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Supplemental Material

The Role of Biodiversity in the Development of Asthma and Allergic Sensitization: A State-of-the-Science Review

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PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4-5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4-5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4-5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	NA
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	NA
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	5

Section and Topic	Item #	Checklist item	Location where item is reported
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	5-7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	NA
Study characteristics	17	Cite each included study and present its characteristics.	5-7
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	NA
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	NA
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	7-13
	23b	Discuss any limitations of the evidence included in the review.	7-13
	23c	Discuss any limitations of the review processes used.	7-8
	23d	Discuss implications of the results for practice, policy, and future research.	10-13
OTHER INFORMATION			

Section and Topic	Item #	Checklist item	Location where item is reported
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	7-8
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	13
Competing interests	26	Declare any competing interests of review authors.	13
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	14

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

NA: not applicable

Table S1. Characteristics of studies included in the comprehensive review (n=82)

Reference, study year (country)	Study population	Study design	Study size	Follow-up period	Definition of health outcome and period of assessment	Method of data collection for exposure assessment and time-period	(Quali)quantitative results
					Outer layer biodiversity		
Ege, et al. [1], 2011 (Germany)	Children (6-13 years)	Case-control	1 511	--	Questionnaires (respiratory and allergic symptoms and asthma diagnosis); atopic sensitization was evaluated by specific IgE antibodies. Cross-sectional survey performed during childhood	Mattress dust samples; single-strand conformation polymorphism (SSCP) gels. Cross-sectional survey performed during childhood	quantitative
Ege, et al. [2], 2012 (Germany)	Children (≈ 8 years)	Cross-sectional	489	--	Questionnaire (asthma); atopic sensitization was evaluated by specific IgE. Cross-sectional survey performed during childhood	Mattress dust samples; single-stranded DNA and analyzed on SSCP gels. Cross-sectional survey performed during childhood	quantitative
Hanski, et al. [3], 2012 (Finland)	Children (14-18 years)	Cross-sectional	118	--	Atopic sensitization was evaluated by skin prick testing and specific IgE. Cross-sectional survey performed during adolescence (2010)	Environmental biodiversity based on land use types surrounding the home within 3km; skin samples, V1-V3 regions of 16S rRNA gene were sequenced. Cross-sectional survey performed during adolescence (2010)	quantitative
Lynch, et al. [4], 2014 (USA)	Children (3 years)	Cohort	560	3 years	Atopic sensitization was evaluated by specific IgE at age three.	Dust samples (living room) collected in the 1st year of life; 16S rRNA gene were sequenced. First year of life	qualitative
Ciaccio, et al. [5], 2015 (USA)	Children (2.4-4.8 years)	Cross-sectional	19 dwellings	--	Questionnaires (asthma). Cross-sectional survey performed during childhood (between October 2008 and November 2011)	Dust samples; 16S rRNA gene were sequenced. Cross-sectional survey performed during childhood (between October 2008 and November 2011)	qualitative
Ruokolainen, et al. [6], 2015 (Finland and Estonian)	Children and young adults (0.5-20 years)	Cross-sectional	1 044	--	Atopic sensitization was evaluated by specific IgE. Cross-sectional survey performed during childhood/early adulthood (between 2003 and 2012)	Environmental biodiversity based on land use types. Cross-sectional survey performed during childhood/early adulthood (between 2003 and 2012)	quantitative
Valkonen, et al. [7], 2015 (Germany, Austria and Switzerland)	Children (6-12 years)	Cross-sectional	224	--	Questionnaire (asthma and atopy). Cross-sectional survey performed during childhood	Mattress dust samples, bands based on the gradient gel electrophoresis (DGGE). Cross-sectional survey performed during childhood	quantitative
Tischer, et al. [8], 2016 (Germany)	Children aged 6 and 10 years	Cohort	189	10 years	Parent-reported questionnaires (Wheezing in the preceding 12 months at age of 6, 12, 18, 24 months and at 4, 6, and 10 years of age); allergen sensitization was determined by skin prick testing at 18, 36 and 60 months	Dust samples (collected after birth from living room floors). 16S rRNA gene were sequenced	quantitative

Birzele, et al. [9], 2017 (Austria)	Children (6-12 years)	Cross-sectional	86	--	Questionnaire (asthma). Cross-sectional survey performed during childhood	Mattress dust and nasal samples. V3-V5 regions of 16S rRNA gene were sequenced. Cross-sectional survey performed during childhood	quantitative
Cavaleiro Rufo, et al. [10], 2017 (Portugal)	Children (8-10 years)	Cross-sectional	858	--	Questionnaire (asthma); allergic sensitization was determined by skin prick testing. Cross-sectional survey performed during childhood	Diversity scores of fungi: number of different fungal species. Cross-sectional survey performed during childhood	quantitative
Campbell, et al. [11], 2017 (14 different countries)	26–54-year-old adults	Cohort	10 201	5 years	Questionnaire and bronchial hyperresponsiveness to define current asthma; atopic sensitization was evaluated by specific IgE at 41.9 (SD: 7.2) years of age	Biodiversity score based on childhood (before 5 years old) exposure to cats, dogs, day care, bedroom sharing and older siblings	quantitative
Dannemiller, et al. [12], 2016 (USA)	Children (5-10 years)	Cross-sectional	196	--	Questionnaires (active asthma, severe asthma); atopic sensitization was evaluated by specific IgE. Cross-sectional survey performed during childhood	Dust samples; V4 regions of 16S rRNA gene were sequenced. Cross-sectional survey performed during childhood	quantitative
Karvonen, et al. [13], 2017 (Finland)	Children (1 and 6 years)	Cohort	410	6 years	Questionnaires (asthma, wheezing, cough and atopic dermatitis, at the age of 2, 12, 18, and 24 months, and thereafter annually); atopic sensitization was evaluated by specific IgE (age of 1 and 6 years)	Dust samples (collected at 2 months of age), qPCR for microbial DNA	quantitative
Donovan, et al. [14], 2018 (New Zealand)	Children (18 years)	Cohort	49 956	18 years	Pharmacy and hospital discharge records (asthma) at 18 years of age	Environmental biodiversity based on vegetation diversity (total number of natural landcover types). Mean lifetime exposure (prenatal to age 18)	quantitative
Lai, et al. [15], 2018 (USA)	Children (average 8.1 years old)	Randomized controlled trial	25	--	Telephone survey of the child's parent or caretaker (asthma) at 8.1 years of age	Dust samples from classrooms and homes; shotgun metagenomics sequencing at 8.1 years of age	quantitative
Loo, et al. [16], 2018 (Singapore)	Children (3-60 months)	Cohort	50	5 years	Questionnaires administered at 3, 6, 9, 12, 15, 18, 24, 36, 48 and 60 months; allergen sensitization was determined by skin prick testing (SPT) at 18, 36 and 60 months. Allergic subjects have a positive SPT to at least one of the tested allergens at year 5 and have ever given positive replies to questions on allergic outcomes. Non-allergic subjects have no positive SPT and answered "no" to all questions on allergy in the first 5 years of life.	Dust samples (bed, sofa, and play area). V3-V4 regions of 16S rRNA gene were sequenced at the year 5.5 follow up	qualitative

O'Connor, et al. [17], 2018 (USA)	Children (3 and 7 years)	Cohort	442	7 years	Questionnaires (asthma) and spirometry with bronchodilation at 7 years of age	Dust samples collected at 3 months of age; 16S rRNA gene were sequenced	qualitative
Pekkanen, et al. [18], 2018 (7 European countries)	Adults (29–55 years)	Cross-sectional	397 (cases: 199; controls: 198)	--	Questionnaire (asthma). Cross-sectional survey performed during adulthood	Mattress dust samples; denaturing gradient gel electrophoresis and qPCR assays. Cross-sectional survey performed during adulthood	quantitative
Valkonen, et al. [19], 2018 (7 European countries)	Adults (29–55 years)	Cross-sectional	397	--	Questionnaire (asthma); atopic sensitization was evaluated by specific IgE. Cross-sectional survey performed during adulthood	Mattress dust samples; qPCR assays. Cross-sectional survey performed during adulthood	qualitative
Karvonen[20], 2019 (Finland)	Children (10.5 years)	Cohort	373	10.5-year follow-up	Parent-reported questionnaires (ever and current asthma) at 10.5-year follow-up	Dust samples (living rooms) at two months of age. V4 regions of 16S rRNA gene were sequenced	quantitative
Kirjavainen, et al. [21], 2019 (Finland)	Children (6 years)	Cohort	431	6 years	Parent-reported questionnaires (ever and current asthma) at 6 years of age; atopic sensitization was evaluated by specific IgE	Dust samples (living room floor from farm and non-farm homes) collected at two months of age. V4 regions of 16S rRNA gene were sequenced	quantitative
Cavaleiro Rufo, et al. [22], 2020 (Portugal)	Children (8-10 years)	Cross-sectional	858	--	Questionnaire (asthma and allergic diseases); allergic sensitization was determined by skin prick testing; spirometry with bronchodilation. Cross-sectional survey performed during childhood	species richness index (SRI): included 4 vertebrate groups (amphibians, birds, reptiles and small mammals), totaling 89 different species. Cross-sectional survey performed during childhood	quantitative
Fu, et al. [23], 2020 (Malaysia)	Children (14-16 years)	Cross-sectional	309	--	Questionnaires (asthma symptoms) and validated asthma score to define asthma severity. Cross-sectional survey performed during childhood/adolescence	Floor dust from classrooms; 16S rRNA gene were sequenced. Cross-sectional survey performed during childhood/adolescence	quantitative
Gangneux, et al. [24], 2020 (France)	Children and adults	Case-control	30 dwellings (cases: 15; controls: 15)	--	Medical diagnosis (asthma) assessed during childhood and adulthood	Dust samples collected during childhood and adulthood; 16S rRNA gene were sequenced	quantitative
Adams, et al. [25], 2021 (Finland and Netherlands)	Children (≈ 9 years)	Cohort	2734	1 year	Questionnaires (respiratory symptoms – wheeze, nocturnal dry cough, rhinitis) administered during late fall/early winter 2008	Settled dust samples from classrooms collected during late winter/early spring 2009, late spring/early summer 2009 and during late winter/early spring 2010; 16S rRNA gene were sequenced	quantitative
Cavaleiro Rufo, et al. [26], 2021 (Portugal)	Children (4 and 7 years	Cohort	1 050	7 years	Questionnaire (asthma and allergic diseases at the ages of 4 and 7)	Species richness index (SRI): included 4 vertebrate groups (amphibians, birds, reptiles and small mammals), totalling 89 different species, assessed at birth	quantitative
Cox, et al. [27], 2021 (USA)	Children (7 and 12 years)	Cross-sectional	170	--	Questionnaires (asthma, rhinitis, and wheeze in the previous 12 months); atopic sensitization was evaluated by skin prick	Dust samples collected at 7 years of age;	quantitative

					testing, radioallergosorbent (RAST) and by specific IgE, assessed at 7 and 12 years of age		
Donovan, et al. [28], 2021 (USA)	Adults	Cross-sectional	26 367 census tracts	--	Census (asthma). Cross-sectional survey performed during adulthood	Plant diversity based on data from the Global Biodiversity Information Facility (GBIF). Cross-sectional survey performed during adulthood	quantitative
Fu, et al. [29], 2021 (China)	Young adults (IQR 20–23 years)	Cross-sectional	357	--	Questionnaires (asthma symptoms) and score of asthma symptoms performed in November and December 2013.	Settled air dust and floor dust samples from dormitory rooms in November and December 2013; 16S rRNA gene were sequenced	quantitative
Fu, et al. [30], 2021 (China)	Children (15-18 years)	Cross-sectional	1332	--	Questionnaires (asthma and rhinitis symptoms) performed in March 2088	Floor dust from classrooms (4 from rural areas and 5 from urban areas) collected in March 2008; 16S rRNA gene were sequenced	quantitative
Hyytiäinen, et al. [31], 2021 (Finland and Germany)	Children (10 years)	Cohort	506	10 years	Atopic sensitization was evaluated by specific IgE at the age of 10 years	Floor dust samples (collected at the child age of 2-3 months); V4 regions of 16S rRNA gene were sequenced	quantitative
Lehtimäki, et al. [32], 2021 (Denmark)	Children (6 years)	Cohort	700	6 years	Questionnaire (asthma by age 6 years based on quantitative symptom algorithm); atopic sensitization was evaluated by skin prick testing and by specific IgE. evaluated at 6 years of age	Environmental biodiversity based on land use types at birth; Airway and gut microbiota samples collected during 1st year of life, V4 region of 16S rRNA gene were sequenced	quantitative
Winnicki, et al. [33], 2022 (Denmark)	Individuals born 1995–2015	Cohort	40 249	23 years	Hospital contacts for asthma ICD-10 diagnoses or filled prescriptions on asthma medication from 1995 to 2018	Danish Biodiversity Map – bioscore (including plants, macrofungi, vertebrates and a subset of insect taxa) assessed during early childhood	qualitative
					Inner layer biodiversity		
Bisgaard, et al. [34], 2007 (Denmark)	Children (5 years)	Cohort	321	5 years	Clinical diagnosis (asthma) assessed at 5 years of age; atopic sensitization was evaluated by specific IgE at 4 years of age	Hypopharyngeal samples collected at 1 month of age; culture approach	quantitative
Hilty, et al. [35], 2010 (Ireland)	Children (1-17 years) and adults (37.6±18.2 – 52.9±11.1 years)	Cross-sectional	24 adults and 23 children	--	Clinical diagnosis (asthma, COPD). Cross-sectional survey performed during childhood and adulthood	Nose and oropharynx samples (adults) and broncho-alveolar lavage (children); 16S rRNA gene were sequenced. Cross-sectional survey performed during childhood and adulthood	qualitative
Bisgaard, et al. [36], 2011 (Denmark)	Children (6 years)	Cohort	411	6 years	Clinical diagnosis (asthma at 6 years); atopic sensitization was evaluated by skin prick testing and by specific IgE during	Stool samples collected at 1 and 12 months of age; 16S rRNA gene were sequenced combined with denaturing	quantitative

					the first 6 years of life (½, 1½, 4, and 6 years of age)	gradient gel electrophoresis and conventional culturing	
Cardenas, et al. [37], 2012 (Ecuador)	Children (±10.2 months)	Case-control	48 (cases: 24 with non-infectious early onset wheezing; controls: 24)	--	Clinical diagnosis (wheeze) assessed at 10.2 months of age	Oropharyngeal samples collected at 10.2 months of age; V3-V5 region of 16S rRNA gene were sequenced	qualitative
Marri, et al. [38], 2013 (USA)	Adults (≈ 26 years)	Cross-sectional	20	--	Questionnaire (asthma). Cross-sectional survey performed during adulthood	Induced sputum samples; V6 region of 16S rRNA gene were sequenced. Cross-sectional survey performed during adulthood	qualitative
Abrahamsson, et al. [39], 2014 (Sweden)	Children (7 years)	Cohort	47	7 years	Questionnaire (asthma) and exhaled nitric oxide at 7 years of age	Stool samples collected during the first year of life (1 week, 1 month, 1 year); 16S rRNA gene were sequenced	quantitative
Park, et al. [40], 2014 (Korea)	Adults (53.4±17.1 to 68.9±7.2)	Cross-sectional	47 (cases: 18 with asthma, 17 with COPD; controls; 12	--	NA Cross-sectional survey performed during adulthood	Oropharynx samples; V1-V3 region of 16S rRNA gene were sequenced. Cross-sectional survey performed during adulthood	quantitative
Arrieta, et al. [41], 2015 (Canada)	Children (3 years)	Case-control	319 (cases: 22 with atopy + wheeze, 87 with atopy, 136 with wheeze; controls: 74)	--	Questionnaire (asthma, wheeze); atopic sensitization was evaluated by skin prick testing at ages 1, 3 years	Stool samples collected during the first 100 days of life; V3 region of 16S rRNA gene were sequenced	qualitative
Denner, et al. [42], 2016 (USA)	Adults (44.2±1.8 and 34.3±3.0 years)	Cross-sectional	58	--	Clinical diagnosis (severe asthma). Cross-sectional survey performed during adulthood	Endobronchial brushings and bronchoalveolar lavage fluid samples; V4 region of 16S rRNA gene were sequenced. Cross-sectional survey performed during adulthood	qualitative
Hevia, et al. [43], 2016 (Spain)	Adults (≈ 39 years)	Cross-sectional (case-control)	43	--	Clinical diagnosis (asthma); atopic sensitization was evaluated by specific IgE and by skin prick testing. Cross-sectional survey performed during adulthood	Stool samples; 16S rRNA gene were sequenced. Cross-sectional survey performed during adulthood	qualitative
Hua, et al. [44], 2016 (USA)	Adults (±45.5 years)	Cross-sectional	1879	--	Questionnaire (asthma). Cross-sectional survey performed during adulthood	Stool samples; V4 region of 16S rRNA gene were sequenced. Cross-sectional survey performed during adulthood	quantitative
Stiemsma, et al. [45], 2016 (Canada)	Children (4 years)	Case-control	76 (cases: 39; controls: 37)	--	Questionnaires (asthma) performed at 4 years of age	Stool samples collected at 3 month and 1 year of age; V3 region of 16S rRNA gene were sequenced	qualitative

Zhang, et al. [46], 2016 (UK)	Adults (35.4±10.3 – 47.9±10.9 years)	Cross-sectional	56	--	Clinical diagnosis (severe asthma). Cross-sectional survey performed during adulthood	Induced sputum samples; V3-V5 region of 16S rRNA gene were sequenced. Cross-sectional survey performed during adulthood	qualitative
Chiu, et al. [47], 2017 (Taiwan)	Children (3-5 years)	Case-control	87 (cases: 32 with asthma, 23 with rhinitis; controls: 32)	--	Clinical diagnosis (asthma) performed between August 2013 to July 2015	Throat swabs collected between August 2013 to July 2015; V3- V4 region of 16S rRNA gene were sequenced	qualitative
Depner, et al. [48], 2017 (Germany, Austria and Switzerland)	Children (12 years)	Cross-sectional	333	--	Questionnaires (asthma). Cross-sectional survey performed during childhood	Throat (327) and nasal (68) samples; Cross-sectional survey performed during childhood	quantitative
Li, et al. [49], 2017 (China)	Adults (39.6±8.6 to 52.0±9.3 years)	Case-control	113 (cases: 49 non-smoking asthma patients, 25 with severe asthma, 24 with non-severe asthma; controls: 15)	--	Severe asthma was defined according to the ERS/ATS guidelines on severe asthma, while asthma severity was based on the GINA criteria; atopic sensitization was evaluated by skin prick testing. Cross-sectional survey performed during adulthood	Induced sputum samples; V3-V5 region of 16S rRNA gene were sequenced. Cross-sectional survey performed during adulthood	quantitative
Ruokolainen, et al. [50], 2017 (Finnish and Russian Karelia)	Children (14-20 years)	Cohort	180	10 years	Questionnaires (asthma); atopic sensitization was evaluated by specific IgE assessed in 2003, 2010 and 2012	Skin microbiota collected in 2012; V1-V3 region of 16S rRNA gene were sequenced	qualitative
Arrieta, et al. [51], 2018 (Ecuador)	Children (5 years)	Case-control	97 (cases: 27 children with atopic wheeze; controls: 70)	--	Questionnaires (wheeze in the previous 12 months and with evidence of atopy based on a positive skin prick test response) performed at 5 years of age	Stool samples collected at 3 months of age; 16S rRNA gene were sequenced	qualitative
Durack, et al. [52], 2018 (USA)	Adults (28-39 years)	Cross-sectional	45	--	Methacholine challenge test (asthma); atopic sensitization was evaluated by specific IgE. Cross-sectional survey performed during adulthood	Bronchial brushings, oral wash and induced sputum samples. In subset of 27 adults, intranasal brushings were also collected; V4 region of 16S rRNA gene were sequenced. Cross-sectional survey performed during adulthood	qualitative
Fazlollahi, et al. [53], 2018 (USA)	Adults (≈ 32 years)	Cross-sectional	72	--	Questionnaire (exacerbated asthma); Clinical diagnosis (asthma). Cross-sectional survey performed during adulthood	Nasal samples; V3-V4 region of 16S rRNA gene were sequenced. Cross-sectional survey performed during adulthood	qualitative

Kim, et al. [54], 2018 (South Korea)	Children (6-10 years)	Case-control	92 (62 cases: 31 with asthma and 30 with asthma in remission; controls: 31)	--	Asthma was diagnosed by pediatric allergists based on symptoms and methacholine challenge test; atopic sensitization was evaluated by skin prick testing and by specific IgE, assessed between June, 2014, and January, 2016	Nasopharyngeal samples collected between June, 2014, and January, 2016; 16S rRNA gene were sequenced	qualitative
Okba, et al. [55], 2018 (Egypt)	Adults (18-45 years)	Case-control	120 (cases: 80; controls: 40)	--	Questionnaire (asthma); atopic sensitization was evaluated by skin prick testing. Cross-sectional survey performed during adulthood	Stool samples; culture-based approach. Cross-sectional survey performed during adulthood	qualitative
Stokholm, et al. [56], 2018 (Denmark)	Children (5 years)	Cohort	690	5 years	Diary records (asthma) at age 5 years	Stool samples collected during the 1st year of life; 16S rRNA gene were sequenced	qualitative
Wang, et al. [57], 2018 (UK)	Adults (36-80 years)	Case-control	221	--	NA Cross-sectional survey performed during adulthood	Stool samples; Cross-sectional survey performed during adulthood	qualitative
Bannier, et al. [58], 2019 (Netherlands)	Children (6 years)	Case-control	252 (cases: 202; controls: 50)	--	Clinical diagnosis (asthma); atopic sensitization was evaluated by specific IgE at 6 years of age	Stool samples collected at 2-4 aged; V3-V4 region of 16S rRNA gene were sequenced	qualitative
Espuela-Ortiz, et al. [59], 2019 (USA)	Children and young adults (6-21 years)	Case-control	114 (cases: 57; controls: 57)	--	Clinical diagnosis (asthma). Cross-sectional survey performed during childhood and early adulthood	Saliva samples; V4 region of 16S rRNA gene were sequenced. Cross-sectional survey performed during childhood and early adulthood	quantitative
Lee, et al. [60], 2019 (South Korea)	Adults (18-45 years; ≥ 65 years)	Cross-sectional	80	--	Clinical diagnosis (airway obstruction reversibility, methacholine challenge test, symptoms, treatment). Cross-sectional survey performed during adulthood	Upper airway nasopharyngeal samples; 16S rRNA gene were sequenced. Cross-sectional survey performed during adulthood	qualitative
Pang, et al. [61], 2019 (China)	Adults (37-41 years)	Case-control	36 (cases: 10 eosinophilic asthma, 14 non-eosinophilic asthma; controls: 12)	--	Clinical diagnosis and spirometry with bronchodilation. Survey performed during adulthood	Induced sputum samples; V3-V4 region of 16S rRNA gene were sequenced. Survey performed during adulthood	qualitative
Powell, et al. [62], 2019 (UK)	Children (24 months)	Cohort	159	24 months	Medical records (wheeze) assessed after the 2 years visit	Oropharyngeal samples collected at six time-points (6 weeks, 6, 9, 12, 18 and 24 months of age); V3-V5 region of 16S rRNA gene were sequenced	qualitative
Samra, et al. [63], 2019 (South Korea)	Children (5-12 years)	Cross-sectional	118	--	Hospital visits (asthma attack) and methacholine/provocholine challenge test; atopic sensitization was evaluated by skin prick testing and by specific IgE. Cross-	Urine bacteria-derived extracellular vesicle (EV)s. Cross-sectional survey performed during childhood	qualitative

					sectional survey performed during childhood		
Thorsen, et al. [64], 2019 (Denmark)	Children (6 years)	Cohort	700	6 years	Daily diary (asthma); atopic sensitization was evaluated by skin prick testing and by specific IgE at 6 years of age	Airways samples collected at age 1 month; 16S rRNA gene were sequenced	quantitative
Al Bataineh, et al. [65], 2020 (United Arab Emirates)	Children (7 years) and adults (52 years)	Case-control	40 (cases: 21 asthmatics; controls: 19)	--	Questionnaire (asthma) Survey performed during childhood and adulthood	Expectorated sputum samples; 16S rRNA gene were sequenced. Survey performed during childhood and adulthood	qualitative
Chiu, et al. [66], 2020 (Taiwan)	Children (4-5 years)	Case-control	60 (cases: 20 with allergic rhinitis, 19 with allergic asthma; controls: 22)	--	Questionnaire (asthma, atopic diseases). Survey performed during childhood	Stool and airway samples; V3-V4 region of 16S rRNA gene were sequenced. Survey performed during childhood	qualitative
Patrick, et al. [67], 2020 (Canada)	Children (5 years)	Cohort	917	5 years	Record from the British Columbia Ministry of Health Chronic Disease Dashboard (asthma) at age 5 years	Stool samples collected at 3 and 12 months of age; 16S rRNA gene were sequenced	quantitative
Ruokolainen, et al. [68], 2020 (Finland and Estonian)	Children (18 months of age)	Cross-sectional	717	--	Atopic sensitization was evaluated by specific IgE at 18 months of age	Stool, nasal and skin samples of 6-month-old; V1-V3 region of 16S rRNA gene were sequenced	qualitative
Toivonen, et al. [69], 2020 (Finland)	Children (7 years)	Cohort	923	7 years	Medical records (asthma) at age 7 years	Nasal samples collected at ages 2, 13, and 24 months; V4 region of 16S rRNA gene were sequenced	quantitative
Ham, et al. [70], 2021 (South Korea)	Adults (49-58.44 years)	Case-control	97 (cases: 42 with non-severe asthma, 32 with severe asthma; controls: 23)	--	Spirometry with bronchodilation and methacholine or mannitol challenge test (asthma) performed between December 2016 and June 2017	Airway (sputum) and stool samples collected between December 2016 and June 2017; V3-V4 region of 16S rRNA gene were sequenced	qualitative
Niemeier-Walsh, et al. [71], 2021 (USA)	Children (12 years)	Cohort	40	12 years	Questionnaire (asthma); atopic sensitization was evaluated by skin prick testing at 12 years of age	Saliva and induced sputum samples collected at age 14 years; 16S rRNA gene were sequenced	quantitative
Samra, et al. [72], 2021 (South Korea)	Children (≈ 10 years)	Cross-sectional	49	--	Atopic sensitization was evaluated by skin prick testing and by specific IgE. Cross-sectional survey performed during childhood	Urine samples (bacterial extracellular vesicles); 16S rRNA gene were sequenced. Cross-sectional survey performed during childhood	qualitative
Schei, et al. [73], 2021 (Norway)	Children (6 years)	Cohort	278	6 years	Questionnaires (asthma) at 6 years of age	Stool samples collected at 4 timepoints between 0 and 2 years	quantitative

Seppo, et al. [74], 2021 (USA)	Children (3 years)	Cohort	104	3 years	Telephone follow-up for allergic symptoms by a paediatric allergist (asthma, respiratory symptoms, atopic diseases) by 3 years of age	Stool samples collected between 2 weeks and 6 months of age; V4 region of 16S rRNA gene were sequenced	qualitative
Turek, et al. [75], 2021 (Australia)	Adults (±56 years)	Cross-sectional	529	--	Questionnaire (asthma). Cross-sectional survey performed during adulthood	Posterior oropharyngeal samples; V4 region of 16S rRNA gene were sequenced. Cross-sectional survey performed during adulthood	qualitative
Bar et al. [76], 2022 (Poland)	Children (6–17 years of age)	Cross-sectional	38 (19 asthmatic and 19 healthy group)	--	Asthma doctor-diagnosed	Exhaled breath condensates and oropharyngeal samples; V3-V4 regions of 16S rRNA gene were sequenced. Cross-sectional survey performed during childhood	quantitative
Lee-Sarwar et al. [77], 2022 (USA)	Children (6 years)	Cohort	657 mother–child pairs	6 years	Questionnaires (asthma) at 3 and 6 years of age; asthma as having early, transient or active asthma phenotypes.	Stool samples collected at ages 3-6 months, 1 and 3 years; V4 region of 16S rRNA gene were sequenced	quantitative
Lee-Sarwar et al. [78], 2022 (USA)	Children (6 years)	Cohort	657 mother–child pairs	6 years	Questionnaires, wheeze proportion between ages 3 and 5 years	Stool samples collected at 3 years of age; V4 region of 16S rRNA gene were sequenced	quantitative
Tsai et al. [79], 2022 (Taiwan)	Children (36 months)	Cross-sectional	87 (36 with allergic respiratory diseases and atopy, 21 with atopy alone, and 30 healthy controls)	--	Asthma doctor-diagnosed (asthma, wheezing symptoms, or use of asthma medication during the last 12 months). Allergic sensitization: total IgE level ≥100 kU/L	Nasopharyngeal swabs collected at 36 month; V3-V4 regions of 16S rRNA gene were sequenced. Cross-sectional survey performed during childhood	quali(quanti)tative
Zheng et al. [80], 2022 (China)	Children (5 to 14 years)	Cross-sectional	57 (20 healthy children, 27 allergic asthmatic children, and 10 non-allergic asthmatic children)	--	Asthma doctor-diagnosed (GINA)	Stool samples; V4 region of 16S rRNA gene were sequenced. Cross-sectional survey performed during childhood	qualitative
Mubanga et al. [81], 2023 (Sweden)	Children (9-14 years)	Cohort	355	--	national health registers and questionnaires (Allergic asthma was defined as a composite outcome based on an asthma diagnosis (questionnaire) and IgE). Groups: Non-allergic asthma, allergy only (IgE+), and allergic asthma	Stool samples	qualitative

Thorsen et al. [82], 2023 (Denmark)	Children (7 years)	Cohort	285	7	Questionnaire (asthma), persistent wheeze/asthma by age 7	Nasopharyngeal swabs from 1-month neonates; V3-V4 regions of 16S rRNA gene were sequenced	quantitative

**results reported as median (minimum-maximum)
***results reported as mean (standard deviation)

Table S2. Main results of studies included in the comprehensive review (n=82) and summary of evidence

Reference, study year (country)	Study population	Covariates	Main results	Summary of evidence on the association*
		Outer layer biodiversity		
Ege, et al. [103], 2011 (Germany)	Children (6-13 years)	Living in a farm	*Bacteria diversity score (number of detectable bands)* PARSIFAL aOR_{asthma} (95 %CI)=0.65 (0.45; 0.94) $aOR_{allergic\ sensitization}$ (95 %CI)=0.86 (0.65; 1.15) GABRIELA aOR_{asthma} (95 %CI)=0.87 (0.73; 1.03) $aOR_{allergic\ sensitization}$ (95 %CI)=0.93 (0.79; 1.11) *PCA 4* PARSIFAL aOR_{asthma} (95 %CI)=0.62 (0.42; 0.91) *PCA 5* PARSIFAL aOR_{asthma} (95 %CI)=0.62 (0.42; 0.91)	↓↓ asthma ↓ allergic sensitization
Ege, et al. [104], 2012 (Germany)	Children (≈ 8 years)	farming, family history of atopy, parental education, and mutually for all associated bands	*Band 248* OR_{asthma} (95% CI)=0.46 (0.24; 0.89) *Band 394* OR_{asthma} (95% CI)=0.56 (0.32; 0.97) *Band 506* OR_{asthma} (95% CI)=0.58 (0.38; 0.88) For a low cut-off: *Band 394* OR_{asthma} (95% CI)=0.17 (0.04; 0.72) *Band 506* OR_{asthma} (95% CI)=0.41 (0.20; 0.83) For a high cut-off: *Band 300* OR_{asthma} (95% CI)=2.42 (1.18; 4.95) *Band 318* OR_{asthma} (95% CI)=2.32 (1.07; 5.06) *Band 427* OR_{asthma} (95% CI)=0.45 (0.23; 0.89)	↓↓ asthma ↑↑ asthma [band 300, 318 (high cut off)]

			PC1env (forested and agricultural land): β_{atopy}= -0.52, *p*=0.0059 *Flowering:* β_{atopy}= -0.10, *p*=0.0016 *Gammaproteobacteria on the skin* β_{atopy}= -0.31, *p*=0.015	
Hanski, et al. [34], 2012 (Finland)	Children (17-18 years)	--		↓↓ atopy
Lynch, et al. [7], 2014 (USA)	Children (3 years)	race/ethnicity, gender, mean perceived stress of the mother in the year after birth, and number of smokers in the home	Children with the highest exposure to specific bacteria during their first year were least likely to develop recurrent wheeze and allergic sensitization	↓ wheeze and allergic sensitization
Ciaccio, et al. [105], 2015 (USA)	Children (2.4-4.8 years)	--	No significant difference in genus-level richness was found between the asthma homes and control homes	no evidence of effect: asthma
Ruokolainen, et al. [35], 2015 (Finland and Estonian)	Children and young adults (0.5-20 years)	age and data set (study cohort)	*Land-use gradient* $OR_{allergic\ sensitization}$=1.00 (*p*=0.997) among children aged 0.5-1 $OR_{allergic\ sensitization}$=0.83 (*p*=0.698) among children aged 1.5-3 $OR_{allergic\ sensitization}$=0.33 (*p*=0.034) among children aged 6-12 $OR_{allergic\ sensitization}$=0.09 (*p*=0.003) among children/young adults aged 13-20 $OR_{allergic\ sensitization}$=0.42 (*p*=0.008) among children/young adults aged 0.5-20	↓↓ allergic sensitization
Valkonen, et al. [106], 2015 (Germany, Austria and Switzerland)	Children (6-12 years)	sex and age	There was also a protective trend (*p*=0.097) of high bacterial diversity (Shannon index) on atopy. Individual bacterial groups and diversity were not clearly associated with asthma. 7 and 2 bands: associated to a protective and adverse risk from developing allergic sensitization, respectively; 5 and 1 bands: associated to be a protective and adverse risk from developing asthma, respectively. exposed non-farm children: *Shannon index* Median (min; max)$_{asthma}$=2.56 (1.93; 2.95) Median (min; max)$_{atopy}$=2.62 (0.68; 3.01) Median (min; max)$_{healthy\ children}$=2.71 (2.30; 3.05) non-exposed non-farm children: *Shannon index* Median (min; max)$_{asthma}$=2.59 (2.36; 2.88)	↓ atopy no evidence of effect: asthma ↕ asthma and allergic sensitization (bands 1, 2, 5, 7) ↓↓ asthma and atopy (median)

			Median (min; max)$_{atopy}$=2.54 (2.01; 3.02) Median (min; max)$_{healthy\ children}$=2.68 (1.87; 3.04)	
Tischer, et al. [107], 2016 (Germany)	Children aged 6 and 10 years	sex, maternal education, and season of dust sampling	*bacterial diversity:* sensitization to aero-allergens at 6y 3rd tertile: aOR (95%CI)=0.45 (0.18; 1.11) sensitization to aero-allergens at 10 years 3rd tertile: aOR (95% CI)=0.45 (0.18; 1.11) wheezing at 10 years 3rd tertile: aOR (95% CI)=1.00 (0.45; 2.06)	↓ allergic sensitization no evidence of effect: wheezing
Birzele, et al. [20], 2017 (Austria)	Children (6-12 years)	farming and for the respective diversity measurement in nasal swabs or mattress dust	Mattress dust: *Richness* aOR$_{asthma}$ (95% CI)=0.48 (0.22; 1.02) Shannon index aOR$_{asthma}$ (95% CI)=0.41 (0.21; 0.83) Nasal samples: *Richness* aOR$_{asthma}$ (95% CI)= 0.63 (0.38; 1.06) Shannon index aOR$_{asthma}$ (95% CI)=0.66 (0.39; 1.12)	↓ asthma
Cavaleiro Rufo, et al. [108], 2017 (Portugal)	Children (8-10 years)	age and height	No significant association were observed between diversity score and asthma 3rd quartile: OR$_{allergic\ sensitization}$ (95% CI)=0.63 (0.40; 0.98) 4th quartile: OR$_{allergic\ sensitization}$ (95% CI)=0.60 (0.40; 0.92)	no evidence of effect: asthma ↓↓ allergic sensitization
Campbell, et al. [87], 2017 (14 different countries)	26–54-year-old adults	age, sex, study center, smoking, family history of allergic disease	lived in an inner city: *microbial load score 2* OR$_{allergic\ sensitization}$ (95% CI)=0.77 (0.55; 1.09) OR$_{current\ asthma}$ (95% CI)=0.80 (0.32; 2.00) OR $_{allergic\ sensitization\ and\ asthma}$ (95% CI)=1.16 (0.47; 2.88) *microbial load score 3* OR$_{allergic\ sensitization}$ (95% CI)=0.70 (0.49; 1.00) OR$_{current\ asthma}$ (95% CI)=0.48 (0.17; 1.34) OR $_{allergic\ sensitization\ and\ asthma}$ (95% CI)=1.26 (0.50; 3.13) *microbial load score 4/5* OR$_{allergic\ sensitization}$ (95% CI)=0.61 (0.41; 0.90) OR$_{current\ asthma}$ (95% CI)=0.31 (0.08; 1.11)	↓ asthma ↓↓ allergic sensitization (microbial load score 3 and 4/5) ↑ allergic sensitization and asthma

			$OR_{\text{allergic sensitization and asthma}}$ (95% CI)=1.57 (0.60; 4.10)	
Dannemiller, et al. [109], 2016 (USA)	Children (5-10 years)	--	*Bacterial richness* $OR_{\text{asthma severity}}$ (95% CI)=0.55 (0.30; 0.99) among all children $OR_{\text{asthma severity}}$ (95% CI)=0.38 (0.16; 0.90) among atopic children *low bacterial richness:* $OR_{\text{asthma severity}}$ (95% CI)=0.77 (0.34; 1.75) among atopic children *Bacterial concentration* $OR_{\text{asthma severity}}$ (95% CI)=1.04 (0.60; 1.82) among all children $OR_{\text{asthma severity}}$ (95% CI)= 1.13 (0.51; 2.49) among atopic children $OR_{\text{asthma severity}}$ (95% CI)=0.94 (0.42; 2.11) among non-atopic children	↕ asthma severity ↓↓ asthma severity (all children) (bacterial richness)
Karvonen, et al. [110], 2017 (Finland)	Children (1 and 6 years)	study cohort, farming, maternal history of allergic diseases, gender, number of older siblings, smoking during pregnancy. Models of sensitization to inhalant allergens are additionally adjusted for floor type of dust sampling	No significant association were observed between microbial quantity or diversity scores and asthma or respiratory symptoms up to the age of 6 years and current asthma and sensitization to inhalant allergen at 6 years of age. *Quantity score* 2nd quintile: $aOR_{\text{asthma ever}}$ (95% CI)=1.73 (0.67; 4.45) 3rd quintile: $aOR_{\text{asthma ever}}$ (95% CI)=2.24 (0.87; 5.75) 4th quintile: $aOR_{\text{asthma ever}}$ (95% CI)=1.78 (0.67; 4.69) 5th quintile: $aOR_{\text{asthma ever}}$ (95% CI)=0.34 (0.09; 1.36) 2nd quintile: $aOR_{\text{current asthma}}$ (95% CI)=1.32 (0.38; 4.61) 3rd quintile: $aOR_{\text{current asthma}}$ (95% CI)=2.01 (0.59; 6.79) 4th quintile: $aOR_{\text{current asthma}}$ (95% CI)=1.86 (0.55; 6.32) 5th quintile: $aOR_{\text{current asthma}}$ (95% CI)=0.39 (0.07; 2.11) 2nd quintile: aOR_{wheezing} (95% CI)=0.65 (0.35; 1.22) 3rd quintile: aOR_{wheezing} (95% CI)=0.89 (0.49; 1.62) 4th quintile: aOR_{wheezing} (95% CI)=0.98 (0.55; 1.75) 5th quintile: aOR_{wheezing} (95% CI)=0.73 (0.43; 1.24) 2nd quintile: $aOR_{\text{allergic sensitization}}$ (95% CI)=2.19 (0.92; 5.23) 3rd quintile: $aOR_{\text{allergic sensitization}}$ (95% CI)=1.42 (0.55; 3.64) 4th quintile: $aOR_{\text{allergic sensitization}}$ (95% CI)=1.32 (0.51; 3.40) 5th quintile: $aOR_{\text{allergic sensitization}}$ (95% CI)=1.50 (0.61; 3.70) *Diversity score*	no evidence of effect: asthma and allergic sensitization ↕ allergic sensitization (diversity score) ↓↓ current asthma, wheezing (diversity score)

			5 score: $aOR_{asthma\ ever}$ (95% CI)=0.69 (0.27; 1.78) 6 score: $aOR_{asthma\ ever}$ (95% CI)=1.03 (0.43; 2.49) 7-8 score: $aOR_{asthma\ ever}$ (95% CI)=0.64 (0.15; 2.76) 5 score: $aOR_{current\ asthma}$ (95% CI)=0.30 (0.10; 0.89) 6 score: $aOR_{current\ asthma}$ (95% CI)=0.35 (0.12; 0.94) 7-8 score: $aOR_{current\ asthma}$ (95% CI)=0.40 (0.07; 2.29) 5 score: $aOR_{wheezing}$ (95% CI)=0.68 (0.38; 1.20) 6 score: $aOR_{wheezing}$ (95% CI)=0.54 (0.30; 0.97) 7-8 score: $aOR_{wheezing}$ (95% CI)=0.14 (0.06; 0.32) 5 score: $aOR_{allergic\ sensitization}$ (95% CI)=2.10 (0.84; 5.27) 6 score: $aOR_{allergic\ sensitization}$ (95% CI)=2.16 (0.86; 5.45) 7-8 score: $aOR_{allergic\ sensitization}$ (95% CI)=0.42 (0.12; 1.50)	
Donovan, et al. [33], 2018 (New Zealand)	Children (18 years)	roads, air pollution, ethnicity, gender, birth outcomes, parents' occupation, parents' education, parents' smoking status, antibiotic use, number of siblings, mesh block size and birth order	*Vegetation diversity* (lifetime) aOR_{asthma} (95% CI)=0.933 (0.885; 0.985)	↓↓ asthma
Lai, et al. [111], 2018 (USA)	Children (average 8.1 years old)	age, gender, ethnicity, and season	*Classroom microbial diversity* $aOR_{asthma\ symptoms}$ (95% CI)=1.07 (1.00; 1.14) *Home microbial diversity* $aOR_{asthma\ symptoms}$ (95% CI)= 1.00 (1.00; 1.00)	↑↑ asthma
Loo, et al. [112], 2018 (Singapore)	Children (3-60 months)	--	no significant difference in Shannon or Simpson's diversity indices of bed, play area and sofa dust samples of the allergic subjects and non-allergic subjects	no evidence of effect: allergic sensitization
O'Connor, et al. [31], 2018 (USA)	Children (3 and 7 years)	gender, race, maternal asthma, and maternal Perceived Stress Scale score	Bacterial α- and β-diversity did not differ significantly between the homes of children that did or did not develop asthma, nor did these diversity measures differ between the homes of the children that did or did not develop atopy at age 7	no evidence of effect: asthma and allergic sensitization
Pekkanen, et al. [113], 2018 (7 European countries)	Adults (29–55 years)	age, sex, parental allergy, current smoking and household density	*Band L3B49_8 (2nd tertile):* aOR_{asthma} (95% CI)=2.499 (1.455; 4.291) *Band L3B53_7 (2nd tertile):*	↑↑ asthma

			aOR_{asthma} (95% CI)=2.206 (1.214; 4.007) *Band L3B57_6 (2nd tertile):* aOR_{asthma} (95% CI)=2.399 (1.378; 4.178) 3rd tertile: aOR_{asthma} (95% CI)=2.319 (1.299; 4.140) *Band L3B71_9 (2nd tertile):* aOR_{asthma} (95% CI)=2.197 (1.214; 3.974)	
Valkonen, et al. [114], 2018 (7 European countries)	Adults (29–55 years)	parental allergy, smoking status, household density, gender, age, and center	No significant associations were observed between microbial species and asthma and allergic sensitization	no evidence of effect: asthma and allergic sensitization
Karvonen[19], 2019 (Finland)	Children (10.5 years)	follow-up time, study cohort, living on a farm, and well-known risk factors for asthma (maternal history of allergic diseases, sex, number of older siblings, and smoking during pregnancy)	*Bacterial richness:* $aOR_{ever\ asthma}$ (95% CI)=0.61 (0.39; 0.95) $aOR_{current\ asthma}$ (95% CI)=0.55 (0.37; 1.12) *Shannon diversity index:* $aOR_{ever\ asthma}$ (95% CI)=0.77 (0.55; 1.07) $aOR_{current\ asthma}$ (95% CI)=0.76 (0.45; 1.30)	↑↑ ever asthma (bacterial richness)
Kirjavainen, et al. [13], 2019 (Finland)	Children (6 years)	living on a farm, cohort, gender, the maternal history of allergic diseases, number of older siblings and smoking during pregnancy. For FaRMI - paternal history of atopic diseases and asthma, maternal and paternal education levels, birth weight, mode of delivery, indoor exposure to dog and/or cat at the age of 2 months, distance to farm, breastfeeding, consumption of farm milk, day-care attendance, regular exposure to passive tobacco smoke at the age of 1 year, house type and	farm-like relative abundance of bacteria/archaea: $aOR_{ever\ asthma}$ (95% CI)=0.40 (0.19; 0.82) $aOR_{ever\ asthma}$ (95% CI)=0.47 (0.27; 0.81) $aOR_{active\ asthma}$ (95% CI)=0.48 (0.23; 0.98)	↑↑ asthma

		age, season, type of vacuumed floor and time from last vacuuming with reference to dust sampling		
Cavaleiro Rufo, et al. [115], 2020 (Portugal)	Children (8-10 years)	age (in years), sex, school, classroom, and maternal education, allergic sensitization status and diagnosis of asthma	*School SRI* $aOR_{asthma\ –\ functional\ criteria}$ (95% CI)= 0.998 (0.992; 1.005) $aOR_{asthma\ –\ diagnosed\ by\ physician}$ (95% CI)=1.004 (0.998; 1.011) $aOR_{asthma\ –\ clinical\ criteria}$ (95% CI)=1.000 (0.992; 1.007)	↕ asthma
Fu, et al. [116], 2020 (Malaysia)	Children (14-16 years)	gender, race, smoking, and parental asthma/allergy	*Number of OTUs* $OR_{asthma\ severity}$ (95% CI)=1.00 (0.99; 1.01)	↑ asthma
Gangneux, et al. [117], 2020 (France)	Children and adults	--	*Shannon index* asthma group (mean±SD): 3.94±0.22 control group: 3.68±0.67, *p*=0.5393).	↑ asthma
Adams, et al. [118], 2021 (Finland and Netherlands)	Children (≈ 9 years)	gender, age, and moisture damage in the home, educational level	*Bacterial richness and diversity* Middle category: $aOR_{symptoms\ score}$ (95% CI)=1.43 (1.36; 1.50) Highest category $aOR_{symptoms\ score}$ (95% CI)= 1.26 (1.09; 1.46)	↑↑ asthma
Cavaleiro Rufo, et al. [119], 2021 (Portugal)	Children (4 and 7 years	distance to the nearest major road, motorway or highway, sex, household crowding, maternal education, neighborhood socioeconomic deprivation and maternal history of diagnosed asthma	$OR_{asthma\ at\ the\ age\ of\ 7}$ (95% CI)=3.58 (1.09; 11.79) $OR_{allergic\ sensitization\ at\ the\ age\ of\ 4}$ (95% CI)=2.00 (1.04; 3.86) $OR_{allergic\ sensitization\ at\ the\ age\ of\ 7}$ (95% CI)=2.35 (1.20; 4.63) Highest tertile of SRI: $OR_{asthma\ at\ the\ age\ of\ 7}$ (95% CI)=2.28 (0.67; 7.64) $OR_{whezzing\ at\ the\ age\ of\ 7}$ (95% CI)=2.51 (1.08; 5.88)	↑↑ asthma, allergic sensitization and wheezing
Cox, et al. [120], 2021 (USA)	Children (7 and 12 years)	race (Black or non-Black), pets, neighborhood socioeconomic status, cockroaches, dust mites, and rodents	*Bacteria associated with the absence of the health outcomes* $OR_{asthma\ at\ 7\ years}$ (95% CI)=0.76 (0.64; 0.91) $OR_{asthma\ at\ 12\ years}$ (95% CI)=0.91 (0.81; 1.01) $OR_{wheeze\ at\ 7\ years}$ (95% CI)=0.84 (0.73; 0.96) $OR_{wheeze\ at\ 12\ years}$ (95% CI)=0.84 (0.69; 1.03) $OR_{allergic\ sensitization\ at\ 7\ years}$ (95% CI)=0.93 (0.87; 1.00) $OR_{allergic\ sensitization\ at\ 12\ years}$ (95% CI)=0.91 (0.83; 1.00) *Bacteria associated with the presence of the health outcomes* $OR_{asthma\ at\ 7\ years}$ (95% CI)=1.06 (0.97; 1.15) $OR_{asthma\ at\ 12\ years}$ (95% CI)=1.16 (1.04; 1.30) $OR_{wheeze\ at\ 7\ years}$ (95% CI)=1.31 (1.15; 1.49) $OR_{wheeze\ at\ 12\ years}$ (95% CI)=1.17 (1.05; 1.31)	↓↓ asthma and wheezing at 7 years ↓ allergic sensitization (bacteria associated with the absence of the health outcomes) ↑↑ asthma at 12 years, wheezing and allergic sensitization (bacteria associated with the

			$OR_{allergic\ sensitization\ at\ 7\ years}$ (95% CI)=1.13 (1.05; 1.22) $OR_{allergic\ sensitization\ at\ 12\ years}$ (95% CI)=1.18 (1.04; 1.34)	presence of the health outcomes)
Donovan, et al. [121], 2021 (USA)	Adults	race, socioeconomic status, air pollution and proximity to roads	*Taxonomic plant diversity* β_{asthma} (95% CI)= -0.0527 (-0.00637; -0.0417)	↓↓ asthma
Fu, et al. [122], 2021 (China)	Young adults (IQR 20–23 years)	gender, smoking and parental asthma	*Bacterial richness* settled air dust: $aOR_{asthma\ symptoms}$ (95% CI)=0.97 (0.86; 1.1) floor dust: $aOR_{asthma\ symptoms}$ (95% CI)=0.85 (0.63; 1.14)	↓ asthma
Fu, et al. [123], 2021 (China)	Children (15-18 years)	Current smoking, gender and parental asthma and allergies	*Number of OTUs* $\beta_{wheezing}$ (95% CI)= -0.2525 (-0.8228; 0.3178) $\beta_{breathlessness}$ (95% CI)= 0.0754 (-0.1659; 0.3167) $\beta_{rhinitis}$ (95% CI)= -1.48 (-4.302; 1.342)	↓ wheezing
Hyytiäinen, et al. [124], 2021 (Finland and Germany)	Children (10 years)	gender, parental atopy, number of older siblings and season of dust sampling in both cohorts; maternal education, living on a farm and cohort, and the number of different pet species indoors in LUKAS; and parental education, study center and age of the mother during delivery in LISA.	*Bacterial richness* LISA cohort Middle tertile: $aOR_{allergic\ sensitization}$ (95% CI)=0.99 (0.62; 1.58) Highest tertile: $aOR_{allergic\ sensitization}$ (95% CI)=0.71 (0.44; 1.15) LUKAS cohort Middle tertile: $aOR_{allergic\ sensitization}$ (95% CI)= 0.84 (0.43; 1.65) Highest tertile: $aOR_{allergic\ sensitization}$ (95% CI)=1.60 (0.66; 3.87) *Shannon index* LISA cohort Middle tertile: $aOR_{allergic\ sensitization}$ (95% CI)=0.76 (0.48; 1.20) LUKAS cohort Middle tertile: $aOR_{allergic\ sensitization}$ (95% CI)=1.98 (1.04; 3.78) Rural children: *Bacterial richness* Middle tertile: $aOR_{allergic\ sensitization}$ (95% CI)=1.34 (0.57; 3.15) Highest tertile: $aOR_{allergic\ sensitization}$ (95% CI)=3.63 (1.05; 12.56) *Shannon index* Middle tertile: $aOR_{allergic\ sensitization}$ (95% CI)=1.83 (0.84; 3.98) Highest tertile: $aOR_{allergic\ sensitization}$ (95% CI)=3.86 (1.06; 14.11) Suburban children: *Bacterial richness*	↕ allergic sensitization ↑↑ allergic sensitization (rural children, bacterial richness, and Shannon index) ↓↓ allergic sensitization (suburban children, bacterial richness)

			Middle tertile: $aOR_{allergic\ sensitization}$ (95% CI)=0.09 (0.01; 0.70) Highest tertile: $aOR_{allergic\ sensitization}$ (95% CI)=0.74 (0.07; 7.92) *Shannon index* Middle tertile: $aOR_{allergic\ sensitization}$ (95% CI)=0.59 (0.12; 2.90) Highest tertile: $aOR_{allergic\ sensitization}$ (95% CI)=2.09 (0.24; 18.44) Farm children: *Bacterial richness* Middle tertile: $aOR_{allergic\ sensitization}$ (95% CI)=2.26 (0.14; 35.54) Highest tertile: $aOR_{allergic\ sensitization}$ (95% CI)=1.43 (0.11; 18.70) *Shannon index* Middle tertile: $aOR_{allergic\ sensitization}$ (95% CI)=5.67 (0.4; 79.77) Highest tertile: $aOR_{allergic\ sensitization}$ (95% CI)=1.43 (0.12; 17.5)	
Lehtimäki, et al. [125], 2021 (Denmark)	Children (6 years)	pet ownership, day care attendance during the first year of life, length of the breast-feeding period, exposure to passive smoking, family income, parental education, number of older siblings, home type, mode of delivery, parental diagnosis of asthma, eczema and rhinitis, and use of antibiotics during the first year of life	*Urbanized airway bacterial profile* at 1 week: OR_{asthma} (95% CI)=1.25 (1.01; 1.55) at 1 month: OR_{asthma} (95% CI)=1.22 (1.00; 1.48) *urbanized gut bacterial profile* at 1 month: OR_{asthma} (95% CI)=1.29 (1.05; 1.59) at 1 year: OR_{asthma} (95% CI)=1.24 (1.02; 1.53) $OR_{any\ allergic\ sensitization}$ (95% CI)=1.28 (1.03; 1.59) $OR_{aeroallergen\ sensitization}$ (95% CI)=1.24 (0.98; 1.57)	↑↑ asthma ↑ aeroallergen sensitization (urbanized gut bacterial profile)
Winnicki, et al. [126], 2022 (Denmark)	Individuals born 1995–2015	Family history of asthma, income, education, age and sex	Medium levels of the bioscore: $aHR_{Medication\ and\ hospital\ diagnosis\ asthma}$ (95% CI): 1.01 (0.95; 1.08) $aHR_{Hospital\ diagnosis\ asthma}$ (95% CI): 0.97 (0.87; 1.09) High levels of the bioscore: $aHR_{Medication\ and\ hospital\ diagnosis\ asthma}$ (95% CI): 1.13 (0.99; 1.28) $aHR_{Hospital\ diagnosis\ asthma}$ (95% CI): 0.72 (0.55; 0.94)	↕ asthma ↓↓ asthma (hospital diagnosis, high levels of the bioscore)
Inner layer biodiversity				
Bisgaard, et al. [57], 2007 (Denmark)	Children (5 years)	sex, gestational age at birth, maternal smoking during the third trimester, maternal use of antibiotics	The prevalence of asthma was 33% in colonized children and 10% in those not colonized (OR (95% CI)=4.57 (2.18; 9.57). No significant association was observed between colonization and allergic sensitization at 4 years (OR (95% CI)=1.28 (0.65; 2.54).	↑↑ asthma ↑ allergic sensitization at 4 years (colonization)

		during the third trimester, breast-feeding, lung function, bronchial responsiveness, and the presence or absence of older children at home		
Hilty, et al. [127], 2010 (Ireland)	Children (1-17 years) and adults (37.6±18.2 – 52.9±11.1 years)	--	*Species* Number of sequences of different phyla and genera were different among the groups (subjects with asthma, COPD and healthy) and considering the sample	--
Bisgaard, et al. [21], 2011 (Denmark)	Children (6 years)	cesarean section, mother's use of antibiotics in third trimester; solely breast feeding of the baby, or having a dog or cat at home at birth	*Band richness* At 1 month $aOR_{current\ asthma}$ (95% CI)=0.98 (0.83, 1.16) $a\beta_{specific\ IgE}$ (95% CI)= -0.127 (-0.227; -0.027) $a\beta_{skin\ prick\ tests}$ (95% CI)= -0.052 (-0.1560; 0.053) At 12 months $aOR_{current\ asthma}$ (95% CI)=0.97 (0.84; 1.12) $a\beta_{specific\ IgE}$ (95% CI)= -0.092 (-0.184; 0.000) $a\beta_{skin\ prick\ tests}$ (95% CI)= -0.101 (-0.211; -0.010)	↓ asthma ↓↓ allergic sensitization (specific IgE, skin prick tests) (band richness at 12 months of age and at 1 month (IgE))
Cardenas, et al. [128], 2012 (Ecuador)	Children (±10.2 months)	--	No differences were found between individuals with wheeze and healthy individuals in species richness, taxa abundances, or evenness as well as in microbial community cluster patterns (β diversity).	no evidence of effect: wheezing
Marri, et al. [55], 2013 (USA)	Adults (≈ 26 years)	--	Samples from asthmatic patients were associated with significantly greater bacterial diversity compared with samples from non-asthmatic subjects	↑↑ asthma
Abrahamsson, et al. [16], 2014 (Sweden)	Children (7 years)	--	*Shannon diversity index* At 1 week $Median_{asthmatic}$ (IQR)=1.34 (0.95; 1.64)* $Median_{non\text{-}asthmatic}$ (IQR)=1.60 (1.42; 1.75)* $Median_{atopic}$ (IQR)=1.71 (1.38; 1.75) $Median_{non\text{-}atopic}$ (IQR)=1.55 (1.42; 1.79) $Median_{healthy}$ (IQR)=1.60 (1.42; 1.80) At 1 month $Median_{asthmatic}$ (IQR)=1.26 (0.92; 1.46) ** $Median_{non\text{-}asthmatic}$ (IQR)=1.58 (1.48; 2.10) ** $Median_{atopic}$ (IQR)=1.62 (1.42; 1.88) $Median_{non\text{-}atopic}$ (IQR)=2.62 (2.22; 3.24) $Median_{healthy}$ (IQR)=1.60 (1.42; 1.75)	↕ (comparing median levels among asthmatic and non-asthmatic and among atopic and non-atopic individuals) ↓↓ asthma at 7 years of age (Shannon diversity index at 1 week and 1 month)

			At 12 months $Median_{asthmatic}$ (IQR)=2.87 (2.26; 3.24) $Median_{non\text{-}asthmatic}$ (IQR)=2.62 (2.25; 3.24) $Median_{atopic}$ (IQR)=2.70 (2.32; 3.21) $Median_{non\text{-}atopic}$ (IQR)=2.62 (2.22; 3.24) $Median_{healthy}$ (IQR)=2.82 (2.32; 3.25) *Number of bacterial OTUs* At 1 week $Median_{asthmatic}$ (IQR)=15 (10; 22) $Median_{non\text{-}asthmatic}$ (IQR)=16 (13; 18) At 1 month $Median_{asthmatic}$ (IQR)=14 (12; 17) $Median_{non\text{-}asthmatic}$ (IQR)=18 (14-22) At 12 months $Median_{asthmatic}$ (IQR)=51 (40; 73) $Median_{non\text{-}asthmatic}$ (IQR)=47 (33; 59) $^{*}p$=0.05, ** p=0.007	
Park, et al. [129], 2014 (Korea)	Adults (53.4±17.1 to 68.9±7.2)	--	*Shannon index* $Mean_{asthma}$ (SD)=2.4 $Mean_{healthy\ individuals}$ (SD)=3.5 (0.7) *Number of OTUs* $Mean_{asthma}$ (SD)=128 (73) $Mean_{healthy\ individuals}$ (SD)=207 (99)	↓↓ ($mean_{asthma}$ < $mean_{healthy\ individuals}$)
Arrieta, et al. [70], 2015 (Canada)	Children (3 years)	--	Gut community composition and diversity did not differ substantially among clinical phenotypes	no evidence of effect: atopy and wheezing
Denner, et al. [130], 2016 (USA)	Adults (44.2±1.8 and 34.3±3.0 years)	--	Specific species Differential feature selection analysis revealed significant differences in microbial diversity between asthmatic and control brush and lavage samples	↕ asthma
Hevia, et al. [131], 2016 (Spain)	Adults (≈ 39 years)	--	Specific species	--
Hua, et al. [132], 2016 (USA)	Adults (±45.5 years)	sex, age, BMI, season, time since last antibiotic use, probiotic and vitamin use	*Shannon index* Middle tertile aOR_{asthma} (95% CI)=1.03 (0.642; 1.64) Lowest tertile	↑↑ asthma (richness, middle tertile)

			aOR_{asthma} (95% CI)=1.35 (0.85; 2.13) *Richness* Middle tertile aOR_{asthma} (95% CI)=1.68 (1.04; 2.71) Lowest tertile aOR_{asthma} (95% CI)=1.52 (0.94; 2.47) *Chao1* Middle tertile aOR_{asthma} (95% CI)=1.58 (0.99; 2.52) Lowest tertile aOR_{asthma} (95% CI)=1.31 (0.82; 2.11)	
Stiemsma, et al. [71], 2016 (Canada)	Children (4 years)	antibiotic use, delivery mode, breastfeeding, sex, parental asthma, atopic dermatitis	Gut microbial community composition at 3 months or 1 year of age did not differ between asthmatics and controls	no evidence of effect: asthma
Zhang, et al. [133], 2016 (UK)	Adults (35.4±10.3 – 47.9±10.9 years)	--	There were no significant differences in alpha diversity between healthy, non-severe and severe asthmatics	no evidence of effect: asthma
Chiu, et al. [134], 2017 (Taiwan)	Children (3-5 years)	age, sex, maternal atopy, passive smoking, older siblings, and household income	Relatively lower Chao1 and Shannon indices were found in children with asthma than in the healthy controls, but these differences were not significant. However, the Chao1 and Shannon indices in the mite-sensitized children with asthma were significantly lower than those in the healthy children without mite sensitization.	no evidence of effect: asthma ↓↓ allergic sensitization
Depner, et al. [59], 2017 (Germany, Austria and Switzerland)	Children (12 years)	Farming	There was no association of bacterial load with asthma status *Bacterial richness* $aOR_{asthma\ in\ nonfarm\ children}$ (95% CI)=0.76 (0.25; 2.31)	no evidence of effect: asthma ↓ asthma (nonfarm children, bacterial richness)
Li, et al. [135], 2017 (China)	Adults (39.6±8.6 to 52.0±9.3 years)	--	Comparison between the three groups (asthmatics, severe and non-severe asthma, healthy individuals) showed that there was no significant difference in species richness and bacterial diversity as assessed by the Chao, Ace, Shannon and Simpson indices. *Number of OTUs* $Mean_{non\text{-}asthmatic}$ (SD)=142.67 (30.89) $Mean_{non\text{-}severe\ asthma}$ (SD)=147.13 (49.85) $Mean_{severe\ asthma}$ (SD)=135.36 (57.10)	no evidence of effect: asthma ↕ (comparing mean between non-asthmatic and (non-)severe asthma)
Ruokolainen, et al. [50], 2017 (Finnish and Russian Karelia)	Children (14-20 years)	--	*Specific species*	--

			The profile of *Acinetobacter lwoffii* in skin samples from sensitized Finns differed from all other samples (R^2=0.0014, p=0.002). No significant differences were found between sensitized and healthy subjects for *Acinetobacter johnsonii*. For *Micrococcus* sp. profiles tended to differ between healthy and sensitized among the Russian subjects (R^2 =0.002, p=0.043)	
Arrieta, et al. [136], 2018 (Ecuador)	Children (5 years)	antibiotic use during pregnancy or the first year of life, duration of antibiotic use during pregnancy or the first year of life, type of delivery, household potable water, number of respiratory tract infections during the first year of life, eosinophilia at 7 months, and number of diarrheal episodes during the first year of life	Atopic wheeze did not explain any significant changes in α- or β-bacterial diversity	no evidence of effect: allergic sensitization
Durack, et al. [137], 2018 (USA)	Adults (28-39 years)	--	Faith's Phylogenetic diversity trended to be higher in allergic asthmatic adults compared to non-allergic non-asthmatics in bronchial brushing samples. No such trend was observed in comparison of the other sample types from the same individuals. No significant difference in the relative abundance of specific genera were observed in any of the four samples between subjects with atopic asthma and healthy subjects.	no evidence of effect: asthma
Fazlollahi, et al. [51], 2018 (USA)	Adults (≈ 32 years)	age, sex, allergic rhinitis, last upper respiratory infection, recent antibiotic use, antihistamine use, nasal steroid use, inhaled steroid use, systemic steroid use	There was a positive trend between nasal bacterial alpha diversity and asthma activity. However, these differences in phylogenic diversity were not statistically significant. Healthy controls, subjects with non-exacerbated asthma, and subjects with exacerbated asthma demonstrated distinct nasal microbiome compositions.	no evidence of effect: asthma
Kim, et al. [138], 2018 (South Korea)	Children (6-10 years)	--	The number of observed OTUs and the Shannon diversity index in control group were lower than those in the asthma and remission groups, but the differences were not statistically significant	no evidence of effect: asthma
Okba, et al. [139], 2018 (Egypt)	Adults (18-45 years)	sex, age, body mass index, time since last antibiotic use, probiotic and vitamin use	Specific species Atopic asthma is significantly associated with gut microbiota *Lactobacilli* and *E. coli*	--

Stokholm, et al. [67], 2018 (Denmark)	Children (5 years)	older siblings, duration of exclusive breastfeeding, hospitalization after birth, antibiotic use, and delivery mode	There were no significant associations between α-diversity (Shannon diversity and Chao1 indices) at any time point and asthma risk. Microbial populations were significantly different at 1 year in children who had asthma at age 5 compared to non-asthmatics (R^2 = 0.6%, p=0.003).	no evidence of effect: asthma
Wang, et al. [140], 2018 (UK)	Adults (36-80 years)	--	The α-diversities at the three levels (genes, MGSs and KEGG) show difference between asthma and control groups.	↕ asthma
Bannier, et al. [141], 2019 (Netherlands)	Children (6 years)	sex, breastfeeding, birth season, atopy parents, siblings, parental smoking status, day care attendance	At preschool age, microbial richness and Shannon index were not different between wheezers and healthy controls.	no evidence of effect: wheezing
Espuela-Ortiz, et al. [53], 2019 (USA)	Children and young adults (6-21 years)	age, sex, or genetic ancestry between cases and controls	*Shannon index* $Mean_{asthma}$ (SD)=2.12 (0.23) $Mean_{healthy\ controls}$ (SD)=2.01 (0.24) *Pielou index* $Mean_{asthma}$ (SD)= 0.81 (0.04) $Mean_{healthy\ controls}$ (SD)=0.79 (0.05)	↑↑ ($Mean_{asthma}$ > $Mean_{healthy\ controls}$)
Lee, et al. [142], 2019 (South Korea)	Adults (18-45 years; ≥ 65 years)	--	Young adults: Bacterial diversity was not significantly different between asthmatics and non-asthmatics Elderly: Bacterial diversity was not significantly different between asthmatics and non-asthmatics	no evidence of effect: asthma
Pang, et al. [143], 2019 (China)	Adults (37-41 years)	--	Eosinophilic asthma and non-eosinophilic asthma showed a significant difference on Chao1, observed species and Shannon indexes among the three groups. Compared with healthy individuals, the asthmatics showed a significant decreased diversity (observed species index), richness (Chao1 and Shannon indexes) and evenness (Pielou evenness index. As for the asthmatics, non-eosinophilic asthma showed a significant decreased diversity, richness and evenness compared with eosinophilic asthma.	↑↑ asthma
Powell, et al. [44], 2019 (UK)	Children (24 months)	ethnicity, family history of atopy (fixed), presence of fever and the use of antibiotics in the 4 weeks prior to visit (time-varying)	Considering Bray–Curtis dissimilarities, no differences in microbiota composition were found between wheezers and non-wheezers.	no evidence of effect: wheezing
Samra, et al. [144], 2019 (South Korea)	Children (5-12 years)	--	Dysbiosis among children with atopic asthma compared to the controls	↑ asthma

			Shannon index (at age 1 month) $Median_{asthma}$ (IQR)=1.56 (1.11; 1.90) *Richness at 2000 reads* $Median_{asthma}$ (IQR)=30 (25-36) *Richness at 10000 reads* $Median_{asthma}$ (IQR)=49 (40-57)	
Thorsen, et al. [15], 2019 (Denmark)	Children (6 years)	paternal asthma, older siblings, and season of birth	*β-diversity* Bray-Curtis=2.21, *p*=0.019 UniFrac=2.27, *p*=0.046 *Bacterial asthma score (abundance)* $aHR_{asthma\ development\ by\ 6\ years}$ (95% CI)=1.36 (1.13; 1.63) $aHR_{transient\ early\ asthma}$ (95% CI)=1.33 (1.04; 1.72) $aHR_{late\text{-}onset\ phenotypes}$ (95% CI)=1.92 (1.23; 3.11) $aHR_{ever\ asthma}$ (95% CI)=1.44 (1.17; 1.79) $aHR_{current\ asthma\ at\ 6\ years}$ (95% CI)=1.61 (1.15; 2.30) $aHR_{asthma\ and\ allergic\ sensitization}$ (95% CI)=1.67 (1.03; 2.69)	↑↑ asthma
Al Bataineh, et al. [145], 2020 (United Arab Emirates)	Children (7 years) and adults (52 years)	--	*Specific species* A significant difference of bacterial composition (Bacteroidetes, Firmicutes, Fusobacteria and Proteobacteria phyla) between asthmatic and non-asthmatic controls was found among asthmatic groups compared to healthy groups	--
Chiu, et al. [146], 2020 (Taiwan)	Children (4-5 years)	--	In the airway microbiota, Chao1 and Shannon indices were significantly reduced in children with mite sensitization and were significantly lower in children with mite-sensitized rhinitis but not asthma than those in the healthy children without mite sensitization. In the stool microbiota, no difference was noted in the bacterial richness and diversity regarding the mite sensitization and its relevance to rhinitis and asthma.	↓↓ allergic sensitization (airway microbiota) no evidence of effect: asthma (airway and stool microbiota) and allergic sensitization (stool microbiota)
Patrick, et al. [147], 2020 (Canada)	Children (5 years)	study centre, sex, presence of older siblings, mode of delivery, birthweight, season of birth, breastfeeding, ethnicity, tobacco smoke exposure, parental atopy, and	*Chao1 index* aOR_{asthma} (95% CI)=0·68 (0·46; 0·99)	↓↓ asthma

		exposure to environmental nitrogen dioxide		
Ruokolainen, et al. [94], 2020 (Finland and Estonian)	Children (18 months of age)	--	In the skin samples from Estonia, diversity tended to be higher in sensitized children as compared to healthy children (p=0.028). Significant differences between healthy and sensitized children were observed both in the nasal and stool samples, but only among Finnish children (MRM on Bray-Curtis: nasal: R_2=0.02; stool R^2=0.01)	↑↑ allergic sensitization
Toivonen, et al. [17], 2020 (Finland)	Children (7 years)	sex, household siblings, parental asthma, and child's eczema at age 13 months	*Shannon index* At 2 months $Median_{asthma}$ (IQR)=1.11 (0.71; 1.38) $Median_{non\text{-}asthma}$ (IQR)=0.92 (0.50; 1.40) At 13 months $Median_{asthma}$ (IQR)=1.29 (0.47; 2.26) $Median_{non\text{-}asthma}$ (IQR)=0.87 (0.45; 1.70) At 24 months $Median_{asthma}$ (IQR)=0.53 (0.29; 1.03) $Median_{non\text{-}asthma}$ (IQR)=0.73 (0.32; 1.31)	↕ asthma (comparing mean value of Shannon diversity index at different moments)
Ham, et al. [148], 2021 (South Korea)	Adults (49-58.44 years)	--	The asthma patients did not differ from the heathy individuals in terms of the α and β diversity of the lung and gut microbiomes. Similarly, the 2 groups did not differ in terms of the relative abundance of microbiome genera or species in the sputum. Stool samples: the healthy individuals and asthma patients did not differ significantly in terms of α diversity, composition, or relative abundance of genera or species.	no evidence of effect: asthma
Niemeier-Walsh, et al. [14], 2021 (USA)	Children (12 years)	gender, asthma status, and mother's education as a measure of socioeconomic status	Sputum: *Shannon index* $Mean_{asthmatics}$ (95% CI)=3.7 (3.6; 3.8) $Mean_{non\text{-}asthmatics}$ (95% CI)=3.6 (3.4; 3.7) *Observed ASVs (amplicon sequence variants)* $Mean_{asthmatics}$ (95% CI)=179 (154; 204) $Mean_{non\text{-}asthmatics}$ (95% CI)=166 (147; 185) *Phylogenetic diversity* $Mean_{asthmatics}$ (95% CI)=8.6 (7.6; 9.6) $Mean_{non\text{-}asthmatics}$ (95% CI)=8.4 (7.8; 9.0)	↑↑ ($Mean_{asthma}$ > $Mean_{non\text{-}asthmatics}$)

Samra, et al. [149], 2021 (South Korea)	Children (≈ 10 years)	--	Bacterial composition, Shannon diversity index and Faith phylogenetic diversity were higher in the allergic subjects compared to the healthy subjects	↓ allergic sensitization
Schei, et al. [18], 2021 (Norway)	Children (6 years)	--	*Bacterial abundance* (at 2 years of age) $OR_{ever\ asthma\ at\ 6\ years}$ (95% CI)=1.21 (0.53; 2.78)	↑ asthma
Seppo, et al. [52], 2021 (USA)	Children (3 years)	maternal atopy, delivery mode, cat and dog exposure, infant gender, maternal and infant antibiotics	α diversity in gut microbiome was not significantly enriched in atopic compared to non-atopic infants.	no evidence of effect: allergic sensitization
Turek, et al. [150], 2021 (Australia)	Adults (±56 years)	--	84 OTUs were in relatively low abundance among asthmatic subjects. Results shows differences in α diversity between asthmatics and unaffected non-smoking subjects.	↓ asthma
Bar et al. [151], 2022 (Poland)	Children (6–17 years of age)	--	EBC samples: Asthmatic children had a higher abundance of bacterial species (Shannon diversity index, mean 3.029±0.462 vs. 2.642±0.424, p=0.026)	↑↑ ($Mean_{asthma}$ > $Mean_{non\text{-}asthmatics}$)
Lee-Sarwar et al. [152], 2022 (USA)	Children (6 years)	sex, race/ethnicity, VDAART study site, and analyses of stool samples collected at age 3-6 months were additionally adjusted for exact age at stool sample collection	Age at stool sample: 3-6 months *Shannon Index* Transient asthma (*vs* no asthma): β (95% CI)=0.001 (-0.17; 0.17) Active asthma (*vs* no active asthma); β (95% CI)=-0.06 (-0.20; 0.08) Early asthma (*vs* no early asthma); β (95% CI)=-0.001 (-0.12; 0.12) *Faith's Phylogenetic Diversity* Transient asthma (*vs* no asthma): β (95% CI)=0.07 (-0.19; 0.32) Active asthma (*vs* no active asthma); β (95% CI)=-0.14 (-0.35; 0.06) Early asthma (*vs* no early asthma); β (95% CI)=-0.02 (-0.19; 0.15) 1 year *Shannon Index* Transient asthma (*vs* no asthma): β (95% CI)=-0.02 (-0.14; 0.10) Active asthma (*vs* no active asthma); β (95% CI)=-0.01 (-0.11; 0.10) Early asthma (*vs* no early asthma); β (95% CI)=-0.06 (-0.15; 0.03) *Faith's Phylogenetic Diversity* Transient asthma (*vs* no asthma): β (95% CI)=-0.04 (-0.13; 0.16) Active asthma (*vs* no active asthma); β (95% CI)=0.07 (-0.10; -0.03) Early asthma (*vs* no early asthma); β (95% CI)=-0.02 (-0.19; 0.15)	↕ asthma ↑ asthma (Shannon index, transient asthma (3-6 months; active and early asthma (3 years). Faith's Phylogenetic Diversity, transient asthma (3-6 months, 3 years); active asthma (1 year, 3 years); early asthma (3 years)) ↓ asthma

			3 years *Shannon Index* Transient asthma (*vs* no asthma): β (95% CI)=-0.02 (-0.12; 0.07) Active asthma (*vs* no active asthma); β (95% CI)=0.07 (-0.02; 0.15) Early asthma (*vs* no early asthma); β (95% CI)=0.03 (-0.04; 0.10) *Faith's Phylogenetic Diversity* Transient asthma (*vs* no asthma): β (95% CI)=0.05 (-0.13; 0.22) Active asthma (*vs* no active asthma); β (95% CI)=0.09 (-0.06; 0.25) Early asthma (*vs* no early asthma); β (95% CI)=0.05 (-0.07; 0.19)	
Lee-Sarwar et al. [153], 2022 (USA)	Children (6 years)	VDAART study site	Fecal alpha diversity was not associated with wheeze proportion (Shannon index: Pearson r=-0.12, *p*=0.21; Simpson index: Pearson r=-0.10, *p*=0.27)	↓ wheezing
Tsai et al. [154], 2022 (Taiwan)	Children (36 months)	--	Children with atopy alone had a significantly lower Chao1 index than healthy controls (*p*=0.035). Higher Shannon index was present in children with atopy alone than in the healthy controls (*p*>0.05)	↑ asthma
Zheng et al. [155], 2022 (China)	Children (5 to 14 years)	age, gender and body mass index	Chao1 (*p* =0.025) and Simpson (*p* =0.024) indices showed significant differences among the three groups (non-allergic asthma, allergic asthma and healthy controls). A higher bacterial richness and a lower diversity in asthma group was observed.	↓↓ asthma
Mubanga et al. [156], 2023 (Sweden)	Children (9-14 years)	twin-pairs	No statistically significant evidence for differences in within-sample alpha diversity between exposure groups (Shannon: *p*=0.59, Simpson: *p*=0.33)	no evidence of effect: asthma
Thorsen et al. [157], 2023 (Denmark)	Children (7 years)	log(library size) and sequencing run	Shannon diversity index: HR (95% CI)=0.72 (0.42; 1.22) Faith's phylogenetic diversity: HR (95% CI)= 1.02 (0.88; 1.18)	↕ asthma

* ↓↓ significant evidence of lower risk (statistically significant, p<0.05); ↓ suggestive evidence of lower risk (trending, but p>0.05); ↕ contradictory findings; ↑ suggestive evidence of higher risk (trending, but p>0.05); ↑↑ significant evidence of higher risk (statistically significant, p<0.05); no evidence of effect (for qualitative results). Arrows represents direction and strength of evidence based on the statistical significance for each study. Some studies contributed more than one results and are represented by different colours. -- covariates (confounders) were not described in the article

aOR: adjusted odds ratio; COPD: Chronic Obstructive Pulmonary Disease; HR; hazard ratio; IQR: interquartile range; MRM: multiple regression on distance matrices; OTUs: operational taxonomic units; PC: principal component; PCA: principal component analysis; SD: standard deviation; SRI; species richness index; 95% CI: 95% confidence interval.

Table S3. Microbiota composition between cases and controls for the main phyla/genera detected or effect estimate for the main phyla/genera detected

Reference, study year (country)	Sample	(Quali)quantitative results	Taxa	Relative abundance (%)*		Effect estimate
				Case	Control	
Bisgaard, et al. [34], 2007 (Denmark)	Airway samples	quantitative (aHR (95% CI) test for wheezing and presence of bacteria)				
			First wheezy episode			
			Streptococcus pneumoniae			1.53 (0.97; 2.40)
			Haemophilus influenzae			1.27 (0.82; 1.97)
			Moraxella catarrhalis			1.76 (1.08; 2.85)
			Staphylococcus aureus			0.97 (0.74; 1.26)
			At least one			1.50 (1.08; 2.10)
			Persistent wheeze			
			Streptococcus pneumoniae			1.41 (0.65; 3.07)
			Haemophilus influenzae			2.73 (1.36; 5.48)
			Moraxella catarrhalis			1.53 (0.72; 3.25)
			Staphylococcus aureus			1.00 (0.59; 1.68)
			At least one			2.01 (1.13; 3.57)
			Acute severe exacerbation			
			Streptococcus pneumoniae			2.02 (0.79; 5.17)
			Haemophilus influenzae			3.78 (1.70; 8.40)
			Moraxella catarrhalis			2.52 (0.92; 5.51)
			Staphylococcus aureus			1.09 (0.58; 2.05)
			At least one			3.14 (1.57; 6.30)
			Hospitalization			
			Streptococcus pneumoniae			2.33 (0.72; 7.54)
			Haemophilus influenzae			4.09 (1.65; 10.15)
			Moraxella catarrhalis			2.93 (1.06; 8.11)
			Staphylococcus aureus			1.32 (0.58; 2.99)
			At least one			3.57 (1.55; 8.23)
Hilty, et al. [35], 2010 (Ireland)	Airway samples	quantitative (numbers of sequences) between asthma and healthy control groups				
			Phyla			
			Proteobacteria	181	27	

			Bacterioidetes	179	151	
			Firmicutes[⊥]	134	103	
			Fusobacteria[⊥]	19	11	
			Actinobacteria[⊥]	12	11	
			Genera			
			Actinobacteria/Corynebacterium[⊥]	0	2	
			Other *Actinobacteria*[⊥]	12	9	
			Bacteroidetes/Prevotella	158	121	
			Other *Bacteroidetes*[⊥]	21	30	
			Firmicutes/Staphylococcus[⊥]	2	3	
			Firmicutes/Streptococcus[⊥]	56	28	
			Firmicutes/Veillonella[⊥]	45	41	
			Other *Firmicutes*[⊥]	31	31	
			Proteobacteria/Haemophilus	108	13	
			Proteobacteria/Neisseria[⊥]	44	11	
			Other *Proteobacteria*	29	3	
			Fusobacterium[⊥]	19	11	
Bisgaard, et al. [36], 2011 (Denmark)	Stool samples	quantitative (risk of asthma; allergic sensitization (Specific IgE, skin prick test (SPT))) (1 month; 12 months)				
			Enterobacteriaceae[⊥]			1 month: 0.94 (0.46; 1.92)$_{asthma}$ 0.062 (-0.372; 0.496)$_{IgE}$ -0.091 (-0.647; 0.465)$_{SPT}$ 12 months: 1.20 (0.40; 3.64)$_{asthma}$ -0.248 (-0.844; 0.347)$_{IgE}$ 0.058 (-0.752; 0.867)$_{SPT}$
			Enterococcaceae[⊥]			1 month: 1.17 (0.55; 2.51)$_{asthma}$ -0.107 (-0.586; 0.372)$_{IgE}$ 0.084 (-0.531; 0.698)$_{SPT}$ 12 months:

				1.30 (0.61 to 2.75)$_{asthma}$ 0.211 (-0.222 to 0.645)$_{IgE}$ -0.066 (-0.616 to 0.484)$_{SPT}$
			Staphylococcaceae	1 month: 1.69 (0.83 to 3.46)$_{asthma}$ 0.508 (0.059 to 0.957)$_{IgE}$ 0.183 (-0.382 to 0.748)$_{SPT}$ 12 months: 0.72 (0.16 to 3.21)$_{asthma}$ 0.146 (-0.513 to 0.805)$_{IgE}$ 0.044 (-1.004 to 1.092)$_{SPT}$
			Anaerobes$^{\perp}$	1 month: 0.94 (0.39 to 2.26)$_{asthma}$ -0.113 (-0.662; 0.437)$_{IgE}$ 0.002 (-0.672; 0.677)$_{SPT}$ 12 months: 1.30 (0.55; 3.07)$_{asthma}$ 0.432 (-0.093; 0.957)$_{IgE}$ 0.496 (-0.112; 1.104)$_{SPT}$
Cardenas, et al. [37], 2012 (Ecuador)	Airway samples	quantitative (OR (95% CI) test for wheezing)		
			Actinobacteria/Actinomyces	1.10 (1.02; 1.20)
			Actinobacteria/Atopobium	2.27 (1.89; 2.71)
			Actinobacteria/Corynebacterium	25.0 (17.0; 36.7)
			Bacteroidetes/Bacteroidales	0.55 (0.44; 0.69)
			Bacteroidetes/Flavobacteriaceae	12.1 (7.55; 19.3)
			Bacteroidetes/Porphyromonas	0.20 (0.15; 0.27)
			Bacteroidetes/Prevotella	1.38 (1.27; 1.50)
			Firmicutes/Gemella	0.40 (0.33; 0.49)
			Firmicutes/Lachnospiraceae	0.39 (0.30; 0.50)
			Firmicutes/Staphylococcus	124.1 (59.0; 161.2)
			Firmicutes/Veillonella	0.59 (0.56; 0.62)
			Fusobacteria/Leptotrichia	0.42 (0.33; 0.53)
			Proteobacteria/Haemophilus	2.12 (1.82; 2.47)
			Proteobacteria/Moraxella	0.79 (0.72; 0.88)
			Proteobacteria/Neisseriaceae	1.19 (1.09; 1.30)

			Proteobacteria/Pasteurellaceae		0.20 (0.13; 0.29)
Marri, et al. [38], 2013 (USA)	Airway samples	quantitative (genera median percentage (%)) between asthma and healthy control groups			
			Proteobacteria	37	15
			Fusobacteria	2	3
			Firmicutes	47	63
			Bacteroidetes	1	1
			Actinobacteria	10	14
			Unknown	3	4
Abrahamsson, et al. [39], 2014 (Sweden)	Stool samples	quantitative (phyla mean relative abundance (%)) (1 week; 1 month; 12 months) $^{\perp}$ from infants who did or did not develop asthma at 7 years of life			
			Actinobacteria	26; 48; 5	23; 34; 14
			Proteobacteria	18; 12; 5	19; 13; 17
			Bacteriodetes	7; 5; 12	14; 17; 10
			Firmicutes	49; 34; 80	44; 36; 70
			Verrucomicrobia	<1; <1; 2	<1; 1; 2
Park, et al. [40], 2014 (Korea)	Airway samples	quantitative (phyla mean relative abundance (%)) between asthma and healthy control groups			
			Firmicutes	59.79	48.37
			Proteobacteria	35.61	29.02
			Bacteroidetes	2.62	16.2
			Actinobacteria	1.62	5.86
			Fusobacteria	0.38	0.45
			Cyanobacteria	0	0.45
			Spirochaetes	0	0.02
			Tenericutes	0	0.02
Denner, et al. [42], 2016 (USA)	Airway samples	qualitative (phyla and genera mean relative abundance (%)) between asthma and healthy control groups			

		("+" and "-" are based on *Figure 1* (of the specific study) for the Relative abundance (%) of bacteria at the phylum and genera level identified in each sampling group)			
			Proteobacteria	++	+
			Firmicutes	+	+
			Bacteroidetes	+	++
			Actinobacteria	+	++
			Lactobacilus	++	+
			Prevotella	+	++
			Actinomyces	-	++
Hevia, et al. [43], 2016 (Spain)	Stool samples	quantitative (phyla mean relative abundance (%))			
			Euryarchaeota$^{\perp}$	3.70	0.0003
			Other$^{\perp}$	6.06	6.62
			Acidobacteria$^{\perp}$	0	6.12
			Actinobacteria	2.61	1.17
			Bacteroidetes$^{\perp}$	27.3	22.4
			Cyanobacteria$^{\perp}$	0.08	0.036
			Firmicutes$^{\perp}$	61.4	67.0
			Fusobacteria$^{\perp}$	0.003	0.00016
			Lentisphaerae$^{\perp}$	0.01	0.019
			Proteobacteria$^{\perp}$	2.13	1.58
			Synergistetes$^{\perp}$	0.0025	0.425
			Tenericutes$^{\perp}$	0.17	0.29
			TM7$^{\perp}$	0.00056	0.00097
			Verrucomicrobia$^{\perp}$	0.25	0.415
			Unassignable;Other$^{\perp}$	0	4.14
			Unclassified;Other$^{\perp}$	0.044	0.032
Stiemsma, et al. [45], 2016 (Canada)	Stool samples	differentially abundant OTUs identified by Deseq2 among asthmatics ("+" and "-" are based on *Figure 1* (of the specific study) for the differentially abundant OTUs decreased and			

		increased in asthmatics; "+": Log2 Fold change >0 (increased in the respective group); "-": Log2 Fold change <0 (decreased in the respective group))				
			3 months			
			Firmicutes	++	-	
			Clostridiaeceae	++	-	
			Clostridium neonatale$^{\perp}$	++	-	
			Clostridiales	-	++	
			Lachnospira$^{\perp}$	-	++	
			1-year			
			RF32	-	++	
			Lachnospiraceae (OTU 15)$^{\perp}$	++	-	
			Lachnospiraceae (OTU 40)	++	-	
			Lachnospiraceae (OTU 26)$^{\perp}$	++	-	
			Rothia	++	-	
			Veillonella$^{\perp}$	++	-	
Zhang, et al. [46], 2016 (UK)	Airway samples	quantitative (OR (95% CI) test for asthma [non-severe; severe])				
			Proteobacteria			2.26 (1.94; 2.64); 1.21 (1.03; 1.40)
			Fusobacteria			0.50 (0.40; 0.63); 0.38 (0.31; 0.48)
			Firmicutes			1.00 (0.87; 1.16); 2.15 (1.89; 2.45)
			Bacteroidetes			0.62 (0.54; 0.71); 0.62 (0.54; 0.70)
Chiu, et al. [47], 2017 (Taiwan)	Airway samples	quantitative (Phylum/Genus mean (+/-, standard deviation) relative abundance (%)) between asthma and healthy control groups				
			Bacteroidetes/Porphyromonas$^{\perp}$	2.35 ± 2.20	2.96 ± 2.83	
			Firmicutes/Moryella$^{\perp}$	0.66 ± 1.59	0.57 ± 1.00	

			Fusobacteria/Fusobacterium[⊥]	4.83 ± 4.54	5.07 ± 5.22	
			Proteobacteria/Aggregatibacter[⊥]	0.62 ± 1.67	0.62 ± 1.25	
			Proteobacteria/Haemophilus[⊥]	5.26 ± 4.57	5.40 ± 5.54	
			Proteobacteria/Neisseria[⊥]	4.33 ± 4.84	2.86 ± 2.42	
			Proteobacteria/Moraxella[⊥]	0.62 ± 2.41	0.50 ± 1.17	
			Firmicutes/Butyrivibrio	0.03 ± 0.07	0.09 ± 0.19	
			Firmicutes/Parvimonas	0.19 ± 0.31	0.48 ± 0.75	
			Firmicutes/Selenomonas	0.61 ± 0.84	0.57 ± 0.72	
Depner, et al. [48], 2017 (Germany, Austria and Switzerland)	Airway samples	quantitative (OR (95% CI) test for asthma) [ł]				
			Proteobacteria (nose)			2.44 (1.07; 5.59)
			Moraxella (nose)			3.78 (2.02; 7.05
Li, et al. [49], 2017 (China)	Airway samples	quantitative (class, order or family median relative abundance (%) for asthma [non-severe; severe])				
			Gammaproteobacteria[⊥]	4.121; 5.507	6.152	
			Enterobacteriales[⊥]	0; 0	0	
			Pseudomonadales[⊥]	0.029; 0.154	0.053	
			Enterobacteriaceae[⊥]	0; 0	0	
			Porphyromonadaceae	3.955; 4.466	6.175	
			Pseudomonadaceae[⊥(NSA vs. healthy)]	0.024; 0.116	0.032	
Arrieta, et al. [51], 2018 (Ecuador)	Stool samples	qualitative (genus relative abundance (%)) between atopic wheeze and healthy control groups ("+" and "-" are based on *Figure 1* (of the specific study) for the Log fold change of OTUs that are significantly (false discovery rate < 0.05) abundant between atopic wheeze and control				

		subjects calculated by using DESeq2; "+": increased in the respective group; "-": decreased in the respective group)			
			Bacteroides	-	++
			Bifidobacterium	-	++
			Veillonella	++	-
Durack, et al. [52], 2018 (USA)	Airway samples	qualitative (frequency distribution of specific genera (%) atopic asthma; atopy without asthma and healthy controls) ("+" and "-" are based on *Figure 4* (of the specific study) for the Frequency distribution of specific genera (present in at least 20% of participants for each group) for OTUs; "+": increased in the respective group; "-": decreased in the respective group)			
			Prevotella	++; +	-
			Haemophilus	+; +	-
			Streptococcus	-; +	+
			Fusobacterium	++; +	--
			Neisseria	++; +	--
			Aggregatibacter	-; +	-
			Other	+; +	++
Fazlollahi, et al. [53], 2018 (USA)	Airway samples	quantitative (phylum relative abundance (%) for asthma [non-exacerbated; exacerbated])			
			Proteobacteria[⊥]	19.4; 17.5	10.1
			Fusobacteria[⊥]	0.7; 0.6	0.4
			Firmicutes[⊥]	44.2; 39.6	48.7
			Others[⊥]	0.6; 0.6	0.8

			Bacteroidetes	3.0; 3.5	1.0
			Actinobacteria[⊥]	32.1; 38.2	39.0
Kim, et al. [54], 2018 (South Korea)	Airway samples	qualitative (phylum relative abundance (%) for asthma and healthy controls) ("+" and "-" are based on *Figure 1* (of the specific study) for the Phylum composition; "+": increased in the respective group; "-": decreased in the respective group)			
			Proteobacteria	-	+
			Firmicutes	+	-
			Fusobacteria	+	-
			Bacteroidetes	+	-
Okba, et al. [55], 2018 (Egypt)	Stool samples	quantitative (relative abundance (%) for asthma and healthy controls)			
			Female		
			Lactobacilli[⊥]	20	10
			E. coli[⊥]	87.5	90
			Kelbsiella[⊥]	20	10
			Proteus[⊥]	12.5	0
			Enterobacter[⊥]	15	30
			Enterococci[⊥]	7.5	0
			Serratia[⊥]	0	0
			Citrobacter[⊥]	5	0
			Bacteroids[⊥]	0	0
			Provedencia[⊥]	2.5	0
			Morganella[⊥]	0	0
			Pseudomonas[⊥]	0	0
			S. aureus[⊥]	0	0
			Male		
			Lactobacilli	35	0
			E. coli[⊥]	86	90
			Kelbsiella[⊥]	25	40

			Proteus[⊥]	17.5	10	
			Enterobacter[⊥]	2.5	0	
			Enterococci[⊥]	2.5	0	
			Serratia[⊥]	2.5	0	
			Citrobacter[⊥]	5	10	
			Bacteroids[⊥]	5	0	
			Provedencia[⊥]	0	0	
			Morganella[⊥]	2.5	0	
			Pseudomonas[⊥]	10	0	
			S. aureus[⊥]	0	10	
Stokholm, et al. [56], 2018 (Denmark)	Stool samples	quantitative (relative abundance (%) for asthma and healthy controls)				
			Roseburia	0.27	0.66	
			Veillonella	0.94	0.29	
			Alistipes	0.04	0.35	
			Flavonifractor	0.05	0.07	
Bannier, et al. [58], 2019 (Netherlands)	Stool samples	quantitative (aOR (95% CI), *Bifidobacterium* as a reference group, for asthma and wheezing)				
			Asthma			
			Bifidobacterium-Blautia			1.454 (0.707; 2.994)
			Prevotella			0.707 (0.276; 1.809)
			Wheezing			
			Bifidobacterium-Blautia			1.167 (0.537; 2.540)
			Prevotella			4.282 (0.940; 19.51)
Espuela-Ortiz, et al. [59], 2019 (USA)	Airway samples	quantitative (genera mean relative abundance (%) between children with and without asthma)				
			Aggregatibacter	2.3	1.6	
			Atopobium	1.2	0.9	
			Streptococcus	13.0	18.3	
			Veillonella	11.1	8.0	
Lee, et al. [60], 2019 (South Korea)	Airway samples	qualitative (young adults; elderly) between asthma and healthy control groups.				

		("+" and "-" are based on *Figure 1* (of the specific study) for the composition of phylum between the groups; "+": increased in the respective group; "-": decreased in the respective group)	*Actinobacteria*[⊥]	+; ++	++; +
			Proteobacteria	++; +	+; ++
Powell, et al. [62], 2019 (UK)	Airway samples	quantitative (differential abundance; wheezing) results based on the longitudinal differential abundance analysis in early-life wheeze. The sign of the difference area provides information on the direction of the abundance shift (e.g., there was an increase in the abundance of a Neisseria OTU over time in children with wheeze)	Early-life wheeze (doctor-confirmed wheeze *vs.* no wheeze)		
			OTU42 Granulicatella (9-12 months)	-1.118	
			OTU43 Prevotella (18-24 months)	-1.147	
			OTU68: Neisseria (9-24 months)	+5.993	
			Early-life wheeze (recurrent wheeze *vs.* no wheeze)		
			OTU42 Granulicatella (9-24 months)	-4.999	
			OTU43 Prevotella (18-24 months)	-2.637	
			OTU68 Neisseria (12-24 months)	+3.581	

			OTU76 Prevotella (12-24 months)	-2.090	
Samra, et al. [63], 2019 (South Korea)	Urine samples	quantitative (mean relative abundance (%) for atopic asthma and healthy control groups))			
			Micrococcaceae	6.39	1.72
			Micrococcaceae(f)	4.59	0.93
			Propionibacteriaceae$^{\perp}$	1.70	0.87
			Propionibacterium$^{\perp}$	1.70	0.86
			Methylobacteriaceae	9.59	1.12
			Methylobacteriaceae(f)	1.74	0.45
			Methylobacterium	7.85	0.67
			Rhizobiaceae$^{\perp}$	4.98	9.36
			Agrobacterium$^{\perp}$	4.69	8.52
			Sphingomonadaceae$^{\perp}$	15.70	11.25
			Sphingomonadaceae(f)	1.93	0.46
			Alcaligenaceae$^{\perp}$	3.67	6.81
			Achromobacter$^{\perp}$	3.60	6.68
			Comamonadaceae$^{\perp}$	5.91	4.52
			Comamonadaceae(f)	1.58	0.71
			Enterobacteriaceae	3.36	8.98
			Enterobacteriaceae(f)	2.84	8.72
			Moraxellaceae$^{\perp}$	3.99	4.42
			Enhydrobacter$^{\perp}$	0.39	0.45
Thorsen, et al. [64], 2019 (Denmark)	Airway samples	quantitative (taxon mean relative abundance (%) between asthma and healthy control groups)			
			Veillonella	4.79e-2	2.83e-2
			Prevotella	6.62e-3	2.65e-3
			Gemella	5.16e-2	3.95e-2
			Bacilli	7.16e-4	4.66e-4
			Bacillales	1.77e-3	1.61e-3
			Lactobacillus	1.48e-2	9.23e-3
			Streptococcus	3.32e-1	3.01e-1
			Neisseria	2.73e-2	2.15e-2
Al Bataineh, et al. [65], 2020 (United Arab Emirates)	Airway samples	quantitative (mean relative abundance (%) for asthma			

and healthy control groups)); sig differences			
	Adults		
	Streptococcus	16.51	7.01
	Granulicatella	0.86	0.56
	Eikenella	0.11	0.21
	Capnocytophaga	0.81	0.83
	Pasteurellaceae_unclassified	0.16	0.13
	Enterobacteriaceae_unclassified	0.13	0.01
	Escherichia	0	0.01
	SR1_unclassified	0.47	0.4
	Cardiobacterium	0.03	0.06
	Butyrivibrio	0	0.06
	Peptococcus	0.02	0.06
	Aggregatibacter	0	0.01
	Bacteroidetes_unclassified	0.02	0.11
	Shuttleworthia	0.01	0.02
	Lactobacillus	0.01	0.02
	RF39_unclassified	0.01	0.03
	Bifidobacterium	0.01	0
	Sphingobium	0	0
	Children		
	Streptococcus	14.18	14.06
	Granulicatella	0.29	0.76
	Eikenella	0.44	0.37
	Capnocytophaga	0.33	0.47
	Pasteurellaceae_unclassified	0.05	0.45
	Enterobacteriaceae_unclassified	0.04	0
	Escherichia	0.04	0
	SR1_unclassified	0.02	0.17
	Cardiobacterium	0.03	0.03
	Butyrivibrio	0	0.01
	Peptococcus	0	0.01
	Aggregatibacter	0.01	0.02
	Bacteroidetes_unclassified	0	0
	Shuttleworthia	0	0
	Lactobacillus	0	0.01
	RF39_unclassified	0	0.01
	Bifidobacterium	0	0

			Sphingobium	0.02	0
Chiu, et al. [66], 2020 (Taiwan)	Airway and stool samples	qualitative (genus relative abundance (%) for asthma and healthy control groups) ("+" and "-" are based on *Figure 1* (of the specific study) for the Airway and stool microbial composition and abundance at the genus level; "+": increased in the respective group; "-": decreased in the respective group)			
			Airway samples		
			Streptococcus	-	+
			Prevotella	-	+
			Fusobacterium	+	+
			Neisseria	+	-
			Leptotrichia	+	-
			Others	+	+
			Stool samples		
			Streptococcus	+	-
			Bifidobacterium	+	-
			Blautia	+	+
			Prevotella	-	-
			Faecalibacterium	-	+
			Ruminococcus	+	-
			Coprococcus	+	+
			Others	-	+
Toivonen, et al. [69], 2020 (Finland)	Airway samples	quantitative (genera mean relative abundance (%) between asthma and healthy control groups)			
			Haemophilus (13 months)	0.11	0.04
			Acinetobacter (13 months)	0.01	0.00
			Alloprevotella (2 months)	0.00	0.00

			Neisseriaceae genus 1 (13 months)	0.03	0.01
			Veillonella (2 months)	0.01	0.01
Niemeier-Walsh, et al. [71], 2021 (USA)	Airway samples	qualitative (relative abundance) between asthma and healthy control groups ("+" and "-" are based on *Figure 5* (of the specific study) for the relative abundance of bacterial phyla in sputum; "+": increased in the respective group; "-": decreased in the respective group)			
			Bacteroidetes	++	+
			Proteobacteria	+	++
Seppo, et al. [74], 2021 (USA)	Stool samples	qualitative (differential bacterial features for atopic symptoms), LDA score (log 10). LDA score ranges between -4 and 4 and represents the differential bacterial features found by LEfSe (linear discriminant analysis effect size) in infants who developed or did not develop atopic symptoms. Higher LDA scores indicate features more characteristic of a group			
			Who developed atopic symptoms		
			Bacteroidetes	LDA score >4 & <5	
			Bacteroidia	LDA score >4 & <5	
			Bacteroidales	LDA score >4 & <5	
			Bacteroides	LDA score >4 & <5	
			Bacteroidaceae	LDA score >4 & <5	

			Lactobacillaceae	LDA score >3 & <4
			Lactobacillus	LDA score >3 & <4
			Eggerthella	LDA score >3 & <4
			Actinomycetales	LDA score >3 & <4
			Who did not develop atopic symptoms	
			Lachnospiraceae	LDA score > -4
Turek, et al. [75], 2021 (Australia)	Airway samples	Quantitative (phylum/genus relative abundance (%) for asthma))		
			phylum increased in asthmatics	
			Proteobacteria	4.74
			Actinobacteria	0.23
			genus decreased in asthmatics	
			Actinomyces	4.29
			Selenomonas	1.48
			Leptotrichia	2.01
			Megasphaera	0.62
			Selenomonas	0.17
			Oribacterium	0.09
			Actinomyces	0.32
			Capnocytophaga	0.33
			Prevotella	0.20
			Streptococcus	0.02
			Selenomonas	0.08
			Unknown	0.14
			Streptococcus	0.02
			Prevotella	0.39
			Actinomyces	0.02
			Unknown	0.08
			Prevotella	0.05
			Prevotella	0.22
			Capnocytophaga	0.08
			Tannerella	0.10
Lee-Sarwar et al. [77], 2022 (USA)	Stool samples	quantitative (OR (95% CI) test for asthma) [ł]		
			Age at stool sample (3-6 months):	

			Staphylococcus		0.24 (0.05; 0.75)$_{\text{transient asthma}}$
			Bacteroides		0.39 (0.22; 0.70)$_{\text{early asthma}}$
Lee-Sarwar et al. [78], 2022 (USA)	Stool samples	quantitative (log-fold change)			
			Top 5 taxa positively associated with wheeze		
			Veillonella	2.1	
			Lachnoclostridium	2.0	
			Monoglobus	1.8	
			Lachnospiraceae (unidentified)	1.5	
			Ruminococcus gnavus group	1.3	
			Top 5 taxa negatively associated with wheeze		
			Sellimonas	-1.8	
			Fusicatenibacter	-1.8	
			Flavonifractor	-1.8	
			Eggerthella	-1.7	
			Intestinimonas	-1.5	
Tsai et al. [79], 2022 (Taiwan)	Nasopharyngeal samples	quantitative (mean±SD (%)), atopy alone and healthy control			
			Firmicutes/Enterococcus	0.34±1.46	1.91±4.63
			Firmicutes/Bacillus	1.83±1.78	0.98±0.93
			Firmicutes/Ruminococcaceae	0.54±0.95	0.29±0.34
			Actinobacteria/Rhodococcus	1.16±4.53	0.09±0.16
			Proteobacteria/Acinetobacter	4.98±12.39	0.07±0.06
			Proteobacteria/Moraxella	4.24±5.96	1.21±1.86
			Proteobacteria/Alkanindiges	0.08±0.23	0.36±0.68
			Proteobacteria/Rickettsia	0.00±0.01	0.23±0.34
			Proteobacteria/Rhizobacter	0.00±0.00	3.28±8.52
			Proteobacteria/Asaia	0.16±0.33	0.00±0.01
Zheng et al. [80], 2022 (China)	Stool samples	quantitative (mean±SD) for allergic and non-allergic asthma; Sig differences			
			Allergic asthmatic		
			Prevotella	1.27±5.26	4.19±9.41
			Lactobacillus	0.42±0.42	0.09±0.12
			Lachnospiraceae ND3007 group	0.53±0.50	0.79±0.28

			Collinsella	0.54±0.88	0.90±0.62
			Terrisporobacter	0.42±0.80	1.32±1.90
			Megamonas	0.15±0.17	0.26±0.19
			Eubacterium eligens group	0.26±0.30	0.82±0.35
			CAG.56	0.26±0.35	0.38±0.27
			Lachnospira	0.30±0.54	0.44±0.17
			Non-allergic asthmatic group		
			Bacteroides	10.08±6.28	20.35±7.09
			Agathobacter	1.72±1.64	3.38±2.16
			CAG.352	1.31±1.00	2.82±1.61
			Ruminococcus	0.95±0.85	1.82±0.80
			Intestinibacter	0.81±0.74	1.14±0.33
			Lachnoclostridium	0.42±0.14	0.68±0.20
			Lactobacillus	1.86±4.00	0.09±0.12
			Turicibacter	0.40±0.35	1.03±1.42
			Lachnospiraceae ND3007 group	0.46±0.55	0.79±0.28
			Collinsella	0.27±0.30	0.90±0.62
			Terrisporobacter	0.12±0.10	1.32±1.90
			Parasutterella	0.23±0.25	0.34±0.24
			Eubacterium eligens group	0.18±0.14	0.82±0.35
			Lachnospira	0.11±0.09	0.44±0.17
Thorsen et al. [82], 2023 (Denmark)	Nasopharyngeal samples	qualitative (Cox regression of time-to-asthma, HR>1 and p>0.05; and DESeq2 analysis comparing abundance of the species between children who later developed asthma vs those who did not, Log2-fold change >0 and p>0.05); Differential abundance analysis was performed at species level using two methods: Cox regression with log-scaled species relative abundance values as predictors from the			

	package survival and DESeq2. All p values were derived from two-sided tests		
		Cox regression:	
		Haemophilus influenzae	HR>1 and p<0.05
		Moraxella linolnii	HR>1 and p<0.05
		Moraxella catarrhalis	HR>1 and p<0.05
		Streptococcus pneumoniae	HR>1 and p>0.05
		DESeq2:	
		Haemophilus influenzae	Log2-fold change >0 and p<0.05
		Moraxella linolnii	Log2-fold change >0 and p>0.05
		Moraxella catarrhalis	Log2-fold change >0 and p>0.05
		Streptococcus pneumoniae	Log2-fold change >0 and p<0.05

*Taxa with significant differences (p<0.05) between cases (individuals with asthma, allergic sensitization or wheezing) and controls (healthy individuals); ⊥ no significant differences between cases and controls; ǀ relative abundance of the main phyla and genera tested for association with asthma.

aHR: adjusted hazard ratio; LDA: linear discriminant analysis; HR: hazard ratio; OR: odds ratio: OTUs: OTUs: operational taxonomic units; SD: standard deviation; 95% CI: 95% confidence interval.

Table S4. Summary of the evidence on the association between outer layer biodiversity and respiratory outcomes (based on information included in Table 1 "*Outer layer biodiversity*")

	Outcome		
Evidence	Asthma	Allergic sensitization	Wheezing
Significant evidence of lower risk	11	6	2
Suggestive evidence of lower risk	3	5	2
Contradictory findings	4	2	0
Significant evidence of higher risk	7	3	2
Suggestive evidence of higher risk	2	2	0
No evidence of effect	6	4	1

Some studies contributed more than one result. Significant evidence of lower risk (statistically significant, $p<0.05$); suggestive evidence of lower risk (trending, but $p>0.05$); contradictory findings; significant evidence of higher risk (statistically significant, $p<0.05$); suggestive evidence of higher risk (trending, but $p>0.05$); no evidence of effect (for qualitative results).

Table S5. Summary of the evidence on the association between inner layer biodiversity and respiratory outcomes (based on information included in Table 1 *"Inner layer biodiversity"*)

	Outcome		
Evidence	Asthma	Allergic sensitization	Wheezing
Significant evidence of lower risk	5	2	0
Suggestive evidence of lower risk	4	1	1
Contradictory findings	6	0	0
Significant evidence of higher risk	8	1	1
Suggestive evidence of higher risk	4	1	0
No evidence of effect	14	4	3

Some studies contributed more than one result. Significant evidence of lower risk (statistically significant, $p<0.05$); suggestive evidence of lower risk (trending, but $p>0.05$); contradictory findings; significant evidence of higher risk (statistically significant, $p<0.05$); suggestive evidence of higher risk (trending, but $p>0.05$); no evidence of effect (for qualitative results).

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