The role of biodiversity in the development of asthma and allergic sensitization: a systematic review and meta-analysis

Jouni Jaakkola[1], Inês Paciência[1], Needhi Sharma[2], Timo Hugg[1], Aino K. Rantala[1], Behzad Heibati[1], Wael K. Al-Delaimy[2], and Maritta Jaakkola[1]

[1]Oulun yliopisto
[2]University of California San Diego

May 26, 2023

Abstract

Changes in land use and climate change have been reported to reduce biodiversity of the environment and human microbiota. This may lead to inadequate and unbalanced stimulation of immunoregulatory circuits and ultimately, to clinical diseases, such as asthma and allergies. We summarised available empirical evidence on the role of inner and outer layers of biodiversity in the development of asthma, asthma-like symptoms, and allergic sensitization. We conducted a systematic search in SciVerse Scopus, PubMed MEDLINE, and Web of Science up to 5 December 2022 to identify relevant studies assessing the relations between inner and outer layers of biodiversity and the risk of asthma, wheezing and/or allergic sensitization. We applied random-effects models to calculate summary effect estimates. The protocol was registered in PROSPERO (CRD42022381725). Of 75 studies, 20 provided effect estimates for the meta-analysis showing an association between high outer layer biodiversity and a low risk of asthma development (Shannon diversity index: OR (95% CI) = 0.77 (0.55; 1.06); bacterial richness: OR (95% CI) = 0.74 (0.57; 0.96)). Although the evidence on the effect of inner layer biodiversity suggested that bacterial diversity was slightly higher among individuals with asthma, there was no clear evidence of a significant association between inner layer biodiversity and the risk of asthma, wheezing or allergic sensitization. The weight of evidence suggests that environmental exposure to high biodiversity may protect from the development of asthma, whereas there was no consistent evidence on any association between inner layer biodiversity and asthma, wheezing or allergic sensitization.

The role of biodiversity in the development of asthma and allergic sensitization: a systematic review and meta-analysis

Short title: Biodiversity, asthma and allergic sensitization

Inês Paciência[1,2], Needhi Sharma[3], Timo T. Hugg[1,2], Aino K. Rantala[1,2], Behzad Heibati[1,2], Wael K. Al-Delaimy[3], Maritta S. Jaakkola[1,2], Jouni J.K. Jaakkola[1,2,4]

[1]Center for Environmental and Respiratory Health Research (CERH), Population Health, University of Oulu, Finland

[2]Biocenter Oulu, University of Oulu, Finland

[3] University of California San Diego - San Diego, Ca, USA

[4]Finnish Meteorological Institute, Helsinki, Finland

Correspondence: Jouni J.K. Jaakkola, MD, PhD, Center for Environmental and Respiratory Health Research (CERH), Population Health, University of Oulu, Aapistie 5a, 90220 Oulu. E-mail: jouni.jaakkola@oulu.fi

Acknowledgments

The authors gratefully acknowledge funding from the University of Oulu and the Academy of Finland Profi Biodiverse Anthropocenes no. 336449 and Academy of Finland grant no. 310371 and no. 310372 310372 (GLORIA consortium).

Funding

Academy of Finland (no. 310372 and no. 336449).

Abstract

Changes in land use and climate change have been reported to reduce biodiversity of the environment and human microbiota. This may lead to inadequate and unbalanced stimulation of immunoregulatory circuits and ultimately, to clinical diseases, such as asthma and allergies. We summarised available empirical evidence on the role of inner and outer layers of biodiversity in the development of asthma, asthma-like symptoms, and allergic sensitization. We conducted a systematic search in SciVerse Scopus, PubMed MEDLINE, and Web of Science up to 5 December 2022 to identify relevant studies assessing the relations between inner and outer layers of biodiversity and the risk of asthma, wheezing and/or allergic sensitization. We applied random-effects models to calculate summary effect estimates. The protocol was registered in PROSPERO (CRD42022381725). Of 75 studies, 20 provided effect estimates for the meta-analysis showing an association between high outer layer biodiversity and a low risk of asthma development (Shannon diversity index: OR (95% CI) = 0.77 (0.55; 1.06); bacterial richness: OR (95% CI) = 0.74 (0.57; 0.96)). Although the evidence on the effect of inner layer biodiversity suggested that bacterial diversity was slightly higher among individuals with asthma, there was no clear evidence of a significant association between inner layer biodiversity and the risk of asthma, wheezing or allergic sensitization. The weight of evidence suggests that environmental exposure to high biodiversity may protect from the development of asthma, whereas there was no consistent evidence on any association between inner layer biodiversity and asthma, wheezing or allergic sensitization.

Keywords

asthma, allergic sensitization, biodiversity, inner layer, outer layer

Introduction

Our planet is experiencing a massive decline in biodiversity, which is largely due to human activities, and which could ultimately lead to the sixth extinction of animal and plant species on the Earth.[1, 2] This global change in the environments can affect ecosystem functioning and lead to significant disruptions of ecosystems, which may threaten the human sources of livelihood and the current way of life. Loss of biodiversity is a global concern and may lead to a variety of possible adverse consequences for the human population.[3] The reasons underlying such loss of biodiversity are complex and have been suggested to be largely linked to the consequences of growing urbanisation and industrialization, climate change, increasing pollution, and increasing utilization of chemicals, which have impact on the environment and microorganisms with which humans coevolve.[4, 5]

Biodiversity was defined by von Hertzen et al. [1] as "*The variability among living organisms from all sources, including, inter alia, terrestrial, marine and other aquatic ecosystems and the ecological complexes of which they are part this includes diversity within species, between species and of ecosystems* ". Haahtela[6] also suggested that micro-organisms play a key role in the link between biodiversity-related environmental changes and human health. Loss of biodiversity and disappearance of natural habitats may reduce the diversity of environmental microbiota, i.e., the biodiversity of the outer layer.[6] According to Haahtela[6], humans are protected by two nested layers of biodiversity, i.e. microbiota of the outer layer and of the inner layer. The outer layer is dependent on the environment we live in (including soil, natural waters, plants, and animals); and the inner layer inhabits the human body (including gut, skin, and airways) and is dependent

on colonization from the outer layer. Furthermore, the diversity and composition of human microbiota (i.e., inner layer) can also be influenced by environmental exposures (i.e., outer layer).[7-9]

In 2011, von Hertzen et al. [1] proposed that loss of biodiversity also leads to immune system dysfunction and increases the risk of chronic inflammatory diseases, including asthma and allergies, chronic obstructive pulmonary disease, type 1 diabetes, obesity and inflammatory bowel diseases, and could therefore have important public health implications. The biodiversity hypothesis proposed by von Hertzen et al. [1] is consistent with the observed declining trends of biodiversity indices, such as Waterbird Population Status Index (WPSI) and Living Planet Index (LPI), and with increasing trends in the prevalence of asthma and allergic rhinitis since the 1970's.[5] Rapidly declining biodiversity may be a contributing factor to another global megatrend, the rapidly increasing prevalence of allergies and other chronic inflammatory diseases among urban people.[5] Increasing evidence suggests that the diversity of human microbiota influences the risk of asthma and allergies.[10] Changes in the development of microbiota, evidenced by low gut and airways microbiota diversity in infancy, has been associated with the development of atopy and asthma later in life.[10, 11] The biodiversity hypothesis has stimulated substantial research on the role of biodiversity for the risk of developing asthma and allergic diseases, but the results have so far been inconsistent.[10, 11] This heterogeneity in results may be related to different definitions and measures of biodiversity, timing and duration of exposure, as well as differences in duration of the follow-ups. Therefore, this systematic review and meta-analysis aims to summarize the current knowledge on the role of biodiversity in the development of asthma, wheezing, and allergic sensitization.

Methods

Selection criteria and data collection

We performed a systematic search of SciVerse Scopus, PubMed MEDLINE, and Web of Science databases from inception of each database up to the 5th December 2022 using the following boolean search commands: ["biodiversity"] AND ["allerg*"] OR ["asthma"] AND ["environment*"] AND ["microbio*"]. The methodology used in this systematic review and meta-analysis followed the PRISMA reporting standards. The protocol was published in the PROSPERO (registration number: CRD42022381725) in December 2022 (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022381725). The full search strategy can be found in the online supplement (p 6).

A study was included in the systematic review and meta-analysis if (i) it was an original randomized controlled trial or an epidemiologic study (cohort, case-control or cross-sectional study); (ii) provided data on the relations between inner and/or outer layers of biodiversity and the risk of asthma, wheezing, and/or allergic sensitization, (iii) included an adequate definition and/or indexes of biodiversity and the main health outcomes (asthma, wheezing and allergic sensitization). Studies reporting only asthma exacerbation as the outcome or assessing the effect of antibiotics, medication or treatment were excluded. Studies assessing only the effect of endotoxins, fungi or virus, diet, breastfeeding, mode of delivery, use of probiotics/prebiotics/symbiotics, pet exposure, exposure to farm, rural, or urban environments, and to natural and green spaces were also excluded.

Exposure

The exposures of interest were the outer and/or inner layer biodiversity.[6] The outer layer is dependent on the environment we live in (including soil, natural waters, plants, and animals). The inner layer inhabits human body (including gut, skin, and airways) and is influenced by colonization from the outer layer.[6] The outer layer biodiversity was defined based on the environmental microbiota (including dust or soil) or on a score of environmental biodiversity (e.g., species richness index, land-use gradient, and plant diversity). The inner

layer biodiversity was defined based on the diversity of human inner microbiota in the skin, stool, urine, and airway samples (including nasal, oropharyngeal, nasopharyngeal, and/or throat) (online supplement p 6).

Outcomes

The primary outcomes included asthma and the symptom wheezing. Different asthma definitions were considered for the inclusion of studies, such as the medical diagnosis, use of asthma medications, or the GINA-based definition.[12] The secondary outcome was allergic sensitization which was defined based on a positive response to IgE antibodies for specific allergens, or a positive skin prick test (SPT).

Data extraction

Three reviewers (IP, NS, BH) independently performed the initial screening by the title and the abstract. After this initial screening, full articles were reviewed by two independent reviewers (TH, AR) and those fulfilling the inclusion criteria were selected for data extraction. When a conflict in assessment arose at any stage of the review, a consensus between the original and two additional reviewers (TH, AR) was required to achieve the resolution. Additional description of the data extraction process is presented in the online supplement (p 6).

Quality assessment and publication bias

The risk of bias was independently assessed by two reviewers (IP and NS) applying the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies.[13] An adapted version of the NOS developed by Herzog et al. [14] was used for cross-sectional studies. The results from the NOS were translated into the Agency for Health Research and Quality standards, and applying these the studies were classified as good, fair or poor.[15]

Statistical methods

A study was included in the meta-analysis if (i) it used a priori recognised measure to assess biodiversity (Shannon diversity index and/or bacterial richness) and (ii) it analysed biodiversity as a continuous variable. Meta-analysis applying the random-effects model was performed on the available data applying the R software, Version 1.4.1106 (dmetar package) and SAS software. To evaluate the effect of biodiversity, the data were summarised as the standardized mean difference (SMD) or the effect estimate (EE) with 95% confidence interval applying the Hedges method and the restricted maximum likelihood (REML) estimator, respectively. The magnitude of heterogeneity between the included studies was estimated using the Higgins I^2 statistic and τ^2. Publication bias was assessed through visual examination of a funnel plot and by applying the Egger's test. Sensitivity analysis was performed according to the risk of bias/quality of evidence by comparing the summary effect estimates obtained by excluding studies with a high risk of bias with those studies considered as being at low and moderate risk of bias.

Results

A total of 1986 studies were screened, 355 of these were assessed for eligibility and 330 were excluded (Figure S1). Reasons for exclusion included non-original studies (221 were narrative reviews/meta-analysis), studies in which outcomes were not relevant for the present objectives, and studies reporting results that were not suitable for inclusion in the present systematic review or meta-analysis. After a full-text review of the 405 studies, 75 studies were included (Figure S1).

Out of 75 included studies, 33 studies were related to the outer layer biodiversity [23 used dust samples and 10 used environmental biodiversity measures (e.g., species richness index, land-use gradient, and plant diversity)] and 42 studies were related to the inner layer biodiversity (2 studies characterized urine and skin

microbiota diversity, 16 studies collected stool samples, and 25 characterize airway microbiota diversity) (Figure 1).

Characteristics of the 75 included studies are shown in Table S1 (and online supplement pp 6-8). Furthermore, 39 of the 75 included studies were classified as poor quality, 5 were classified as fair quality, and 31 were classified as good quality (Table S1). Study design limitations were mainly due to unadjusted potential confounders and/or self-reported outcome.

3.1. Outer layer biodiversity

The summary results on the association between outer layer biodiversity and asthma, wheezing, and allergic sensitization are shown in Table S2 (and online supplement p 7).

Studies included in meta-analysis

Shannon diversity index

Figure 2 presents the forest plot for the association between Shannon diversity index based on dust sampling techniques and the risk of asthma. The summary effect estimate indicated a protective effect, but it was not statistically significant (OR (95% CI) = 0.77 (0.55; 1.06), I^2 = 72.4%, p =0.027) (Figure 2). The funnel plot (Figure S3) suggested an asymmetric pattern, but the Egger's test for publication bias was not statistically significant (t=3.16,p =0.195).

Bacterial richness

The summary effect estimate (odds ratio) for the association between bacterial richness and asthma [OR (95% CI) = 0.74 (0.57; 0.96)] was consistent with the hypothesis that exposure to higher biodiversity, assessed as bacterial richness, has a protective effect on the development of asthma (Figure 3). There was considerable heterogeneity (I^2=71.8%, p =0.003) across the studies (Figure 3). The funnel plot (Figure S4) was asymmetric, indicating some publication bias (Egger's test: t=5.15, p =0.007).

3.2. Inner layer biodiversity

Table S2 summarises the evidence on the association between inner layer biodiversity and asthma, wheezing, and allergic sensitization (online supplement pp 7-8).

Studies included in meta-analysis

Shannon diversity index

The mean/median of the Shannon diversity index among individuals with and without asthma was reported in 7 studies. However, the study conducted by Park et al. [16] was excluded based on quality. The random effects model (n=6) provided a significantly increased standardized mean difference [SMD (95% CI) = 0.31 (0.14; 0.48)], indicating that the bacterial diversity was slightly higher among individuals with asthma (Figure 4). There was no significant heterogeneity between study-specific estimates (I^2=0%, p =0.88) (Figure 4), but the sensitivity analysis including the study conducted by Park et al.[16] increased heterogeneity up to 60% (Figure S6).

Bacterial richness

The mean/median of the bacterial richness/abundance among individuals with and without asthma was reported in 6 studies. The study conducted by Park et al. [16] was excluded because of low quality. The summary standardised mean difference (95% CI) from the random effects model (n=5) was 0.25 (0.06; 0.44) (Figure 5), indicating that bacterial richness/abundance was slightly higher among individuals with

asthma. Consistent with Shannon diversity index, there was no significant heterogeneity between study-specific estimates (I^2=0%, p =0.70) (Figure 5), but when including the study conducted by Park et al. [16] the heterogeneity increased to 52% (Figure S10).

The funnel plots (Figure S14 and S15) show an apparently asymmetrical pattern that may be indicative of publication bias. Despite this apparent asymmetry, Egger's tests for publication bias were not statistically significant (t=-1.43, p =0.226 for studies on Shannon diversity index, and t=-0.45, p =0.680 for studies on bacterial richness), suggesting absence of publication bias.

The meta-analysis of 4 study-specific effect estimates, investigating associations between bacterial richness and asthma, showed no significant association between bacterial richness and asthma [OR (95% CI) = 1.14 (0.83; 1.56)] (Figure 6). The forest plot shown in Figure 6 demonstrates significant heterogeneity (I^2=62.0%, p =0.048) across the studies. The funnel plot (Figure S16) suggested an asymmetric pattern; however, the Egger's test indicated no publication bias (t=-0.26, p =0.819).

Discussion

Based on a systematic search, ours is the first systematic review and meta-analysis aiming to summarize current knowledge on the role of outer (environmental) and inner layer (human microbiota) biodiversity in the development of asthma, wheezing, and allergic sensitization. The systematic review and meta-analysis showed a protective trend of exposure to high environmental biodiversity on the development of asthma, wheezing, and allergic sensitization. Although the evidence on the effect of inner layer biodiversity suggested that bacterial diversity was slightly higher among individuals with asthma, there was no clear evidence of a significant association between inner layer biodiversity and the risk of asthma, wheezing or allergic sensitization.

Validity of results

In addition to the four databases, we also searched the reference lists of all the relevant articles identified. Our meta-analysis included also evidence from longitudinal studies on biodiversity and respiratory outcomes,[17, 18, 20-26] which allowed assessment of the time-dependent effects related to outer and inner layer biodiversity on the development of asthma, wheezing, and allergic sensitization. Both funnel plot and Egger's test showed an asymmetric pattern when addressing the effect of exposure to bacterial richness (outer layer biodiversity), but no significant publication bias was observed for the other exposure indicators.

The small number of studies included in the meta-analysis did not allow conduction of subgroup analyses. The different sampling methods applied and different types of samples (including stool and airway samples) may also complicate the comparison of different studies. We used NOS to evaluate the risk of bias.[13] Overall, the rather low scores on the quality scale were achieved (Table S1). Study design-related limitations were largely due to potential unadjusted confounding, which varied from study to study, as well as due to self-reported outcomes, which may have increased heterogeneity in the summary estimates of the present study. In addition, heterogeneity and validity of self-reported outcomes may lead to information bias. The variation in the outcome assessment method may have had impact on the ability to reach consistent summary effect estimates, which on the other hand may have contributed to heterogeneity of the study results. However, as there were only a limited number of studies identified, we were not able to perform sensitivity analysis according to the outcome definitions.

Synthesis with previous knowledge

Although the evidence on the role of biodiversity in the development of respiratory outcomes was inconsistent, the findings of the present systematic search and meta-analysis suggested that the effects related to the inner and outer layer biodiversity on asthma, wheezing, and allergic sensitization were variable. However, caution

is needed when interpreting the summary results, because of small number of studies included, as well as due to heterogeneity in definitions of exposure and outcomes, and confounders that were adjusted for.

Previous studies have reported an association between early life environmental exposures and airways inflammation.[11, 27] These studies reported that those children who had contact with animals and allergens during early life were less likely to develop asthma.[7, 28, 29] Furthermore, exposure to higher environmental biodiversity, assessed based on land use or vegetation types, has been associated with a lower risk of respiratory outcomes, such as asthma and allergic sensitization.[30-32]Moreover, the biodiversity hypothesis proposed that contact with natural environments including environmental microbiota enriches the human microbiome, promotes immune balance, and protects from developing allergies and/or inflammatory diseases [6]. While exposure to beneficial microbiota seems to play an important role, the complexity of different routes of exposure to microbiota and their timing, duration, intensity and frequency make studying the role of outer and inner biodiversity on respiratory health challenging.[33] Several previous studies have investigated the association between the composition of the immediate living environment and health, and found that the composition and diversity of environmental microbiota seem to differ among different land use types.[31, 34, 35] Environments, such as traditional farms [36, 37] and green spaces[32, 38] which contain enriched and specific microbial exposures, may be protective against asthma and allergies. More recently a systematic review and meta-analysis reported that the associations between exposure to green spaces and asthma (current and ever) and allergic rhinitis were inconsistent.[39] The authors suggested that their result may be explained by a variable balance between the positive and negative effects related to biodiversity exposure.[39] According to Hanski et al.[31], environmental biodiversity, human microbiota, and the function of the immune system are dynamic and complex systems including different components which interact with each other. Their study hypothesised that the association between environmental biodiversity and atopy reflects the immunologic responses that have been developed by individuals with long-term exposure to specific environmental microbiota and allergens.[31] Ruff et al.[40] have also suggested that the drastic changes in modern environments and lifestyles may have reduced microbial biodiversity and led to an imbalance of the evolutionarily processes, which in turn may have led to more unstable and less resilient microbiota. This change in the microbiota – *dysbiosis* – may, consequently, alter the balance maintained in the gut, skin and airway microbiomes, impair immune homeostasis and increase the risk of many chronic inflammatory diseases, such as asthma and allergic diseases.

Furthermore, the diversity and composition of human microbiota is also influenced by several environmental exposures.[7-9] A study conducted in the Russian Karelia and the Finnish Karelia showed significant differences in the skin and nasal microbiota composition between the countries.[41] The microbial diversity was higher in the Russian samples than in the Finnish samples. However, no significant associations were observed between nasal and skin microbiota diversity and asthma among the Finnish individuals.[41]Consistently, a study including 72 adults participants (20 with asthma exacerbation, 31 with non-exacerbated asthma and 21 healthy individuals) found no statistically significant difference in Faith's phylogenetic diversity among these three study groups.[42] A recent cohort of mother-infant pairs from USA also showed that alpha diversity in gut microbiome was not significantly enriched in atopic compared to non-atopic infants.[43] On the other hand, Espuela-Ortiz et al. [44] reported significant differences in both Shannon diversity index and Pielou index between individuals with asthma and those without asthma. These results are consistent with the studies conducted by Huang et al. [45] and Marri et al.[46] regarding alpha diversity in airway samples. Huang et al. [45] reported a significantly higher bacterial diversity among individuals having asthma compared with control individuals. The authors suggested that bacterial diversity (variation in composition and relative abundance of specific phylotypes) is associated with the degree of bronchial hyperresponsiveness in individuals having asthma treated with inhaled corticosteroids.[45] Consistently with our systematic review and meta-analysis, the results of these previous studies on microbiota diversity and respiratory outcomes are variable.

In addition to diversity, several studies have suggested that the composition of human and environmental microbiota may contribute to the development of asthma and allergies.[11, 22, 47, 48] The microbiota composition may be related to a decrease in diversity, promoting less resilient microbiota. This would alter the ecosystem provided by the microbiota and the balance of the immune system response.[49] Furthermore, most

studies addressing the role of biodiversity in development of respiratory outcomes have analysed only single point in time in cross-sectional studies, which has not allowed assessment of responses of the immune system to changes in human microbiome caused by exposure to environmental and biological factors.[50] Another important limitation in the previous studies has been that the link between biodiversity and pathophysiological mechanisms underlying asthma may have been confounded by the asthma subtype and the inflammatory process.[50]Based on this systematic review and meta-analyses, there is a need for population-based longitudinal studies, including: (i) cohort studies, especially in previously under-represented populations (e.g., in Asian and African regions); (ii) studies that apply the same or similar definition of the outcome; (iii) studies with recruitment at an early developmental phase (e.g. from preconception) and having a longitudinal follow-up to identify critical periods of exposure in the life course and to better understand mechanisms linking environmental exposures and changes in microbiome composition, diversity and/or function to development of asthma and allergic sensitization. Furthermore, climate change is affecting biodiversity of both outer and inner layers. Climate change is responsible for environmental degradation and loss of biodiversity in plants, animals, and microorganisms, thus affecting the distribution, composition, and interactions between microorganisms. Climate change can also disrupt the relation between environmental microorganisms and humans, resulting in loss of inner layer biodiversity.[51, 52] Therefore, understanding how the interactions between outer and inner layer, biodiversity, human being, and immune system respond to climate change is also needed for assessing the role of biodiversity in the development of asthma, wheezing, and allergic sensitization.

Conclusion

The present systematic review and meta-analysis provides evidence that exposure to higher environmental biodiversity has a protective effect on the development of asthma, allergic sensitization, and wheezing. Although the evidence on the effect of inner layer (human microbiota) biodiversity suggested that bacterial diversity was slightly higher among individuals with asthma, there was no consistent evidence of an association between inner layer biodiversity and asthma, wheezing or allergic sensitization.

Conflict of interest

Authors declare no conflicts of interest.

Author Contributions

JJKJ, IP and MSJ identified the need for this systematic review and meta-analysis. All authors contributed to the design of the review protocol. IP, NS and BH conducted the initial screening and selected the studies for inclusion. IP extracted the data from the included studies. TH and AR reviewed the initial screening and checked the data from the included studies. JJKJ checked the data from the included studies. IP and NS performed the study quality assessment. JJKJ supervised all the steps. All steps from screening to quality assessment were done in consultation with the wider review team. IP analyzed the data and drafted the manuscript. All authors contributed to the critical revision and approved the final version of the manuscript.

Data availability statement

All datasets generated and analysed, including the study protocol, search strategy, list of the included and excluded studies, data extracted, and quality assessment are available in the Article and upon request from the corresponding author.

References

1. von Hertzen L, Hanski I, Haahtela T. Natural immunity. Biodiversity loss and inflammatory diseases are two global megatrends that might be related. *EMBO reports* 2011;**12** (11):1089-93.

2. Ceballos G, Ehrlich PR, Dirzo R. Biological annihilation via the ongoing sixth mass extinction signaled by vertebrate population losses and declines. *Proceedings of the National Academy of Sciences*2017;**114** (30):E6089-E96.

3. Díaz S, Fargione J, Chapin FS, 3rd, Tilman D. Biodiversity loss threatens human well-being. *PLoS biology* 2006;**4** (8):e277.

4. Marselle MR, Lindley SJ, Cook PA, Bonn A. Biodiversity and Health in the Urban Environment. *Current Environmental Health Reports*2021;**8** (2):146-56.

5. Haahtela T, Holgate S, Pawankar R, et al. The biodiversity hypothesis and allergic disease: world allergy organization position statement. *The World Allergy Organization journal* 2013;**6** (1):3.

6. Haahtela T. A biodiversity hypothesis. *Allergy*2019;**74** (8):1445-56.

7. Lynch SV, Wood RA, Boushey H, et al. Effects of early-life exposure to allergens and bacteria on recurrent wheeze and atopy in urban children. *The Journal of allergy and clinical immunology*2014;**134** (3):593-601.e12.

8. Haahtela T, Laatikainen T, Alenius H, et al. Hunt for the origin of allergy - comparing the Finnish and Russian Karelia. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology* 2015;**45** (5):891-901.

9. Lehtimäki J, Karkman A, Laatikainen T, et al. Patterns in the skin microbiota differ in children and teenagers between rural and urban environments. *Scientific reports* 2017;**7** :45651.

10. Riiser A. The human microbiome, asthma, and allergy. *Allergy, Asthma & Clinical Immunology* 2015;**11** (1):35.

11. Ver Heul A, Planer J, Kau AL. The human microbiota and asthma. *Clinical reviews in allergy & immunology*2019;**57** (3):350-63.

12. Global Initiative for Asthma. A Pocket Guide for Asthma Management and Prevention (for Adults and Children Older than 5 years). A Pocket Guide for Health Professionals Updated 2021. 2021.

13. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;**25** (9):603-5.

14. Herzog R, Álvarez-Pasquin MJ, Díaz C, Del Barrio JL, Estrada JM, Gil Á. Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? a systematic review. *BMC Public Health* 2013;**13** (1):154.

15. Penson D, Krishnaswami S, Jules A, Seroogy J, McPheeters M. Newcastle-Ottawa quality assessment form for cohort studies. *Ottawa: Ottawa Hospital Research Institute* 2012.

16. Park H, Shin JW, Park SG, Kim W. Microbial communities in the upper respiratory tract of patients with asthma and chronic obstructive pulmonary disease. *PloS one* 2014;**9** (10):e109710.

17. Abrahamsson TR, Jakobsson HE, Andersson AF, Björkstén B, Engstrand L, Jenmalm MC. Low gut microbiota diversity in early infancy precedes asthma at school age. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology*2014;**44** (6):842-50.

18. Toivonen L, Karppinen S, Schuez-Havupalo L, et al. Longitudinal Changes in Early Nasal Microbiota and the Risk of Childhood Asthma. *Pediatrics* 2020;**146** (4).

19. Lee JJ, Kim SH, Lee MJ, et al. Different upper airway microbiome and their functional genes associated with asthma in young adults and elderly individuals. *Allergy* 2019;**74** (4):709-19.

20. Kirjavainen PV, Karvonen AM, Adams RI, et al. Farm-like indoor microbiota in non-farm homes protects children from asthma development. *Nature Medicine* 2019;**25** (7):1089-95.

21. Niemeier-Walsh C, Ryan PH, Meller J, Ollberding NJ, Adhikari A, Reponen T. Exposure to traffic-related air pollution and bacterial diversity in the lower respiratory tract of children. *PloS one*2021;**16** (6):e0244341.

22. Thorsen J, Rasmussen MA, Waage J, et al. Infant airway microbiota and topical immune perturbations in the origins of childhood asthma.*Nature Communications* 2019;**10** (1):5001.

23. Schei K, Simpson MR, Øien T, Salamati S, Rudi K, Ødegård RA. Allergy-related diseases and early gut fungal and bacterial microbiota abundances in children. *Clinical and translational allergy*2021;**11** (5):e12041.

24. Karvonen AM, Kirjavainen PV, Täubel M, et al. Indoor bacterial microbiota and development of asthma by 10.5 years of age. *The Journal of allergy and clinical immunology*2019;**144** (5):1402-10.

25. Birzele LT, Depner M, Ege MJ, et al. Environmental and mucosal microbiota and their role in childhood asthma. *Allergy*2017;**72** (1):109-19.

26. Bisgaard H, Li N, Bonnelykke K, et al. Reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age. *The Journal of allergy and clinical immunology* 2011;**128** (3):646-52.e1-5.

27. Dick S, Friend A, Dynes K, et al. A systematic review of associations between environmental exposures and development of asthma in children aged up to 9 years. *BMJ open*2014;**4** (11):e006554.

28. O'Connor GT, Lynch SV, Bloomberg GR, et al. Early-life home environment and risk of asthma among inner-city children. *The Journal of allergy and clinical immunology*2018;**141** (4):1468-75.

29. Ownby DR, Johnson CC, Peterson EL. Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6 to 7 years of age. *Jama* 2002;**288** (8):963-72.

30. Donovan GH, Gatziolis D, Longley I, Douwes J. Vegetation diversity protects against childhood asthma: results from a large New Zealand birth cohort. *Nature Plants* 2018;**4** (6):358-64.

31. Hanski I, von Hertzen L, Fyhrquist N, et al. Environmental biodiversity, human microbiota, and allergy are interrelated.*Proceedings of the National Academy of Sciences of the United States of America* 2012;**109** (21):8334-9.

32. Ruokolainen L, von Hertzen L, Fyhrquist N, et al. Green areas around homes reduce atopic sensitization in children. *Allergy*2015;**70** (2):195-202.

33. Ruokolainen L, Fyhrquist N, Haahtela T. The rich and the poor: environmental biodiversity protecting from allergy. *Current Opinion in Allergy and Clinical Immunology* 2016;**16** (5).

34. Mhuireach G, Johnson BR, Altrichter AE, et al. Urban greenness influences airborne bacterial community composition. *Science of The Total Environment* 2016;**571** :680-7.

35. Tischer C, Kirjavainen P, Matterne U, et al. Interplay between natural environment, human microbiota and immune system: A scoping review of interventions and future perspectives towards allergy prevention. *Science of The Total Environment*2022;**821** :153422.

36. von Mutius E, Vercelli D. Farm living: effects on childhood asthma and allergy. *Nature reviews Immunology*2010;**10** (12):861-8.

37. Müller-Rompa SEK, Markevych I, Hose AJ, et al. An approach to the asthma-protective farm effect by geocoding: Good farms and better farms.*Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology*2018;**29** (3):275-82.

38. Ferrante G, Asta F, Cilluffo G, De Sario M, Michelozzi P, La Grutta S. The effect of residential urban greenness on allergic respiratory diseases in youth: A narrative review. *World Allergy Organization Journal* 2020;**13** (1):100096.

39. Wu B, Guo X, Liang M, et al. Association of individual green space exposure with the incidence of asthma and allergic rhinitis: a systematic review and meta-analysis. *Environmental science and pollution research international* 2022;**29** (59):88461-87.

40. Ruff WE, Greiling TM, Kriegel MA. Host–microbiota interactions in immune-mediated diseases. *Nature Reviews Microbiology*2020;**18** (9):521-38.

41. Ruokolainen L, Paalanen L, Karkman A, et al. Significant disparities in allergy prevalence and microbiota between the young people in Finnish and Russian Karelia. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology*2017;**47** (5):665-74.

42. Fazlollahi M, Lee TD, Andrade J, et al. The nasal microbiome in asthma. *The Journal of allergy and clinical immunology*2018;**142** (3):834-43.e2.

43. Seppo AE, Bu K, Jumabaeva M, et al. Infant gut microbiome is enriched with Bifidobacterium longum ssp. infantis in Old Order Mennonites with traditional farming lifestyle. *Allergy*2021;**76** (11):3489-503.

44. Espuela-Ortiz A, Lorenzo-Diaz F, Baez-Ortega A, et al. Bacterial salivary microbiome associates with asthma among african american children and young adults. *Pediatric pulmonology*2019;**54** (12):1948-56.

45. Huang YJ, Nelson CE, Brodie EL, et al. Airway microbiota and bronchial hyperresponsiveness in patients with suboptimally controlled asthma. *Journal of Allergy and Clinical Immunology*2011;**127** (2):372-81.e3.

46. Marri PR, Stern DA, Wright AL, Billheimer D, Martinez FD. Asthma-associated differences in microbial composition of induced sputum. *The Journal of allergy and clinical immunology*2013;**131** (2):346-52.e1-3.

47. Arrieta M-C, Stiemsma LT, Dimitriu PA, et al. Early infancy microbial and metabolic alterations affect risk of childhood asthma.*Science Translational Medicine*2015;**7** (307):307ra152-307ra152.

48. Stiemsma LT, Arrieta MC, Dimitriu PA, et al. Shifts in Lachnospira and Clostridium sp. in the 3-month stool microbiome are associated with preschool age asthma. *Clinical science (London, England : 1979)*2016;**130** (23):2199-207.

49. Fiuza BSD, Fonseca HF, Meirelles PM, Marques CR, da Silva TM, Figueiredo CA. Understanding asthma and allergies by the lens of biodiversity and epigenetic changes. *Frontiers in immunology*2021;**12** :623737.

50. Alamri A. Diversity of microbial signatures in asthmatic airways.*International journal of general medicine*2021;**14** :1367-78.

51. Jain PK, Purkayastha SD, De Mandal S, Passari AK, Govindarajan RK. Chapter 13 - Effect of climate change on microbial diversity and its functional attributes. In: De Mandal S, Bhatt P, editors. Recent Advancements in Microbial Diversity: Academic Press; 2020. p. 315-31.

52. Cavicchioli R, Ripple WJ, Timmis KN, et al. Scientists' warning to humanity: microorganisms and climate change. *Nature Reviews Microbiology* 2019;**17** (9):569-86.

Figure legends

Figure 1 Characterization of the studies included based on outer or inner layer biodiversity.

Figure 2 Forest plot for the association between Shannon diversity index and asthma.

Figure 3 Forest plot for the association between bacterial richness and asthma.

Figure 4 Forest plot for the standardized mean difference of the Shannon diversity index among individuals with and without asthma.

Figure 5 Forest plot for the standardized mean difference of the bacterial richness among individuals with and without asthma.

Figure 6 Forest plot for the association between bacterial richness and asthma.

Hosted file

Figure 1.docx available at https://authorea.com/users/447746/articles/645585-the-role-of-biodiversity-in-the-development-of-asthma-and-allergic-sensitization-a-systematic-review-and-meta-analysis

Hosted file

Figure 2.docx available at https://authorea.com/users/447746/articles/645585-the-role-of-biodiversity-in-the-development-of-asthma-and-allergic-sensitization-a-systematic-review-and-meta-analysis

Hosted file

Figure 3.docx available at https://authorea.com/users/447746/articles/645585-the-role-of-biodiversity-in-the-development-of-asthma-and-allergic-sensitization-a-systematic-review-and-meta-analysis

Hosted file

Figure 4.docx available at https://authorea.com/users/447746/articles/645585-the-role-of-biodiversity-in-the-development-of-asthma-and-allergic-sensitization-a-systematic-review-and-meta-analysis

Hosted file

Figure 5.docx available at https://authorea.com/users/447746/articles/645585-the-role-of-biodiversity-in-the-development-of-asthma-and-allergic-sensitization-a-systematic-review-and-meta-analysis

Hosted file

Figure 6.docx available at https://authorea.com/users/447746/articles/645585-the-role-of-biodiversity-in-the-development-of-asthma-and-allergic-sensitization-a-systematic-review-and-meta-analysis