), p<0.01**	Sex, ethnicity, maternal age, parity, pre-pregnancy weight, socioeconomic status, school grade, alcohol and antibiotic use during pregnancy, birth weight, season of birth, delivery mode, birth order, anti-reflux medication use, breastfeeding, diet, sleep duration, time spent watching television, DVDs, or videos
			< 1 y Yes Registry			Exposure to AB in first y of life not associated with increased risk. • aOR 1.90 (95%CI 0.86-4.23), p=0.11	

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Table 1 (*continued*)

			1-2 y Yes Registry			Exposure to AB in second y of life not associated with increased risk. • aOR 1.69 (95%CI 0.75-3.82), p=0.20 More than 9 AB courses in first 2 y of life associated with increased risk. • **aOR 2.41 (95%CI 1.07-5.41), p=0.03**	
Leong et al.[81] New Zealand 2020	Single-centre retrospective cross-sectional study (4)	23,921; 151,359 nr; 124,506 nr; 26,853	< 2 y No Medical records	4 y	BMI	Exposure to AB in first 2 y of life associated with increased risk. • **aOR 1.04 (95%CI 1.04-1.05), p=nr**	Sex, ethnicity, maternal age, parity and diabetes, living area, socioeconomic status, hyperemesis gravidarum, prolonged hospitalisation during pregnancy, gestational age, birth weight, season of birth, delivery mode, prolonged hospitalisation during the first 2 y of life, number of days overseas during first 2 y of life
Stark et al.[133] USA 2019	Multicentre retrospective cohort study (2b)	46,993; 333,353 36,899; 241,502 10,094; 91,851	< 2 y Yes Medical records	3 y	BMI ≥ 95th percentile	Exposure to AB in first 2 y of life associated with increased risk. • **HR 1.26 (95%CI 1.23-1.28), p=nr** • 1 AB course: aHR 1.12 (95%CI 1.09-1.15), p=nr • 2 AB courses: aHR 1.23 (95%CI 1.20-1.26), p=nr • 3 AB courses: aHR 1.33 (95%CI 1.29-1.37), p=nr • ≥ 4 AB courses: aHR 1.42 (95%CI 1.37-1.46), p=nr • penicillins: aHR 1.11 (95%CI 1.09-1.13), p=nr • cephalosporins: aHR 1.03 (95%CI 1.01-1.06), p=nr • macrolides: aHR 1.12 (95%CI 1.10-1.15), p=nr • sulfonamides boys: aHR 1.05 (95%CI 1.01-.1.10), p=nr • sulfonamides girls: aHR 1.19 (95%CI 1.14-1.15), p=nr	Sex, delivery mode, medication use

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Table 1 (*continued*)

Kelly et al.[72] Ireland 2019	Multicentre cross-sectional study (3b)	1,034; 8,186 682*; 5,285 352*; 2,901	2-3 y No Parent questionnaire	3 y	BMI	Exposure to AB between second and third y of life not associated with increased risk. • OR 1.07 (95%CI 0.75-1.52), p=0.26 • 1 AB course: OR 0.88 (95%CI 0.61-.127), p=nr • 2 AB courses: OR 0.95 (95%CI 0.66-1.38), p=nr • 3 AB courses: OR 1.16 (95%CI 0.80-1.69), p=nr • ≥ 4 AB courses: **OR 1.60 (95%CI 1.11-2.31), p=0.04**	
		470; 8,186 279*; 4,594 191*; 3,592	4-5 y No Parent questionnaire	5 y		Exposure to AB between fourth and fifth y of life not associated with increased risk. • 1 AB course: OR 1.15 (95%CI 0.80-1.64), p=0.09 • 2 AB courses: OR 1.04 (95%CI 0.65-1.67), p=0.20 • 3 AB courses: OR 1.16 (95%CI 0.63-2.16), p=0.59 • ≥ 4 AB courses: OR 1.37 (95%CI 0.74-2.53), p=0.37	
Block et al.[27] USA 2018	Multicentre retrospective cohort study (2b)	40,797; 310,947 24,162; 180,739 16,635; 130,208	< 2 y Yes Registry	5 y	BMI z-score	Exposure to AB in first 2 y of life associated with increased risk. • **aOR 1.05 (95%CI 1.03-1.07), p=nr** Results according to antibiotic class nr	Age, sex, prematurity, ethnicity, asthma, corticosteroid use, number of infections
Edmonson et al.[45] USA 2017	Multicentre randomised controlled trial (1b)	74; 607 29; 302 45; 305	2 m-6 y Yes Randomly assigned	2 m-6 y	BMI z-score	Exposure to AB in first 6 y of life not associated with increased risk. • aOR 0.65 (95%CI 0.33-1.28), p=0.22 Results according to antibiotic class nr	Age, sex, ethnicity, parental education, health insurance, vesicoureteral reflux, hydronephrosis, scarring or pyelonephritis on baseline scan, breastfeeding
Li et al.[83] USA 2017	Multicentre prospective cohort study (2b)	nr; 216,306 nr; 138,417 nr; 77,889	< 1 y No Registry	1-18 y	BMI z-score	Exposure to AB in first y of life not associated with increased risk. • aOR 1.01 (95% CI, 0.98-1.04), p=nr	Ethnicity, maternal age, pre-pregnancy BMI, antibiotic use and infection during pregnancy, prematurity, birth weight, infection type and severity

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Ville et al.[147] USA 2017	Single-centre prospective cohort study (2b)	10; 97 5; 16 5; 81	< 6 m No Parent questionnaire	2 y	BMI	Exposure to AB in first 6 m of life associated with increased risk. • **aOR 6.15 (95%CI 1.03-36.70), p<0.05**	Sex, maternal BMI, weight for length z-score at birth, breastfeeding
Scott et al.[125] USA 2016	Multicentre retrospective cohort study (2b)	1,306; 21,714 951; 14,870 355; 6,844	< 2 y Yes Medical records	4 y	BMI z-score	Exposure to AB in first 2 y of life associated with increased risk. • **aOR 1.24 (95%CI 1.09-1.41), p=nr** Results according to antibiotic class nr	Age, country, maternal and sibling obesity, maternal diabetes, urban environment, Townsend score, delivery mode
Bailey et al.[25] USA 2014	Single-centre prospective cohort study (2b)	9,822; 65,480 6,967*; 45,181 2,855*; 20,299	< 2 y No Medical records	2-5 y	BMI	Exposure to AB in first 2 y of life associated with increased risk. • **OR 1.11 (95%CI 1.03-1.19), p=nr** (from[240]) • 1 AB course: RR 1.03 (95% CI, 0.97-1.09), p=0.31 • 2 AB courses: RR 1.04 (95%CI 0.96-1.13), p=0.36 • 3 AB courses: RR 1.04 (95%CI 0.95-1.14), p=0.37 • ≥ 4 AB courses: **RR 1.11 (95%CI 1.02-1.21), p=0.02** • < 6 m of life: **RR 1.11 (95%CI 1.03-1.19), p=nr**	
Murphy et al.[99] 18 countries 2014	Multicentre cross-sectional study (3b)	nr; 74,946 nr; nr nr; nr	< 1 y No Parent questionnaire	5-8 y	BMI z-score	Exposure to AB in first y of life associated with increased risk. • **OR 1.02 (95%CI 1.00-1.04), p=nr** (from[240]) • boys: +0.107 SD units, p<0.01 • girls: +0.008 SD units, p=0.75	
Trasande et al.[143] USA	Single-centre prospective cohort study (2b)	793; 8,881 622*; 6,598 171*; 2,283	< 6 m No Parent questionnaire	38 m	BMI z-score	Exposure to AB in first 6 m of life not associated with increased risk. • aOR 1.23 (95%CI nr), p=0.10	Ethnicity, parity, parental education, BMI, and socioeconomic status; smoking during pregnancy, birth weight,

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2013		793; 8,881 603*; 6,598 190*; 2,283	6-14 m No Parent questionnaire			Exposure to AB in first 6 to 14 m of life not associated with increased risk. • aOR 1.11 (95%CI nr), p=0.37	breastfeeding, diet, timing of solid food introduction, sleep duration, time spent watching television and in car
		793; 8,881 613*; 6,598 180*; 2,283	15-23 m No Parent questionnaire			Exposure to AB in first 15 to 23 m of life not associated with increased risk. • aOR 1.20 (95%CI nr), p=0.14	
		706; 8,881 537*; 6,598 169*; 2,283	< 6 m No Parent questionnaire	7 y		Exposure to AB in first 6 m of life not associated with increased risk. • aOR 1.06 (95%CI nr), p=0.66	
		706; 8,881 531*; 6,598 175*; 2,283	6-14 m No Parent questionnaire			Exposure to AB in first 6 to 14 m of life not associated with increased risk. • aOR 1.05 (95%CI nr), p=0.70	
		706; 8,881 534*; 6,598 172*; 2,283	15-23 m No Parent questionnaire			Exposure to AB in first 15 to 23 m of life not associated with increased risk. • aOR 0.99 (95%CI nr), p=0.93	
Ajslev et al.[14] Denmark 2011	Multicentre prospective cohort study (2b)	378; 22,368 nr; 1,628 nr; 20,740	< 6 m No Parent questionnaire	7 y	BMI (> 85th percentile)	Exposure to AB in first 6 m of life associated with increased risk among children of normal-weight mothers. • **aOR 1.54 (95%CI 1.09-2.17), p=nr** Exposure to AB in first 6 m of life associated with decreased risk among children of obese mothers. • **aOR 0.54 (95%CI 0.30-0.98), p=nr**	Sex, maternal age and smoking; parity, pre-pregnancy BMI, gestational weight gain, paternal BMI, socioeconomic status, birth weight, delivery mode, breastfeeding

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Growth failure							
Uzan-Yulzari et al.[145] Israel 2021	Multicentre prospective cohort study (2b)	Boys: nr; 6,316 nr; 673 nr; 5,643	< 2 w No Medical records	6 y	Weight z-score BMI z-score	Exposure to AB in first w of life not associated with decreased weight gain in boys. • weight z-score: -0.43 (95%CI -0.96- -0.00), p=0.05 • BMI z-score: -0.11 (95%CI -0.68-0.47), p=0.71	
		Girls: nr; 6,115 nr; 478 nr; 5,637				Exposure to AB in first w of life not associated decreased weight gain in girls. • weight z-score: 0.28 (95%CI -0.21-0.77), p=0.26 • BMI z-score: 0.62 (95%CI -0.19-1.44), p=0.13	
Kamphorst et al.[71] Netherlands 2019	Multicentre prospective cohort study (2b)	nr, 436 nr; 151 nr 285	< 1 w Yes Parent questionnaire	1 y	Weight	Exposure to AB in first w of life associated with decreased weight gain. • weight gain: **6.26 kg (SE 0.07 kg) vs 6.47 (SE 0.06 kg), p<0.05** Results according to antibiotic class nr	
Rogawski *et al.*[203] India 2015	Single-centre prospective cohort study (2b)	140; 497 nr; 276 nr; 221	< 6 m No Parent questionnaire	6 m-3 y	Weight-for-age (WAZ)	Exposure to AB in first 6 m of life not associated with decreased weight gain. • RR 0.98 (95%CI 0.86-1.13), p=nr	
		68; 497 nr; 276 nr; 221			Weight-for-height (WHZ) z-scores	Exposure to AB in first 6 m of life not associated with decreased weight gain. • RR 0.96 (95%CI 0.78-1.18), p=nr	
Juvenile idiopathic arthritis							
Horton et al.[64] USA 2015	Multicentre nested case-control study (3b)	152; 1,672 133; 1,280 19; 392	Before diagnosis Yes Medical records	1-15 y	ICD-9 and ICD-10 codes	Exposure to AB associated with increased risk. • **aOR 2.10 (95%CI 1.20-3.50), p<0.01** • AB within 1 y before diagnosis: **aOR 2.90 (95% 1.60-5.30), p<0.01** • 1-2 AB courses: aOR 1.50 (95%CI 0.80-2.70), p=0.16 • 3-5 AB courses: **aOR 2.50 (95%CI 1.40-4.40), p<0.01** • > 5 AB courses: **aOR 3.00 (95%CI 1.60-5.60), p<0.01** Results according to antibiotic class nr	Age, sex, autoimmune disease, number of infections

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Arvonen et al.[18] Finland 2015	Multicentre case-control study (3b)	1,298; 6,477 644; 2,986 654; 3,491	< 1 y Yes Registry	< 13 y	ICD 10 codes	Exposure to AB in first y associated with increased risk. • **OR 1.20 (95%CI 1.10-1.40), p=nr** • penicillins: **OR 1.20 (95%CI 1.10-1.40), p=nr** • cephalosporins: **OR 1.30 (95%CI 1.10-1.70), p=nr** • macrolides: OR 1.20 (95%CI 1.02-1.40), p=nr • sulfonamides: OR 1.20 (95%CI 0.90-1.50), p=nr • lincosamides: OR 1.00 (95%CI 0.10-8.90), p=nr	
		1,298; 6,477 1,015; 4,737 283; 1,740	< 2 y Yes Registry			Exposure to AB in first 2 y associated with increased risk. • **OR 1.40 (95%CI 1.20-1.60), p<0.01** • penicillins: OR 1.50 (95%CI 1.30-1.70), p=nr • cephalosporins: OR 1.30 (95%CI 0.99-1.60), p=nr • macrolides: OR 1.30 (95%CI 1.10-1.50), p=nr • sulfonamides: OR 1.30 (95%CI 0.90-1.70), p=nr • lincosamides: **OR 3.50 (95%CI 1.30-9.70), p=0.01**	
		1,298; 6,477 1,158; 5,529 140; 948	Before diagnosis Yes Registry			Exposure to AB from birth to diagnosis associated with increased risk. • **OR 1.60 (95%CI 1.30-1.90), p<0.01** • penicillins: OR 1.80 (95%CI 1.50-2.20), p=nr • cephalosporins: **OR 1.60 (95%CI 1.40-1.80), p=nr** • macrolides: OR 1.50 (95%CI 1.20-1.90), p=nr • sulfonamides: OR 1.60 (95%CI 1.20-2.20), p=nr • lincosamides: **OR 6.60 (95%CI 3.70-11.70), p=nr**	
Psoriasis							
Horton et al.[65] USA 2016	Multicentre nested case-control study (3b)	845; 9,295 710; 7;053 135; 2,242	< 2 y before diagnosis Yes Medical records	1-15 y	ICD-9 codes	Exposure to AB within 2 y before diagnosis associated with increased risk. • **aOR 1.20 (95%CI 1.00-1.50), p=0.05** Results according to antibiotic class nr	Age, sex, country, socioeconomic status, infections, number of GP visits

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Type 1 diabetes							
Antvorskov et al.[171] Denmark 2020	Multicentre prospective cohort study (2b)	322; 91,998 235; 64,793 87; 27,205	< 2 y Yes Registry	14.3 y (mean)	ICD-10 codes	Exposure to AB in first 2 y of life not associated with increased risk. • aHR 1.26 (95%CI 0.89-1.79), p=nr • penicillins: aHR 1.30 (95%CI 0.92-1.85), p=nr • macrolides/lincosamides/ streptogramins: aHR 1.29 (95%CI 0.75-2.22), p=nr	Breastfeeding
Wernroth et al.[152] Sweden 2020	Multicentre prospective cohort study (2b)	1,297; 797,318 347; 189,682 950; 607,636	< 1 y Yes Registry	< 10 y	ICD-10 codes	Exposure to AB in first y of life associated with increased risk. • **aHR 1.19 (95%CI 1.05-1.36), p=nr** • narrow-spectrum: **HR 1.26 (95%CI 1.09-1.47), p=nr** • broad-spectrum: 1.06 (95%CI 0.80-1.40), p=nr Results according to antibiotic class nr	Age, sex, maternal age, parental country of birth, education, income and type 1 diabetes; living area, population density, smoking during pregnancy, gestational age, season of birth, delivery mode
Tapia et al.[140] Norway 2018	Multicentre prospective cohort study (2b)	403, 101,842 nr; 32,386 nr; 69,456	< 18 m Yes Parent questionnaire	7.4 y (mean)	ICD-10 codes	Exposure to AB in first 6 m of life not associated with increased risk. • aHR 1.05 (95%CI 0.68-1.63), p=0.82 • 1 AB course: aHR 1.10 (95%CI 0.83-1.41), p=0.51 • ≥ 2 AB courses: aHR 1.03 (95%CI 0.65-1.65), p=0.88 Results according to antibiotic class nr	Sex, maternal age, education and type 1 diabetes; parity, pre-pregnancy BMI, smoking during pregnancy, birth weight, number of infections, medication use
Mikkelsen et al.[94] Denmark 2016	Multicentre prospective case-control study (3b)	1,578; 14,188 1,366; 12,239 212; 1,949	< 2 y No Registry	< 16 y	ICD-10 codes	Exposure to AB in first 2 y of life not associated with increased risk. • 1-4 AB courses: OR 1.02 (95%CI 0.85-1.22), p=nr • > 5 AB courses: OR 1.01 (95%CI 0.85-1.22), p=nr	

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						• narrow-spectrum 1-4 AB courses: OR 0.90 (95%CI 0.78-1.03), p=nr • narrow-spectrum ≥ 5 AB courses: OR 0.98 (95%CI 0.80-1.21), p=nr • broad-spectrum 1-4 AB courses: OR 1.11 (95%CI 0.98-1.24), p=nr • broad-spectrum ≥ 5 AB courses: OR 1.15 (95%CI 0.95-1.39), p=nr	
Clausen et al.[36] Denmark 2016	Multicentre prospective cohort study (2b)	1,503; 858,201 1,107; 615,782 396; 242,419	< 2 y Yes Registry	2-14 y	Hospital discharge or prescription records	Overall exposure to AB in first 2 y of life not associated with increased risk. • aHR 1.06 (95%CI 0.94-1.19), p=nr • narrow-spectrum: aHR 1.02 (95%CI 0.92-1.13), p=nr • broad-spectrum: **aHR 1.13 (95%CI 1.02-1.25), p=nr** Exposure to broad-spectrum AB in first 2 y of life associated with increased risk in children delivered by delivery mode. • **aHR 1.70 (95%CI 1.15-2.51), p=nr** Results according to antibiotic class nr	Age, sex, parental education, age and type 1 diabetes, parity, delivery mode
Hviid et al.[204] Denmark 2009	Multicentre prospective cohort study (2b)	454; 606,420 373; 538,298 81; 68,122	< 9 y Yes Registry	< 9 y	ICD-10 codes	Exposure to AB in first w of life not associated with increased risk. • aRR 1.16 (95%CI 0.91-1.50), p=nr • penicillins: aRR 1.10 (95%CI 0.90-1.34), p=nr • macrolides: aRR 1.15 (95%CI 0.92-1.43), p=nr	Age, ethnicity, season

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Fluorosis							
Hong *et al.*[63] USA 2011	Single-centre prospective case-control study (3b)	68; 192 62; 174 6; 18	< 32 m Yes Parent questionnaire	13 y	Fluorosis risk index	Overall exposure to AB in first 32 m of life not associated with increased risk. • amoxicillin: RR 1.07 (95%CI 0.54-2.12), p=0.85	
Autism spectrum disorders							
Aversa et al.[172] USA 2021	Multicentre prospective cohort study (2b)	142; 14,572 108; 10,220 34; 4,352	< 2 y Yes Medical records	6-11 y	ICD-9 and ICD-10 codes	Exposure to AB in first 2 y of life not associated with increased risk. • aHR 1.19 (95%CI 0.81-1.75), p=0.39 Girls • penicillins: **HR 0.39 (95%CI 0.16-0.95), p=0.04** • cephalosporins: **HR 2.77 (95%CI 1.09-7.02), p=0.03** • macrolides: HR 1.21 (95%CI 0.47-3.14), p=0.70 • sulfonamides: HR 1.08 (95%CI 0.24-4.81), p=0.92 Boys • penicillins: HR 0.96 (95%CI 0.62-1.47), p=0.84 • cephalosporins: **HR 1.89 (95%CI 1.25-2.84), p<0.01** • macrolides: HR 0.83 (95%CI 0.55-1.28), p=0.41 • sulfonamides: HR 1.13 (95%CI 0.54-2.35), p=0.75	Sex, ethnicity, maternal age, education and smoking; antibiotic use during pregnancy, birth weight, delivery mode
Axelsson et al.[21] Denmark 2019	Multicentre prospective cohort study (2b)	8,267; 671,606 Penicillins: 6,316; 483,423 1,951; 188,183 Broad-spectrum: 4,943; 377,254 3,324; 294,352	< 2 y Yes Registry	< 15 y	ICD-10 codes	Exposure to AB in first y of life associated with increased risk. • **OR 1.26 (95%CI 1.20-1.33), p<0.01*** • penicillins: aHR 1.09 (95%CI 0.91-1.29), p=nr • **OR 1.16 (95%CI 1.11-1.21), p<0.01*** • broad-spectrum AB: **aHR 1.16 (95%CI 1.01-1.36), p=nr**	Sex, maternal age and smoking; parental education, age difference, marital status epilepsy and psychiatric history; parity, preeclampsia or hypertension, gestational diabetes, antibiotic use and infections during pregnancy, Apgar score, delivery mode, use of CPAP or ventilator, asphyxia

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Hamad et al.[57] Canada 2018	Multicentre prospective cohort study (2b)	2,965; 214,834 1,355; 94,024 1,610; 120,810	< 1 y Yes Registry	18 m-18 y	ICD-9 and ICD-10 codes	Exposure to AB in first y of life not associated with increased risk. • aHR 0.91 (95%CI 0.84-0.99), p=0.05 • 1 AB course: aHR 0.92 (95%CI 0.83-1.01), p=nr • 2 AB courses: aHR 0.89 (95%CI 0.78-1.01), p=nr • 3 AB courses: aHR 0.93 (95%CI 0.79-1.09), p=nr • ≥ 4 AB courses: aHR 0.90 (95%CI 0.76-1.06), p=nr • penicillins: **aHR 0.92 (95%CI 0.84-1.00), p<0.05** • macrolides: **aHR 0.87 (95%CI 0.77-0.99), p<0.05**	Age, sex, maternal age, and mental disorders (mood and anxiety disorders, schizophrenia, diabetes, prenatal infections), parity, living area, socioeconomic status, healthcare access, antidepressants use during pregnancy, size for gestational age, season of birth, delivery mode, birth complications, multiple birth, childhood medical disorders (epilepsy, infections, neonatal jaundice, asthma and diagnosis with other developmental disability disorder), breastfeeding
Attention deficit hyperactivity disorder							
Aversa et al.[172] USA 2021	Multicentre prospective cohort study (2b)	1,085; 14,572 841; 10,220 244; 4,352	< 2 y Yes Medical records	6-11 y	ICD-9 and ICD-10 codes	Exposure to AB in first 2 y of life associated with increased risk. • **aHR 1.32 (95%CI 1.15-1.53), p<0.01** Girls • penicillins: **HR 1.50 (95%CI 1.14-1.96), p<0.01** • cephalosporins: HR 1.21 (95%CI 0.92-1.59), p=0.18 • macrolides: HR 1.03 (95%CI 0.79-1.34), p=0.85 • sulfonamides: HR 0.65 (95%CI 0.38-1.10), p=0.11 Boys • penicillins: HR 1.08 (95%CI 0.91-1.27), p=0.38 • cephalosporins: HR 1.18 (95%CI 1.00-1.39), p=0.05 • macrolides: HR 1.09 (95%CI 0.93-1.28), p=0.28 • sulfonamides: HR 1.19 (95%CI 0.89-1.58), p=0.23	Sex, ethnicity, maternal age, education and smoking; antibiotic use during pregnancy, birth weight, delivery mode

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Axelsson et al.[22] Denmark 2019	Multicentre prospective cohort study (2b)	17,971; 671,592 Penicillins: 2,822; 106,170 15;149; 565,422 Broad-spectrum: 11,365; 377,238 6,606; 294,354	< 2 y Yes Registry	2-17 y	ICD-10 codes	Exposure to AB in first 2 y of life not associated with increased risk. • **OR 1.47 (95%CI 1.42-1.53), p<0.01*** • penicillins: aHR 0.98 (95%CI 0.90-1.07), p=nr • **OR 1.35 (95%CI 1.31-1.40), p<0.01*** • broad-spectrum AB: aHR 0.99 (95%CI 0.92-1.06), p=nr	Sex, maternal age, parental education, age difference, marital status, epilepsy, and ADHD history, parity, preeclampsia or hypertension, gestational diabetes, antibiotic use and infections during pregnancy, Apgar score, delivery mode, instrument use at delivery, induction of labour or contraction, use of CPAP or ventilator, asphyxia, maternal smoking
Hamad et al.[58] Canada 2019	Multicentre prospective cohort study (2b)	6,087; 69,738 3,045; 34,869 3,042; 34,869	< 1 y Yes Registry	> 4 y	ICD-9 and ICD-10 codes	Exposure to AB in first y of life not associated with increased risk. • aHR 1.02 (95%CI 0.97-1.08), p=nr • 1 AB course: aHR 0.94 (95%CI 0.87-1.02), p=nr • 2 AB courses: aHR 1.09 (95%CI 0.94-1.27), p=nr • 3 AB courses: aHR 1.09 (95%CI 0.83-1.43), p=nr • ≥ 4 AB courses: **aHR 1.57 (95%CI 1.23-2.00), p=nr** • penicillins: **aHR 1.11 (95%CI 1.03-1.19), p=nr** • macrolides: **aHR 1.11 (95%CI1.04-1.34), p=nr**	Age, sex, maternal age, antidepressants use and infections during pregnancy, size for gestational age, season of birth, delivery mode, birth order, birth complications, childhood medical disorders (asthma, epilepsy, infections, neonatal jaundice, diagnosis with other developmental disorder), breastfeeding
Slykerman et al.[130] New Zealand 2019	Multicentre prospective cohort study (2b)	nr; 446 nr; 376 nr; 70	< 2 y No Parent questionnaire	11 y	Psychologist-administered, parent-reported and self-reported measures[1]	Exposure to AB in first 2 y of life associated with increased risk. • **aOR 2.40 (95%CI 1.00-5.90), p=0.02**	Income, delivery mode, probiotic use, breastfeeding

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Table 1 (*continued*)

Neurodevelopmental disorders							
Aversa et al.[172] USA 2021	Multicentre prospective cohort study (2b)	751; 14,572 563; 10,220 188; 4,352	< 2 y Yes Medical records	6-11 y	ICD-9 and ICD-10 codes	Exposure to AB in first 2 y of life associated with increased risk of learning disorders. • **aHR 1.21 (95%CI 1.03-1.43), p=0.02** Girls • penicillins: HR 1.18 (95%CI 0.88-1.58), p=0.28 • cephalosporins: HR 1.36 (95%CI 0.99-1.85), p=0.06 • macrolides: HR 0.93 (95%CI 0.68-1.28), p=0.67 • sulfonamides: HR 0.96 (95%CI 0.56-1.64), p=0.87 Boys • penicillins: HR 1.06 (95%CI 0.87-1.29), p=0.56 • cephalosporins: **HR 1.48 (95%CI 1.21-1.80), p<0.01** • macrolides: **HR 0.79 (95%CI 0.65-0.98), p=0.03** • sulfonamides: HR 1.03 (95%CI 0.71-1.51), p=0.87	Sex, ethnicity, maternal age, education and smoking; antibiotic use during pregnancy, birth weight, delivery mode
Slykerman et al.[130] New Zealand 2019	Multicentre prospective cohort study (2b)	nr; 446 nr; 376 nr; 70	< 2 y No Parent questionnaire	11 y	Psychologist-administered, parent-reported and self-reported measures[1]	Exposure to AB in first 6 m of life associated with lower overall cognitive and verbal comprehension abilities, increased risk of problems with metacognition, executive function, impulsivity, hyperactivity, ADHD, anxiety and emotional problems. • **full scale IQ: mean difference -5.70 (95%CI -10.30, -1.20), p=0.04** • **verbal comprehension index: mean difference -8.40 (95%CI -14.00, -2.80), p=0.02** • metacognition index: aOR 2.20 (95%CI 0.90, 5.50), p=0.05 • **impulsivity/hyperactivity: aOR 2.10 (95%CI 0.90-5.00), p=0.02** • **executive function: aOR 3.80 (95%CI 1.20-11.70), p=0.04** • **emotional problems: aOR 9.20 (95%CI 2.00-43.00), p<0.01** • **hyperactivity: aOR 8.20 (95%CI 0.90-73.10), p<0.01** • **total anxiety score: aOR 5.40 (95%CI 1.40-20.70), p<0.01**	Income, delivery mode, probiotic use, breastfeeding

(*continued on next page*)

Table 1 (*continued*)

* calculated from reported data

[1]WISC-IV (Wechsler Intelligence Scale for Children-fourth edition), CPT 3 (Conners Continuous Performance Test-third edition), CANTAB (Cambridge Automated Neuropsychological Test Battery), BRIEF (Behavior Rating Inventory of Executive Function), Conners 3, SDQ (Strengths and Difficulties Questionnaire), MASC 2 (Multidimensional Anxiety Scale for Children), CES-DC (Center for Epidemiological Studies for Children)

AB – antibiotic
ADHD – attention deficit hyperactivity disorder
a – adjusted
ASD – autism spectrum disorders
ATC – anatomical-therapeutic-chemical
BASME – Barn, Alleergi, Miljö, Stockhol, Epidemiologi
BMI – body mass index
CI – confidence interval
ECRHS II – European Community Respiratory Health Survey second version
GP – general practitioner
HLA – human leucocyte antigen
HR – hazard ratio
IBD – inflammatory bowel disease
ICD-10-CA – international classification of disease, tenth revision, Canadian Edition
ICD-9-CM – international classification of disease, ninth revision, clinical modification
ICD-9/10 – international classification of disease, ninth/tenth revision
IgE – immunoglobulin E
IRR – incidence rate ratio
ISAAC – International Study of Allergy and Asthma in Childhood
JIA – juvenile idiopathic arthritis
LRTI – lower respiratory tract infections
m – month
nr – not reported
OR – odds ratio
RP – ratio of proportion
RR – risk ratio
RRR – prevalence ratio
SPT – skin prick test
w – week
y – year

diagnosed by ISAAC questionnaire, ICD codes, skin prick test or serum IgE levels in 1,859,024 children (45,479 cases) (Table 1).[42,46,51,61,82,91,93,96,115,161,163,172,178,183,185] Of the 15 studies, 13 (87%) investigated the effect of antibiotic exposure in the first two years of life.[42,46,51,82,93,96,115,161,163,172,178,183,185] Nine (60%) reported a significantly increased incidence of food allergies in children who were exposed to antibiotics.[61,91,96,115,161,163,172,178,183,185] Two studies reported a positive correlation between the risk of developing food allergies and the number of antibiotic courses.[61,115] One study reported that the risk of developing food allergies was higher when children were exposed in the first year of life compared to the second or third year of life.[115] Four studies investigated the effect of different antibiotic classes.[61,91,163,172] One reported an increased risk of food allergies only after the exposure to cephalosporins, but not penicillins, macrolides and sufonamides.[172] Three studies reported an increased risk of all investigated antibiotic classes: penicillins, cephalosporins and macrolides[61]; penicillins, cephalosporins, macrolides and sulfonamides[163]; and penicillin, amoxicillin, cephalosporins, macrolides and trimethoprim/sulfamethoxazole,[91] respectively.

All studies provided sufficient data to be included in the meta-analysis (supplementary Fig. 3).[42,46,51,61,82,91,93,96,115,161,163,172,178,183,185] Of the 659,863 children exposed to antibiotics 16,703 (2.5%) developed food allergies compared to 28,776 (2.4%) of the 1,199,161 children not exposed to antibiotics. Overall, antibiotic exposure was associated with an increased risk of developing food allergies (OR 1.35, 95%CI 1.20–1.52, $p < 0.01$) (Fig. 2).

Allergic rhinoconjunctivitis

Forty studies investigated the association between antibiotic exposure and the risk of developing allergic rhinoconjunctivitis diagnosed by ISAAC questionnaire, ICD codes or parent's-reported diagnosis in 1,554,337 children (359,568 cases with one study not reporting number of cases) (Table 1).[16,29,32,35,37,43,48–50,59,60,74,82,93,96–98,102,103,110,112,129,150,154,155,157,158,161,162,172,176–178,181,182,186–190] Of the 40 studies, 38 (95%) investigated the effect of antibiotic exposure in the first five years of life (35 (88%) in the first two years of life).[16,29,32,35,37,43,48–50,59,60,74,82,93,96–98,102,103,110,112,129,150,157,158,161,162,172,176–178,172,181,186–190] Twenty-nine (73%) reported a significantly increased incidence of allergic rhinoconjunctivitis in children who were exposed to antibiotics.[16,29,35,37,43,48–50,59,60,74,82,96,97,102,103,110,129,150,157,158,161,172,176,181,186–189] One study reported that the risk of developing allergic rhinitis was higher when children were exposed to antibiotics in the third year of life compared to the second or first year of life.[29] Three studies reported that the risk increased after more than one antibiotic course,[29,103,176] while another could not confirm this finding.[182] Four studies investigated the effect of antibiotic class.[29,157,172,182] One study reported that the risk of developing allergic rhinoconjunctivitis was higher after exposure to cephalosporins and macrolides compared to penicillins and sulfonamides,[172] and one study after exposure to cephem compared to penicillins or macrolides.[157] Two studies did not find a difference between antibiotic classes and the risk of allergic rhinoconjunctivitis.[29,182]

Twenty-seven (68%) studies provided sufficient data to be included in the meta-analysis (supplementary Fig. 4).[16,32,35,37,43,48,49,59,74,82,93,96,97,102,103,112,154,157,158,161,162,172,176,178,181,188,190] Of the 200,029 children exposed to antibiotics 61,899 (30%) developed allergic rhinoconjunctivitis compared to 204,006 (28%) of the 718,124 children not exposed to antibiotics. Overall, antibiotic exposure was associated with an increased risk of allergic rhinoconjunctivitis (OR 1.66, 95%CI 1.51–1.83, $p < 0.01$) (Fig. 2).

Wheezing

Thirty-two studies investigated the association between antibiotic exposure and the risk of developing wheezing in 220,415 children (29,229 cases) diagnosed by ISAAC questionnaire, ICD codes or parent-reported diagnosis (Table 1).[13,15,37,40,49,56,59,60,79,80,95,97,103–105,115,119,126,137,154,155,157,161,162,164–166,178,191–194] Of the 32 studies, 29 (91%) investigated the effect of antibiotic exposure in the first five years of life (26 (81%) in the first two years of life).[13,15,37,40,49,56,59,60,69,79,80,95,97,103–105,115,119,126,137,157,161,162,164,165,178,191–194]

Twenty-seven (84%) reported a significantly increased incidence of wheezing in children who were exposed to antibiotics.[13,15,37,49,56,59,60,79,95,97,103,104,115,119,126,137,154,155,161,164–166,178,191–194] Five studies reported that the risk of developing wheezing increased with the number of antibiotics courses.[13,103,115,178,191] One study reported that the risk of wheezing was higher after exposure to cephem compared to penicillins or macrolides[157] and one study after exposure to macrolides compared to other antibiotic classes.[137]

Twenty-seven (84%) studies provided sufficient data to be included in the meta-analysis (supplementary Fig. 5).[13,15,37,40,49,56,59,79,80,95,97,103–105,115,119,154,155,157,161,162,166,178,191–194] Of the 94,076 children exposed to antibiotics 16,172 (17%) developed wheezing compared to 11,169 (9%) of the 120,466 children not exposed to antibiotics. Overall, antibiotic exposure was associated with an increased risk of developing wheezing (OR 1.81, 95%CI 1.65–1.97, $p < 0.01$) (Fig. 2).

Asthma

Sixty-three studies investigated the association between antibiotic exposure and the risk of developing asthma mainly diagnosed by ISAAC questionnaire, ICD codes or parent-reported diagnosis in 12,366,759 children (312,230 cases with two studies not reporting number of cases) (Table 1).[12,13,32,34,37,39,41,43,48–50,52,55,59,69,75–77,80,82,88,92,93,96–98,101–104,109,111,112,115,116,126,132,134,135,150,153–157,159,161,162,164,167–169,172,176–178,181,182,191,195–197,175] Of the 63 studies, 59 (94%) investigated the effect of antibiotic exposure in the first five years of life (56 (89%) in the first two years of life).[12,13,31,32,37,39,41,43,48–50,52,55,59,69,75–77,80,82,88,93,96–98,101–104,109,111,112,115,116,126,132,134,135,150,153,156,157,159,161,162,164,167–169,172,176–178,172,181,191,195–197]

Fifty-four (86%) reported a significantly increased incidence of asthma in children who were exposed to antibiotics.[12,13,31,34,37,39,41,43,48–50,52,55,69,75–77,82,88,92,93,96,97,101–104,109,111,115,116,126,132,134,135,150,154,156,157,159,161,162,164,168,169,172,176,178,172,181,191,195–197] However, one study only after two courses of antibiotics.[115] One study reported that the risk of developing asthma was higher when higher doses of antibiotics were used.[34] Another study reported that the risk of asthma was not increased after antibiotic exposure in the first six months of life, but it was increased when exposed during the first three years of life[12]; and one study that the effect of antibiotics on the incidence of asthma was stronger in children with younger age at onset.[197] Six studies reported that the risk of asthma was highest after exposure to macrolides,[34,69,92,111,195] three studies that it as higher after exposure to cephalosporins compared to penicillins and macrolides,[69,157,182] and one study after exposure to penicillins, cephalosporins and macrolides compared to sulfonamides.[172] One study reported that the risk of asthma was higher after exposure to broad-spectrum compared to narrow-spectrum antibiotics.[197] Many studies reported that the risk of

developing asthma increased with the number of antibiotics courses[13,32,48,76,103,109,111,115,116,154,176,178,181,182,191,195,197,175] and one study that the risk was higher after higher doses of antibiotics.[34] Two studies did not find an association between antibiotic exposure and the development of asthma after adjusting for number of illnesses or chest infections.[135,153] One study found a higher risk in girls to develop asthma after exposure to antibiotics.[39]

Fifty-one (81%) studies provided sufficient data to be included in the meta-analysis (supplementary Fig. 6).[12,13,31,32,34,37,39,41,43,48,49,55,59,69,75,77,80,82,88,92,93,96,97,101–104,109,111,115,116,132,134,135,153,154,156,157,161,162,167–169,172,176,178,181,191,195,196] Of the 909,797 children exposed to antibiotics 122,450 (13%) developed asthma compared to 128,778 (10%) of the 1,245,440 children not exposed to antibiotics. Overall, antibiotic exposure was associated with an increased risk of developing asthma (OR 1.96, 95%CI 1.76–2.17, $p < 0.01$) (Fig. 2).

Allergic symptoms

Four studies including 24,840 children (5019 cases) investigated the association between antibiotic exposure and the development of allergic symptoms without specifying the symptoms or reporting results separately for atopic dermatitis, allergic rhinitis, food allergies, wheezing or asthma (Table 1).[61,82,177,183] All four studies investigated the effect of antibiotic exposure in the first year of life.[61,82,177,183] Three (75%) of the studies reported a significantly increased risk of developing allergic symptoms in children who were exposed to antibiotics.[61,82,183] One study reported that the risk of allergic sensitisation increased with the number of antibiotic courses and that it was higher after exposure to penicillin compared to cephalosporins and macorlides.[61]

Three (75%) studies could be included in the meta-analysis (supplementary Fig. 7).[61,82,183] Of the 17,906 children exposed to antibiotics 3634 (20%) developed allergic symptoms compared to 906 (15%) of 6009 children not exposed to antibiotics. The overall OR for developing allergic symptoms after antibiotic exposure was 1.93, 95%CI 1.66–2.26, $p < 0.01$ (Fig. 2).

Infantile colic

One study investigated the association between antibiotic exposure and the development of infantile colic in 436 neonates (74 cases) (Table 1 and supplementary Fig. 8).[105] Of the 151 neonates exposed to antibiotics in the first week of life, 33 (22%) developed infantile colic compared to 41 (14%) of the 285 neonates not exposed. The OR was 1.66 (95%CI 1.00–2.77, $p = 0.05$) (Fig. 2 and supplementary Fig. 8).

Abdominal pain

One study investigated the association between antibiotic exposure and the development of abdominal pain in 2732 children (245 cases) diagnosed by a validated questionnaire (Table 1 and supplementary Fig. 9).[144] Of the 861 children exposed to antibiotics in the first two years of life, 87 (10%) developed abdominal pain compared to 144 (8%) of the 1793 children not exposed to antibiotics. Of the children exposed to antibiotics between the age of nine to twelve years these numbers were 94 (9%) of 1045 and 151 (9%) of 1687, respectively. The risk of abdominal pain increased with the number of antibiotic courses and was highest after exposure to tetracycline compared to other antibiotics. Overall, the evidence did not support an association between exposure to antibiotics and the incidence of abdominal pain later in life (Fig. 2 and supplementary Fig. 9). OR 1.01 (95%CI 0.77–1.32, $p = 0.37$).

Inflammatory bowel disease

Six studies investigated the association between exposure to antibiotics and the development of inflammatory bowel disease (IBD) in 2481,433 children (1617 cases) (Table 1).[30,68,78,106,127,148] Four (67%) studies investigated the effect of antibiotic exposure in the first year of life.[30,78,127,148] Five (83%) of the studies reported a significant association between antibiotic exposure and developing IBD.[68,78,106,127,148] One study reported a higher association between Crohn's disease than ulcerative colitis[68] and another study an association between antibiotic exposure and developing Crohn's disease but not ulcerative colitis.[148] Two studies found an association between the number of antibiotic courses and the risk of IBD.[30,78] However two other studies could not confirm this association.[106,148] One study reported that the risk was highest after exposure to metronidazole, penicillins, cephalosporins and fluoroquinolones compared to other antibiotic classes,[78] one after cephalosporins,[148] and one that it was after exposure to penicillins compared to macrolides.[68]

All six studies were included in the meta-analysis (supplementary Fig. 10).[30,68,78,106,127,148] Of the 1,650,507 children exposed to antibiotics 976 (0.06%) developed IBD compared to 641 (0.08%) of the 830,926 children not exposed to antibiotics. Overall, the evidence did not support an association between antibiotic exposure and developing IBD (OR 1.19, 95%CI 0.83–1.71, $p = 0.35$) (Fig. 2).

Celiac disease

Four studies investigated the association between antibiotic exposure and developing celiac disease by ICD codes, antibody measurement or the criteria by the European Society for pediatric Gastroenterology, Hepatology and Nutrition in 1728,197 children (4.547 cases) (Table 1).[44,73,172,199] All of the studies were done in children less than 4 years of age (three (75%) in children less than 2 years of age).[44,73,172,199] Two (50%) of the studies found a positive association between antibiotic exposure and developing celiac disease.[44,172] One study reported that the risk was highest in girls after exposure to penicillins[172] and one study did not find a difference in the risk of celiac disease after exposure to different antibiotic classes.[73]

Three (75%) studies were included in the meta-analysis (supplementary Fig. 11).[44,172,199] Of the 531,197 children exposed to antibiotics 1149 (0.22%) developed celiac disease compared to 2615 (0.23%) of the 1160,442 children not exposed to antibiotics. Overall, the evidence did not support an association between antibiotic exposure and developing celiac disease (OR 1.21, 95%CI 0.80–1.83, $p = 0.37$) (Fig. 2).

Increased weight gain or overweight

Seventeen studies investigated the association between antibiotic exposure and the risk of developing increased weight gain or overweight evaluated by weight, weight-for-age z-scores, body mass index (BMI), BMI z-scores, or fat percentage in 569,527 children (137,744 cases with five studies not reporting number of cases) (Table 1).[14,23,27,33,54,71,75,89,121,124,131,143,170,172,176,200–202] Of the 17 studies, 16 (94%) investigated the effect of antibiotic exposure in the first five years of life (15 (88%) in the first two years of life).[162–171] Overall, 12 (71%) studies reported a significant increased weight gain in children who were exposed to antibiotics.[23,27,38,54,71,121,124,131,143,172,201,202] Three studies reported that the strongest association with antibiotic exposure and developing increased weight gain was observed after exposure to macrolides.[121,124,201] Two studies reported that the association between antibiotic exposure and increased weight gain was stronger in boys.[23,121] In two studies the risk of increased weight gain

increased the number of antibiotic courses given[33,121] and in one study an association could only be found when antibiotics were given in the first six months of life.[143] In contrast, another study did not find increased weight gain after antibiotic exposure in the first six months of life but in first two years of life.[54] Four studies found a higher risk of overweight after exposure to macrolides,[54,89,121,124] while no clear influence of different antibiotic classes and the risk of increased weight gain could be found in other studies.[33,172,201,202]

Of the 17 studies, 10 (59%) provided sufficient data to be included in the meta-analysis (supplementary Fig. 12).[14,23,27,33,38,89,121,124,143,172] Of the 311,694 children exposed to antibiotics 90,234 (29%) developed increased weight gain or overweight compared to 47,429 (23%) of the 207,084 children not exposed to antibiotics. Overall, the OR for developing increased weight gain or overweight after antibiotic exposure was 1.18, 95% CI 1.11 to 1.26, $p < 0.01$ (Fig. 2).

Obesity

Fourteen studies investigated the association between antibiotic exposure and the risk of developing obesity evaluated by BMI or BMI z-scores in 1,233,944 children (128,132 cases with two studies not reporting number of cases) (Table 1).[14,25,27,33,45,72,81,83,99,125,133,143,147,172] Of the 14 studies, 13 (93%) investigated the effect of antibiotic exposure in the first five years of life (12 (86%) in the first two years of life).[14,25,27,33,72,81,83,99,125,133,143,147,172] Overall, nine (64%) studies reported a significant increased incidence of obesity in children who were exposed to antibiotics.[14,25,27,81,99,125,133,147,172] Three studies reported that the risk of obesity increased with the number of antibiotic courses.[33,72,133] One study reported that the risk of developing obesity was highest with antibiotic exposure in the first six months of life.[25] One study found an increased risk of obesity only after exposure to trimethoprim/sulfamethoxazole but not penicillins, cephalosporins and macrolides.[33] No influence of different antibiotic classes and the risk of increased weight gain was found in two other studies.[133,172]

Of the 14 studies, 10 (71%) provided sufficient data to be included in the meta-analysis (supplementary Fig. 13).[25,27,33,45,72,125,133,143,147,172] Of the 508,908 children exposed to antibiotics 72,186 (14%) developed obesity compared to 30,996 (12%) of the 260,057 children not exposed to antibiotics 47,429 (23%). The overall OR for developing obesity after antibiotic exposure was 1.21, 95% CI 1.05 to 1.40, $p < 0.01$ (Fig. 2).

Growth failure

Three studies investigated the association between antibiotic exposure and growth failure evaluated by weight, weight z-scores or weight-for-height z-scores in 13,364 children.[71,145,203] Only one study found that antibiotics were associated with decreased weight gain, this was a small study investigating antibiotic exposure in the first week of life and weight at one year of age.[71]

Juvenile idiopathic arthritis

Two studies investigated the association between antibiotic exposure and the risk of developing juvenile idiopathic arthritis (JIA) by evaluating ICD codes in 8149 children (1450 cases).[18,64] One study investigated antibiotic exposure in the first and second year of life and any antibiotic exposure before diagnosis[18] and the other study any antibiotic exposure before diagnosis.[64] The risk of developing JIA was increased after antibiotic exposure at all these time points. In the first year of life the strongest association was found after exposure to penicillins and cephalosporins and at the later time points after exposure to lincosamides and cephalosporins.[18] One study reported that the risk of JIA increased with the number of antibiotic courses.[64]

Both studies were included in the meta-analysis the OR was 1.74 (95%CI 1.21–2.52), $p < 0.01$) (Fig. 2 and supplementary data Fig. 14).[18,64] Of the 6809 children exposed to antibiotics 1291 (19%) developed JIA compared to 159 (12%) of the 1340 children not exposed to antibiotics.

Psoriasis

One study investigated the association between antibiotic exposure and the risk of developing psoriasis by evaluating ICD codes in 9295 children (845 cases).[65] They investigated antibiotic exposure in the two years before diagnosis. The OR was 1.75 (95%CI 1.44–2.11), $p < 0.01$ (adjusted OR 1.20 ((95%CI 1.00–1.50), $p = 0.05$)) (Fig. 2 and supplementary data Fig. 15). Of the 7053 children exposed to antibiotics 710 (10%) developed psoriasis compared to 135 (6%) of the 2242 children not exposed to antibiotics.

Type 1 diabetes

Six studies investigated the association between antibiotic exposure and the risk of developing type 1 diabetes in 2,469,967 children (5557cases).[36,94,140,152,171,204] The diagnosis was mainly made by ICD codes; in one study by hospital discharge or prescription records. Of the six studies, five (83%) evaluated antibiotic exposure before the age of two years.[36,94,140,152,171] Only one of the studies reported an increased risk of developing type 1 diabetes in children who were exposed to antibiotics, this was in children who had an exposure in the first year of life.[152] No association between the number of antibiotic courses and the risk of type 1 diabetes could be found.[94,140] Two studies found a slightly higher risk of type 1 diabetes after exposure to broad-spectrum antibiotics[36,94] and one after exposure to macrolides compared to penicillins.[204]

Five (83%) studies were included in the meta-analysis the overall OR was 0.99 (95%CI 0.82–1.19), $p = 0.93$) (Fig. 2 and supplementary data Fig. 16).[36,67,94,152,171] Of the 1,420,794 children exposed to antibiotics 3428 (0.24%) developed type 1 diabetes compared to 1726 (0.18%) of the 947,331 children not exposed to antibiotics.

Fluorosis

One study investigated the association between antibiotic exposure and the development of fluorosis.[63] The study did not find an increased risk of developing fluorosis in children who were exposed to antibiotics. The OR was 1.11 (95%CI 0.40–3.09), $p = 0.85$) (Fig. 2 and supplementary data Fig. 17). Of the 174 children exposed to antibiotics 62 (36%) developed fluorosis compared to 6 (33%) of the 18 children not exposed to antibiotics.

Autism spectrum disorders

Three studies investigated the association between antibiotic exposure and the risk of developing autism spectrum disorders evaluated by ICD codes in 901,012 children (11,374 cases).[21,57,172] All three studies investigated antibiotic exposure in the first two years of life.[21,57,172] Two studies found an association between antibiotic exposure and the development of autism spectrum disorders.[21,172] However, one study only after exposure to cephalosporins and not penicillins, macrolides or sulfonamides.[172] The other study reported that the risk of autism was higher for broad-spectrum antibiotics compared to penicillins.[21] Two studies reported a decreased risk of autism spectrum disorders after exposure to penicillins and one after exposure to macrolides.[57,172] The one study which investigated the effect of the number of antibiotic

courses on the risk of autism spectrum disorders could not find an association.[57]

All three studies were included in the meta-analysis the overall OR was 1.19 (95%CI 1.04–1.36), $p = 0.01$) (Fig. 2 and supplementary data Fig. 18).[21,57,172] Of the 587,667 children exposed to antibiotics 7779 (1.3%) developed autism spectrum disorders compared to 3595 (1.1%) of the 313,345 children not exposed to antibiotics.

Attention deficit hyperactivity disorder

Four studies investigated the association between antibiotic exposure and the development of attention deficit hyperactivity disorders (ADHD) in 756,348 children (25,143 cases with one study not reporting number of cases).[22,58,130,172] They evaluated children by ICD codes. All four studies evaluated antibiotic exposure before two years of age.[22,58,130,172] Two studies reported a significant increased risk of developing ADHD in children who were exposed to antibiotics.[130,172] One study could not find a difference in the risk of developing ADHD after exposure to penicillins or broad-spectrum antibiotics,[22] while another study found an increased risk after exposure to penicillin in girls compared to other antibiotic classes.[172]

Three (75%) studies were included in the meta-analysis and the overall OR was 1.30 (95%CI 0.97–1.75), $p = 0.08$) (Fig. 2 and supplementary data Fig. 19).[22,58,172] Of the 528,497 children exposed to antibiotics 18,073 (3%) developed ADHD compared to 7070 (3%) of the 227,405 children not exposed to antibiotics.

Neurodevelopmental disorders

Two studies investigated the association between antibiotic exposure and the development of neurodevelopmental disorders.[130,172] Both studies evaluated antibiotic exposure before two years of age. The first study found an increased risk of developing learning disorders in children who were exposed to antibiotics in the first two years of life (Fig. 2 and supplementary data Fig. 20).[172] The second study found that exposure to antibiotics in first 6 months of life was associated with lower overall cognitive and verbal comprehension abilities, an increased risk of developing problems with metacognition, executive function, impulsivity, hyperactivity, ADHD, anxiety and emotional problems.[130]

Discussion

Our rigorous systematic review and meta-analysis suggest an association between antibiotic exposure and the development of several immunological, metabolic, and neurobehavioural adverse long-term health outcomes in children. For developing wheezing and asthma the risk is nearly double in children who are exposed to antibiotics, for JIA and allergic rhinoconjunctivitis up to 75% higher, for food allergies and atopic dermatitis up to 38% higher and for increased weight gain, overweight and obesity 20% higher. No association was found between antibiotic exposure and the risk of developing allergic sensitisation, abdominal pain, inflammatory bowel diseases, celiac disease, type 1 diabetes, psoriasis, fluorosis. There is limited data in relation to the association between antibiotic exposure and developing neuropsychological diseases, however three studies suggest an association between antibiotic exposure and the development of ADHD or learning disorders.[22,130,172]

Our findings are in line with these from smaller systematic reviews which indicated that antibiotic exposure is associated with the development of allergic symptoms such as allergic rhinoconjunctivitis, atopic dermatitis, food allergies, as well as asthma and obesity, but not celiac disease or autism spectrum disorder.[205–218] In contrast, previous reviews have reported an association between antibiotic exposure and the development of inflammatory bowel diseases, especially Crohn's disease.[219–222] However, these reviews either included less studies, did not pool the results from different studies or included children who were born preterm.

There is an association between the timing, number and type of antibiotic exposure and the risk of adverse health outcomes. Most of the studies included in this review investigated early-life exposure to antibiotics (in the first two years of age). This coincides with the time when antibiotic consumption is at its highest.[4,5] Up to 70% of children receive antibiotics during the second year of life.[4,5] One of the main reasons for antibiotic exposure in this age group are respiratory tract infections, including otitis media, for which antibiotics could be deferred or even avoided.[223–225] Additionally, many studies show that the risk of adverse long-term health outcomes increases with the number of antibiotic courses, particularly for asthma.[13,25,29,32,61,64,76,78,93,103,109,111,115,116,121,123,148,154,176,181,182,191,195,197,198,201] Moreover, the risk of adverse long-term health outcomes is often higher for antibiotics with a broad-spectrum including cephalosporins and macrolides.[18,21,34,36,57,58,61,69,78,91,92,111,121,123,137,157,163,172,182,195,197] These findings underline the importance of antibiotic stewardship, specifically to avoid antibiotics for infections that are likely viral and to use the most narrow-spectrum antibiotic possible.[226] A recent large population-based prospective study showed that a reduction in the incidence of asthma in children correlated with the decrease in antibiotic exposure during infancy.[227]

One of the most probable mechanism underlying the association between antibiotic exposure and adverse long-term health outcomes is changes in the microbiota. It is well known that antibiotics cause profound changes in the microbiota.[228,229] The disruption of intestinal microbiota in the early-life period, during which the microbiota and the immune response develop concurrently, is likely associated with the development of immune- and non-immune-mediated diseases.[230,231] Even transient perturbations of the microbiota during this 'critical window' may compromise immune tolerance and inflammatory responses.[232]

The disruption of intestinal microbiota in the early-life period has been associated with an increased risk of development of the same diseases as antibiotic exposure, including allergies, eczema, asthma, chronic inflammatory bowel disease, obesity and type 1 diabetes.[125,230,233,234] In adolescents with ADHD, perturbations of the intestinal microbiota has also been described.[235]

The strengths of this review are the comprehensive literature search and depth of the review. Most of the included studies defined outcomes using validated tools, adjusted their estimates appropriately, and investigated antibiotic exposure in the first two years of life, which decreases heterogeneity. However, any antibiotic exposure beyond this period could impact the outcome and ignoring them could dilute the effect observed. The same is true for any antibiotic exposure not measured due to the multiple potential sources (e.g. emergency department, general practice, hospital, relative, other country, self-administration), and the availability of antibiotics over the counter in some settings.

The studies included are also limited by their observational nature and potential bias, mainly recall. There are also other potential confounding factors, for example the possibility that early or frequent respiratory infections for which antibiotics are prescribed increase the risk of subsequent asthma. In addition, it can be difficult to differentiate the effect of antibiotic exposure from that of the infection being treated.

Protopathic bias, a false conclusion on a causal relationship between exposure and outcome, is also important to consider. For example, it is possible that children who are predisposed to immune-mediated diseases are more likely to have infections that need antibiotics or seek antibiotics. For example, early symptoms of undiagnosed asthma could be mis-

taken for a respiratory tract infection and be treated with antibiotics. Furthermore, the risk of infection in children with a predisposition to immune-mediated diseases is increased in the years preceding the diagnosis,[236] and therefore causation could be in the opposite direction. Likewise for autism spectrum disorders, in which symptoms can be present from birth but is rarely diagnosed before three years of age, difference in antibiotic exposure could reflect difference in practice. Finally, many unmeasured socio-economics factors could also influence both the exposure to antibiotics and the outcomes.

However, the fact that, in many studies, an association between antibiotic exposure and adverse health-outcomes was only found after broad-spectrum antibiotics and the influence of number of doses of antibiotics supports the notion that antibiotics are the cause.

In summary, the studies in our review suggest that antibiotic exposure plays an important role in the development of childhood immune disorders, likely through disruption of the microbiota during early-life.[227] Although a definite causal association cannot be determined from these studies, the results support the meticulous application of sound antibiotic stewardship to avoid potential adverse long-term health outcomes. It also questions the use of antibiotic prophylaxis outside well-recognised indications. Further assessment of long-term outcomes should be included within RCTs comparing antibiotic treatment or prophylaxis to placebo. Future studies are needed to provide evidence-based interventions to prevent adverse long-term outcomes when antibiotics cannot be avoided, such as modifying the intestinal microbiota with directed pre- and probiotics, bacteriophages, or microbial DNA.[237–239]

Declaration of Competing Interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

Quynh A Duong: Investigation, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Laure F Pittet:** Writing – review & editing. **Nigel Curtis:** Writing – review & editing. **Petra Zimmermann:** Investigation, Formal analysis, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.01.005.

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