Early-life environment and the risk of eczema at 2 years – meta-analyses of six Finnish birth cohorts

Short running title: Early-life environment and the risk of eczema at 2 years

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Abstract

Background: Urban-related nature exposures are suggested to contribute to the rising prevalence of allergic diseases despite little supporting evidence. Our aim was to evaluate the impact of twelve land cover classes and two greenness indices around homes at birth on the development of doctor-diagnosed eczema by the age of two years, and the influence of birth season.

Methods: Data from 5 085 children were obtained from six Finnish birth cohorts. Exposures were provided by the Coordination of Information on the Environment in three predefined grid sizes. Adjusted logistic regression was run in each cohort and pooled effects across cohorts were estimated using fixed or random effect meta-analyses.

Results: In meta-analyses neither greenness indices (NDVI or VCDI, 250m x 250m grid size), nor residential or industrial/commercial areas were associated with eczema by age of two years. Coniferous forest (adjusted odds ratio 1.19; 95% confidence interval 1.01-1.39 for the middle and 1.16; 0.98-1.28 for the highest *vs.* lowest tertile), and mixed forest (1.21; 1.02-1.42 middle *vs.* lowest tertile) were associated with elevated eczema risk. Higher coverage with agricultural areas tended to associate with elevated eczema risk (1.20; 0.98-1.48 *vs.* none). In contrast, transport infrastructure was inversely associated with eczema (0.77;0.65-0.91 highest *vs.* lowest tertile).

Conclusion: Greenness around the home during early childhood does not seem to protect from eczema. In contrary, nearby coniferous and mixed forests may increase eczema risk, as well as being born in spring close to forest or high-green areas.

Key Messages:

Land cover classes and greenness indicative of natural exposures around the home do not seem to protect from eczema. Effects of nearby coniferous forests and especially in those born in spring, may increase the eczema risk.

Key words: Atopic dermatitis; coniferous; eczema; greenness; land cover

Abbreviations:

CI	Confidence interval
CLC	CORINE Land Cover
CORINE	The Coordination of Information on the Environment
FLORA	The FLORA Study
HELMi	The Health and Early Life Microbiota
ISAAC	The International Study of Asthma and Allergies in Childhood
IQR	Interquartile range
KuBiCo	The Kuopio Birth Cohort
NDVI	The Normalized Difference Vegetation Index
OR	Odds ratio
SD	Standard deviation
STEPS	The STEPS Study
Th2	T-helper-2
VCDI	The Vegetation Cover Diversity Index

Introduction

Eczema most often starts in infancy, affects 20-30% of children and is prevalent also in adults. Eczema is a chronically relapsing, pruritic inflammatory skin disease and associated with elevated risk of food allergy, asthma, allergic rhinitis, and other immune-mediated inflammatory diseases.[1,2] It is typically (but not always) mediated by imbalance towards a T-helper-2 (Th2) response and exaggerated IgE responses to allergens but has a variety of clinical manifestations and expressivity, in which defects of the epidermal barrier are central.[1,2] The epidemic increase in the prevalence of chronic pro-inflammatory outcomes including atopic diseases has been speculated to originate from changes in environmental exposures, such as urbanization and reduced biodiversity.[3,4] Thereby, early-life exposure to green environments have been proposed to reduce the prevalence of atopic diseases by stimulating the development and maturation of immunological regulatory pathways, which are essential for the homeostatic immunological responsiveness.[5–7] However, studies on the exposures of environmental greenness have shown tendencies for both reduced and elevated risks for childhood allergic diseases, and results in meta-analyses are heterogenous.[6,8–13]

Doctor-diagnosed eczema serves as an indicator of defective epithelial barrier and early aberrant immunological responsiveness.[1,2,14,15] Environmental exposures may contribute to the risk of eczema by impairing the skin barrier integrity and through the defective epithelial barrier in genetically susceptible individuals although the exact mechanism is unclear.[2,16] The type of vegetation and forests and the amount of greenness influence the quantity and quality of microbial and allergen exposures and co-exposures, that have been associated with the risk of allergic diseases. Potential mechanisms have recently been reviewed.[3,4] Here, we conducted meta-analyses in six Finnish birth cohorts to evaluate the impact of residential location and its land cover classes and greenness indices at birth, as well as season of birth on the development of doctor-diagnosed eczema by the age of two years. We used twelve land cover classes and two greenness indices based on the European-wide Coordination of Information on the Environment (CORINE) Land Cover (CLC) data around residential location at birth. This large dataset of six birth cohorts including over 5000 infants from three areas of Finland allows replicable meta-analysis that accounts for geographical variation in land cover classes and greenness.

Methods

Study subjects and design

Six Finnish prospective birth cohorts included in this study were FLORA Study (FLORA)[17], LUKAS[18], STEPS Study (STEPS)[19], FinnBrain[20], Kuopio Birth Cohort (KuBiCo)[21], and Health and Early Life Microbiota (HELMi)[22] (Tables S1 and S2). All cohorts had ongoing follow-ups aiming to characterize the health effects of environmental exposures (Table 1 and Figure 1). We included children with information about birth address, doctor-diagnosed eczema by the age of two years and *a priori* selected confounders of child sex, maternal history of atopic diseases (asthma, hay fever and/or eczema), the number of older siblings (0, 1, ≥2), and the highest parental (either mother or father) educational level used as the proxy of family socio-economic status (Figure S1), which often explains part of the morbidity variance. Due to study design, two additional adjustments were used in LUKAS (living on farm and cohort; LUKAS1 or LUKAS2, respectively).[18] Originally, all cohorts were conducted in accordance with the Declaration of Helsinki, approved by the Ethics Committees of individual hospital districts.

Outcome

The study outcome was doctor-diagnosed eczema. In four cohorts, the outcome of eczema was defined as parental report of lifetime prevalence of doctor-diagnosed eczema ever by the child age of two years using the standardized questions from the International Study of Asthma and Allergies in Childhood (ISAAC).[14] In FLORA, the outcome was doctor-diagnosed eczema based on the Williams's criteria.[23] In HELMi, the eczema definition was based on two questions on doctor-diagnosed and/or parent-reported rash (Table S2).

Residential location at birth

All children's addresses at birth were provided by the Digital and Population Data Service Agency (DVV, Helsinki, Finland) and geocoded into the EUREF-based coordinates. These coordinates were used to acquire different land cover classes and greenness indices from the CLC, the European-wide standardized land cover map coordinated by the European Environment Agency (Copenhagen, Denmark) (Table S3).[24]

Exposures of land cover classes and greenness indices

Percentage of twelve land cover classes were calculated from the original CLC classes: coniferous forest; mixed forest; broad-leaved forest; agricultural areas; transport infrastructure; residential areas; industrial/commercial; herbaceous vegetation; sport/leisure; bare surface; wetlands; and water bodies. Urban greyness included residential areas and industrial/commercial areas (Tables S3, S4). The greenness indices were defined as the Normalized Difference Vegetation Index (NDVI)[25] and the Vegetation Cover Diversity Index (VCDI) based on the Simpson's Diversity Index formula.[26] Each land cover class and greenness index were calculated within predefined grid sizes of 250 m x 250 m, 750 m x 750 m and 1250 m x 1250 m for all initially recruited children in each cohort (Table S5, Figure S2).

Statistics

In all cohorts, data on outcome and confounders were collected through parental questionnaires and the variables were harmonized between cohorts (Table S2). The birth seasons were categorized as winter (Dec-Feb), spring (March-May), summer (June-Aug) and autumn (Sep-Nov). Land cover classes and greenness indices were classified into tertiles (with the lowest tertile as the reference category) using the same cut-off values in individual cohorts (Table S5). For land cover classes which were not present in more than 33.3% of the observations, the 0% category was used as reference category, and values above 0% were evenly divided into two groups (low and high). In the main analyses, predefined 250 m x 250 m grid size was used, and the other two grid sizes were used in sensitivity analyses. The risk of doctor-diagnosed eczema was assessed with binary logistic regression using the *a priori* selected confounders (Tables S1, S2, Fig S1) . The models for coniferous forest and atopic eczema were carefully tested for seven additional potential covariates (*eg*. breastfeeding, cat and dog ownership, day care attendance), but as none changed the estimates of exposure by >10% in any of the cohorts, they were not included in the analyses. Effect modification by season of birth for three forests classes, agricultural areas, herbaceous vegetation and two greenness indices was tested using variables for interaction. The interaction was significant in all classes except herbaceous vegetation (p value for interaction term < .20 at least in two cohorts).

Meta-analyses were performed using the fixed effects method with the DerSimonian-Laird estimator for the between-study variance: if heterogeneity was observed (I^2 index $p < .05$), a random effect method was used.[27] See more in detail in the Supporting Information. Meta-analyses, box-plot graphics and heat maps were performed using the R Studio version 4.1.2.

Results

Study population

In total, 5085 children from six birth cohorts were included (Table 1, Figure 1). Of them, 52% were boys; 51% had maternal history of allergic diseases; 51% had high parental educational level, 35% middle and 13% low; 50 % had no siblings, 32% had one and 18% had two or more. More than 73% of children lived at the same address until the age of two years. The eczema prevalence was 19%-29% across cohorts. In the comparison between eligible and non-eligible children using the *a priori* defined confounders, eligible children had more often higher parental educational level (in STEPS, FinnBrain and LUKAS), had more often older siblings (in HELMi and KuBiCo) and were more often girls than boys (in KuBiCo) (Table S6). Detailed population characteristics and distributions of exposures are reported in Tables 1, S1, S4 and S6.

The levels of land cover classes and greenness indices in children with and without eczema are shown in Figure S3. The correlations between land cover classes and greenness indices were low (mainly *r* between - 0.15 and 0.15), whereas forest areas correlated moderately with each other or with greenness indices (Figure S4A). Each land cover class and greenness index in 250 m x 250 m grid correlated with 750 m x 750 m grid (*r* 0.39-0.79) (Figure S4B) and somewhat less with 1250 m x 1250 m grid (*r* 0.26-0.73) (Figure S4C).

Firstly, the associations between exposures and outcome were conducted within each cohort individually adjusted for all confounders (Table S7). Additionally, the analyses were reanalyzed without adjusting for the parental educational level (the family socio-economic status) and respectively adjusting for birth season to study their independent effects: the results remained unchanged.

Secondly, the combined effects across cohorts were estimated with the meta-analyses using the estimates of individual cohorts in 250 m x 250 m grid. Surrounding coniferous forest was associated with elevated risk of eczema compared to those living in neighborhoods with less such forest. The association was statistically significant only between the middle and the lowest tertiles and no dose response was observed (Table 2 and Figure 2). Similarly, the risk of eczema was elevated in the mixed forest middle tertile, but no association was seen with the highest tertile. Also, a higher coverage of agricultural areas tended to be associated with elevated risk of eczema. In contrast, transport infrastructure was associated with lower risk of eczema. Urban greyness (residential areas and industrial/commercial), sport/leisure, broad-leaved forest, herbaceous vegetation, bare surface, blue areas (wetlands and water bodies), green color (NDVI), or amount of different vegetation types (VCDI) were not associated with eczema (Table 2). The results did not change in sensitivity analysis by excluding the high-risk cohort FLORA. After Bonferroni correction for multiple testing, only transport infrastructure (high *vs.* low) was statistically significant (p = .05).

Sensitivity analyses

Different grid sizes

The role of broader surroundings was estimated with grid sizes 750 m x 750 m and 1250 m x 1250 m. The associations of eczema with the coniferous and mixed forests, agricultural areas and transport infrastructure became weaker or disappeared (Table 3).

Homogeneity of the outcome

HELMi cohort was excluded from the analyses as not having validated ISAAC-based or Williams's criteria for the outcome. The association between coniferous forest and eczema was strengthened (higher risk estimates) (OR 1.22; 95% CI 1.03-1.45 for middle and 1.21; 1.01-1.45 for highest *vs*.

lowest tertile), while the other estimates remained unchanged (mixed forest, agricultural areas and transport infrastructure) (Table S8).

Living in the same home

The role of long-term exposure was studied by including only children who had lived the entire two years at the address of birth. The associations remained mostly similar except the association between mixed forest and eczema became stronger (higher risk estimates) in comparison to the effect seen in the whole study population (Table S9).

Season of birth

The season of birth itself was not associated with the development of eczema (Figure S5). When the analyses of land cover classes and greenness indices were stratified by season, the children being born in spring and living surrounded by any forest type or higher greenness tended to have elevated risk for the development of eczema (Table 4 and Figure S5). Similar tendency was seen in children who were born in autumn and were surrounded by broad-leaved or coniferous forests. In contrast, the risk of eczema was lower in children who were born in winter and were surrounded by broad-leaved forest or had higher NDVI (Figure S6).

Discussion

Nature-related exposures have been suggested to contribute to the prevalence of allergic diseases, though with little supporting evidence. In our meta-analyses of over 5000 Finnish children from six different cohorts we neither found inverse associations with nature-related exposures nor positive association with urban-related exposures proxied by land-cover classes and greenness indices calculated around the birth address. In contrast, exposure to coniferous and mixed forests and agriculture areas in the nearest living environment were associated with elevated eczema risk in early childhood. Broad-leaved forests tended to have a similar association. On the contrary, transport infrastructure was associated with lower eczema risk. Children born in spring, surrounded by any forest type or higher greenness tended to have elevated eczema risk.

We found that the emergence of eczema increased by closeness of forests, but the risk depended on the type of surrounding greenness: coniferous and mixed forests and agriculture areas, but not broad-leaved forests, within 250 m from homes were associated with elevated eczema risk. Our finding is partly in line with a meta-analysis of Parmes and co-workers on 8000 European children with 3-14 years of age showing that increase in surrounding green space and particularly coniferous forests within 500 m buffer increased the risk for wheezing, asthma, and allergic rhinitis, but not eczema.[12] The differences between our current and their study included different outcomes (eczema *vs.* other atopic outcomes), outcome ages (under two *vs.* over three years), coniferous species (Nordic *vs.* Southern European), and the coverage of coniferous forests (65-93% *vs.* 2-11%, respectively).[14] In Finland, coniferous forests consisting of pine trees and spruces are by far the most abundant whereas broad leaved forests are scarce (in the current study coverages 80% *vs.* 38%, respectively). Some elements of the biodiversity hypotheses state that contact with natural environments enriches the human microbiome, promotes immune balance and protects from allergy and inflammatory disorders.[3,4] Coniferous forests might be relatively scarce of potentially immunomodulating antigens and/or microbes that could contribute to prevention of allergy. They differ from other land cover classes with respect to soil features resulting in different microbial abundancies, diversity, composition and functional communities of soil bacterial and fungal network structures. [28–30] Also, pine pollen could potentially be an immunomodulating substance, especially when abundant, but also irritating and impair the skin barrier.[31]

We found that only the nearest surroundings contributed to the eczema risk in young children. The only exception was with broad-leaved forest where we saw a tendency of increased risk when the size of the surrounding area was larger (1250 m). As far as we know, there are no other previous studies that have considered this topic in children under two years of age. Thus, the findings from our study should be confirmed in further studies. In the study of Parmes and co-workers the surrounding of green space and coniferous forests with 300-1000 m buffer radius was found to increase the risk for allergic diseases in children with 3-14 years of age.[12] On the contrary, Ruokolainen *et al.* found that green environment (forest and agricultural land together) around homes lowered the risk of sensitization in children 6 years of age and older.[6] They used bigger buffer size of 0.5-10 km of radius and suggested that bigger buffer size (within 2-5 km) was a good predictor in older children.[6 32] Based on recent reports on the connection between outdoor green and indoor microbiota, the health effects of specific types of surrounding greenness could thus be mediated via indoor microbiota modifications and subsequent infant exposure indoors.[32–34] We aim toto explore this possible mechanism deeper in our future analyses.

In our study the season of birth tended to modify the associations between surrounding greenness and eczema: especially children born in spring who lived near forests had elevated eczema risk. In contrast, the eczema risk was lower in those who were born in winter and lived near broad-leaved forests or where the NDVI was higher. One could hypothesize that children born in spring may have been exposed to tree pollens during the first months of life, a period crucial in immunological development.[29,30,35] Early-life pollen exposures have been associated with the risk of allergic sensitization which is associated with the development of allergic diseases and expression of symptoms and thus early diagnosis. In addition, pollen exposure may disrupt the skin epithelial barrier predisposing to eczema and pathogenic Th2 responses as suggested by the epithelial barrier hypothesis.[16,36] Calov *et al*. showed in their meta-analysis that being born in fall and winter in the Northern Hemisphere was a risk factor for eczema but they focused only on skin barrier effects, .[37] In our study, birth season itself was not associated with eczema. Depending on the birth season, we suggest that the presence of certain environmental exposures during different stages of child development might shape the immune responses in young children.

A somewhat surprising finding of our study was that transport infrastructure in close proximity was associated with less eczema. This finding could at least partly be explained by the risk effect of the forests: transport infrastructure occupies forest acreage allowing them to protect against eczema due to negative correlation between transport infrastructure and forest areas.[33] Unfortunately, we did not have measurements of air pollution in any cohort, which might have helped to find out more about the effect of transport infrastructure. Neither the greenness including green color (NDVI), amount of different vegetation types (VCDI) or herbaceous vegetation nor urban greyness (residential areas; industrial/commercial), sport/leisure, bare surface, or blue areas (wetlands; water bodies) were associated with eczema. We expected to see a protective effect of NDVI on eczema, but we found a protective effect only in children born in winter. In previous studies, NDVI- and greenness-derived measures have shown a tendency for elevated risk for childhood allergic outcomes but findings were heterogenous.[8–13] It has been speculated that green space overall or NDVI-derived exposure may be insensitive measures without specifying definitive data on species composition or help elucidate mechanisms, and therefore may not adequately capture qualities most relevant to allergic outcomes.[8,10,13]

Our study included individual level data of over 5000 children with high-resolution data on their living environment. We intended to minimize the demographic and geographical inconsistencies so that each targeted region in Finland – metropolitan area, west coast and east - included two cohorts, increasing congruence and evidence-basis of the results.[10–13] Precision and identical basis for the exposure assessment was ensured by using identical EUREF-based coordinates for the birth address from the national registry. The benefit of using CLC values was that the data is comprehensive, replicable and relatively constant over time. Although the cohorts were recruited in different decades, the background data and outcome definition were similar across cohorts, which was seen as overall great homogeneity in the meta-analyses. For the outcome, we chose the clinical manifestation of doctor-diagnosed eczema by congruent age of two years, mostly based on the standardized questions of ISAAC that are ideal for the entity of eczema in small children[14], although we acknowledge that parental reporting leaves some uncertainty in the assessment.[141,14,38] We do not expect major differences in access to healthcare overall, because majority of the children in the six cohorts are from typical Finnish towns or their surroundings, and the prevalence of study outcome was also 19-29% that is equal to previous studies in young children ensuring the reliability and generalizability of our data and results.[1,2,15] In addition, the prevalence of maternal allergic diseases in our study was equal to the Finnish overall prevalence of hay fever and other allergic nasal symptoms in women.[38] The potential confounder selection for more favorable results was reduced as the confounders were selected *a priori*. One of the confounders that differed between the eligible and non-eligible children was the parental educational level. A challenge in longitudinal studies is to sustain families' adherence, which is often poorer in families with lower parental educational level or socio-economic status. It is known that family socio-economic status often explains part of the morbidity variance. Therefore, we also performed analyses of individual cohorts with excluding the parental educational level from the adjustments and the findings remained unchanged. We acknowledge that socio-economic status is a complex and multifaced concept and we used only one measure of it. In observational studies, it is impossible, to account for all potential confounders and it is always possible that the observations reflect unmeasured factors. There might also be some residual confounding *ie.* adjustment using a confounder does not completely remove the effect of the confounding variable.

Allergen-specific IgE was not tested in the meta-analysis (available only in LUKAS at one and in FLORA at the age of two years) and therefore the imbalance towards Th2 response and atopic type of eczema could not be assessed in the whole study population. On the other hand, test positivity indicating Th2-related response mainly appears later in childhood. The use of CLC has also its limitations: CLC land cover classes are planned for use on large regional areas, and thus, they may have too generalized level for use in small local analyses, as we had with 250 m distance. The internal definition of CLC lacks the opportunity for deeper discussion about biodiversity as detailed inspection of vegetation and habitat is lost. Therefore, more accurately characterized data on biodiversity by using more specific environmental exposures of coniferous forest types (pine trees, spruces, mixed), diversity of microbial features or biomass (swamp, mineral land *etc.*) could be informative in future studies of diversity.

In conclusion, our results do not support the hypothesis that greenness and nature-related exposures around home would prevent and the urban-related exposures increase the risk of allergic diseases in small children. While our observational study cannot prove causality, the mechanisms of the novel and somewhat surprising associations need to be addressed in further studies.

Author contributions

Acquisition of data: all authors.

Study concept and design: ML, PVK, CG-I, JV, JuP and AMK.

Conduction of the statistical analyses: ML, KB, BH, KK, JaP and AMK.

Interpretation of data: ML, CG-I, HaL, JaP, JV, JuP and AMK.

Drafting of the manuscript: ML, PVK and AMK.

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References

1. Weidinger S, Novak N. Atopic dermatitis. The Lancet. 2016;387:1109–22.
2. Leung DYM, Berdyshev E, Goleva E. Cutaneous barrier dysfunction in allergic diseases. Journal of Allergy and Clinical Immunology. 2020;145:1485–97.
3. Ruokolainen L, Fyhrquist N, Haahtela T. The rich and the poor: Environmental biodiversity protecting from allergy. Curr Opin Allergy Clin Immunol. 2016;16:421–6.
4. Haahtela T. A biodiversity hypothesis. Allergy: European Journal of Allergy and Clinical Immunology. 2019;74:1445–56.
5. von Mutius E, Vercelli D. Farm living: Effects on childhood asthma and allergy. Nat Rev Immunol. 2010;10:861–8.
6. Ruokolainen L, Von Hertzen L, Fyhrquist N, Laatikainen T, Lehtomäki J, Auvinen P, et al. Green areas around homes reduce atopic sensitization in children. Allergy: European Journal of Allergy and Clinical Immunology. 2015;70:195–202.
7. Ruokolainen L, Parkkola A, Karkman A, Sinkko H, Peet A, Hämäläinen AM, et al. Contrasting microbiotas between Finnish and Estonian infants: Exposure to Acinetobacter may contribute to the allergy gap. Allergy: European Journal of Allergy and Clinical Immunology. 2020;75:2342–51.
8. Gernes R, Brokamp C, Rice GE, Wright JM, Kondo MC, Michael YL, et al. Using high-resolution residential greenspace measures in an urban environment to assess risks of allergy outcomes in children. Science of the Total Environment. 2019;668:760–7.
9. Lovasi GS, O’Neil-Dunne JPM, Lu JWT, Sheehan D, Perzanowski MS, Macfaden SW, et al. Urban tree canopy and asthma, wheeze, rhinitis, and

allergic sensitization to tree pollen in a New York city birth cohort. Environ Health Perspect. 2013;121:494–500.

10. Fuertes E, Markevych I, Bowatte G, Gruzieva O, Gehring U, Becker A, et al. Residential greenness is differentially associated with childhood allergic rhinitis and aeroallergen sensitization in seven birth cohorts. Allergy: European Journal of Allergy and Clinical Immunology. 2016;71:1461–71.
11. Tischer C, Gascon M, Fernández-Somoano A, Tardón A, Materola AL, Ibarluzea J, et al. Urban green and grey space in relation to respiratory health in children. European Respiratory Journal. 2017;49:1502112.
12. Parmes E, Pesce G, Sabel CE, Baldacci S, Bono R, Brescianini S, et al. Influence of residential land cover on childhood allergic and respiratory symptoms and diseases: Evidence from 9 European cohorts. Environ Res. 2020;183:108953.
13. Lambert KA, Bowatte G, Tham R, Lodge CJ, Prendergast LA, Heinrich J, et al. Greenspace and atopic sensitization in children and adolescents—a systematic review. Int J Environ Res Public Health. 2018;15:1–12.
14. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International study of asthma and allergies in childhood (ISAAC): Rationale and methods. In: European Respiratory Journal. 1995. p. 483–91.
15. Illi S, Von Mutius E, Lau S, Nickel R, Grüber C, Niggemann B, et al. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. Journal of Allergy and Clinical Immunology. 2004;113:925–31.
16. Akdis CA. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? Vol. 21, Nature Reviews Immunology. 2021. p. 739–51.

17. Kukkonen K, Savilahti E, Haahtela T, Juntunen-Backman K, Korpela R, Poussa T, et al. Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases: A randomized, double-blind, placebo-controlled trial. Journal of Allergy and Clinical Immunology. 2007;119:192–8.

18. Karvonen AM, Hyvärinen A, Roponen M, Hoffmann M, Korppi M, Remes S, et al. Confirmed moisture damage at home, respiratory symptoms and atopy in early life: A birth-cohort study. Pediatrics. 2009;124:329–38.

19. Lagström H, Rautava P, Kaljonen A, Räihä H, Pihlaja P, Korpilahti P, et al. Cohort profile: Steps to the healthy development and well-being of children (the STEPS Study). Int J Epidemiol. 2013;42:1273–84.

20. Karlsson L, Tolvanen M, Scheinin NM, Uusitupa HM, Korja R, Ekholm E, et al. Cohort Profile: The FinnBrain Birth Cohort Study (FinnBrain). Int J Epidemiol. 2018;47:15–16j.

21. Huuskonen P, Keski-Nisula L, Heinonen S, Voutilainen S, Tuomainen TP, Pekkanen J, et al. Kuopio birth cohort - design of a Finnish joint research effort for identification of environmental and lifestyle risk factors for the wellbeing of the mother and the newborn child. BMC Pregnancy Childbirth. 2018;18:1–9.

22. Korpela K, Dikareva E, Hanski E, Kolho KL, De Vos WM, Salonen A. Cohort profile: Finnish Health and Early Life Microbiota (HELMi) longitudinal birth cohort. BMJ Open. 2019;9:1–7.

23. Williams H, Jburney P, Pembroke A, Hay R. The U.K. Working Party’s Diagnostic Criteria for Atopic Dermatitis. III. Independent hospital validation. British Journal of Dermatology. 1994;131:406–16.

24. Kosztra B, Büttner G, Hazeu G, Arnold S. Updated CLC illustrated nomenclature guidelines. . Wien, Austria; 2017 Sep.

25. Markevych I, Schoierer J, Hartig T, Chudnovsky A, Hystad P, Dzhambov AM, et al. Exploring pathways linking greenspace to health: Theoretical and methodological guidance. Vol. 158, Environmental Research. 2017. p. 301–17.

26. Ritsema van Eck J, Koomen E. Characterising urban concentration and land-use diversity in simulations of future land use. Annals of Regional Science. 2008;42:123–40.

27. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177–88.

28. Singavarapu B, Beugnon R, Bruelheide H, Cesarz S, Du J, Eisenhauer N, et al. Tree mycorrhizal type and tree diversity shape the forest soil microbiota. Environ Microbiol. 2021;

29. Siles JA, Margesin R. Seasonal soil microbial responses are limited to changes in functionality at two Alpine forest sites differing in altitude and vegetation. Sci Rep. 2017;7:2204.

30. Hui N, Jumpponen A, Francini G, Kotze DJ, Liu X, Romantschuk M, et al. Soil microbial communities are shaped by vegetation type and park age in cities under cold climate. Environ Microbiol. 2017;19:1281–95.

31. Gastaminza G, Lombardero M, Bernaola G, Antepara I, Muñoz D, Gamboa PM, et al. Allergenicity and cross-reactivity of pine pollen. Clinical and Experimental Allergy. 2009;39:1438–46.

32. Dockx Y, Täubel M, Bijnens EM, Witters K, Valkonen M, Jayaprakash B, et al. Residential green space can shape the indoor microbial environment. Environ Res. 2021;201:111543.

33. Parajuli A, Grönroos M, Siter N, Puhakka R, Vari HK, Roslund MI, et al. Urbanization reduces transfer of diverse environmental microbiota indoors. Front Microbiol. 2018;9:84.
34. Hyytiäinen HK, Jayaprakash B, Kirjavainen P v., Saari SE, Holopainen R, Keskinen J, et al. Crawling-induced floor dust resuspension affects the microbiota of the infant breathing zone. Microbiome. 2018;6:25.
35. Susanto NH, Schoos AMM, Standl M, Lowe AJ, Dharmage SC, Svanes C, et al. Environmental grass pollen levels in utero and at birth and cord blood IgE: Analysis of three birth cohorts. Environ Int. 2018;119:295–301.
36. Smith AR, Knaysi G, Wilson JM, Wisniewski JA. The Skin as a Route of Allergen Exposure: Part I. Immune Components and Mechanisms. Vol. 17, Current Allergy and Asthma Reports. 2017.
37. Calov M, Alinaghi F, Hamann CR, Silverberg J, Egeberg A, Thyssen JP. The Association Between Season of Birth and Atopic Dermatitis in the Northern Hemisphere: A Systematic Review and Meta-Analysis. Journal of Allergy and Clinical Immunology: In Practice. 2020;8:674-680.e5.
38. Koponen P, Borodulin K, Lundqvist A, Sääksjärvi K, Koskinen S. Health, functional capacity and welfare in Finland – FinHealth 2017 study. National Institute for Health and Welfare (THL), Report 4/2018, in Finnish. 2018.

TABLE 1. The six Finnish birth cohorts.

Cohort	**Recruitment area of Finland** (Fig 1)	**Birth years**	**Recruited at birth, N**	**Included in the study, n (%)**[†]	**CLC version**	**CLC data time consistency**
FLORA Study[17]	Helsinki metropolitan	2000-2003	1 018	914 (89.8)	CLC2006	2006 +/-1 year
LUKAS[18]	Eastern and Middle	2002-2005	442	387 (87.8)	CLC2006	2006 +/-1 year
STEPS Study[19]	Southwestern	2008-2010	1 805	839 (45.9)	CLC2006	2006 +/-1 year
FinnBrain[20]	Southwestern and Åland Islands	2011-2015	3 837	1 177 (29.3)	CLC2012	2012 +/- 1 year
KuBiCo[21]	Eastern	2012-2020	5 752	1 037 (18.0)	CLC2012	2012 +/- 1 year
HELMi[22]	Helsinki metropolitan	2016-2018	1 065	731 (68.6)	CLC2018	2018 +/- 1 year
			13 919	5 085 (36.5)		

[†]Children with available data of outcome by age of two years and *a priori* selected and always adjusted confounders: child sex, maternal history of atopic diseases (asthma, hay fever and/or eczema), number of older siblings, the highest parental (either mother or father) educational level, and living on farm and cohort (only in LUKAS). *CLC*, the CORINE Land Cover; *HELMi*, Health and Early Life Microbiota; *KuBiCo*, Kuopio Birth Cohort.

TABLE 2. Main results of the meta-analyses for the associations between land cover classes and greenness indices and the development of doctor-diagnosed eczema by the age of two years in the 250 m x 250 m grid.

Land cover classes and greenness indices	Tertiles/classes	All cohorts 5 085		Doctor-diagnosed eczema by the age of two years				
						Heterogeneity		
		N	%†	**aOR**	**95% CI**	I^2	*p*	E
Coniferous forest	lowest tertile	1752	22.4	1				
	middle	1764	25.7	**1.19**	**1.01, 1.39**	0%	.86	F
	highest	1569	24.5	1.16	0.98, 1.38	0%	.81	F
Mixed forest	lowest tertile	1729	23.1	1				
	middle	1643	25.4	**1.21**	**1.02, 1.42**	0%	.87	F
	highest	1713	24.2	1.07	0.90, 1.28	9%	.36	F
Broad-leaved forest	None (0%)	3164	24.2	1				
	low	863	24.8	1.06	0.88, 1.27	0%	.48	F
	high	1058	23.9	0.97	0.81, 1.15	15%	.32	F
Agricultural areas	None (0%)	3698	24.1	1				
	low	671	23.0	0.93	0.64, 1.36	64%	.02	R
	high	716	26.3	1.20	0.98, 1.48	0%	.77	F
Transport infrastructure	None (0%)	2216	25.4	1				
	low	1364	23.5	0.86	0.73, 1.01	0%	.78	F
	high	1505	17.4	**0.77**	**0.65, 0.91**	35%	.17	F
Residential areas	lowest tertile	1599	24.3	1				
	middle	1667	25.4	0.92	0.70, 1.21	56%	.04	R
	highest	1819	23.1	1.07	0.90, 1.26	0%	.77	F
Commercial/ Industrial	None (0%)	1728	25.2	1				
	low	1674	23.4	0.92	0.78, 1.08	0%	.55	F
	high	1683	24.1	0.96	0.81, 1.12	0%	.68	F
Herbaceous vegetation	lowest tertile	2150	25.7	1				
	middle	1584	22.9	0.89	0.75, 1.05	0%	.81	F
	highest	1351	23.4	0.94	0.78, 1.13	0%	.78	F
Sport/ leisure	None (0%)	4179	24.5	1				
	low	473	24.5	1.03	0.70, 1.50	59%	.03	R
	high	433	21.7	0.94	0.64, 1.37	55%	.05	R
Bare surface	None (0%)	4820	24.2	1				
	low	133	24.1	0.99	0.65, 1.51	0%	.70	F
	high	132	24.2	1.11	0.72, 1.69	0%	.50	F
Wetlands	None (0%)	4943	24.2	1				
	low	72	25.0	1.06	0.59, 1.89	0%	.65	F
	high	70	22.9	1.04	0.58, 1.90	0%	.52	F
Water bodies	None (0%)	4581	24.1	1				
	low	257	28.4	1.25	0.93, 1.68	0%	.70	F
	high	247	22.3	0.89	0.64, 1.23	7%	.37	F
NDVI	lowest tertile	1838	24.3	1				
	middle	1568	23.3	0.94	0.79, 1.11	0%	.87	F
	highest	1679	25.0	0.99	0.83, 1.19	8%	.36	F
VCDI	lowest tertile	1638	24.0	1				
	middle	1555	23.8	0.97	0.82, 1.14	0%	.66	F
	highest	1674	25.1	1.09	0.81, 1.46	65%	.01	R

Analyses of individual cohorts were adjusted for *a priori* selected confounders: sex, maternal history of allergic diseases, parental educational level, and the number of older siblings. In LUKAS also living on farm and cohort. Cut-offs for tertiles/classes, see Table S5. Significant ($p < .05$) results are in bold text. *aOR*, adjusted odds ratio; *CI*, confidence interval; E, effect of heterogeneity; *F*, fixed effect; I^2: percentage of variation across studies that is due to heterogeneity rather than chance or an intuitive and simple expression of the inconsistency of studies' results; *NDVI*, the Normalized Difference Vegetation Index; *R*, random effect; *VCDI*, the Vegetation Cover Diversity Index.

%† Percentage of eczema in tertiles.

TABLE 3. Results of the meta-analyses for the associations between land cover classes and greenness indices and the development of doctor-diagnosed eczema by the age of two years with growing distances of 750 m x 750 m and 1250 m x 1250 m grids in all cohorts.

		Doctor-diagnosed eczema by the age of two years									
		750 x 750m					**1 250 x 1 250m**				
				Heterogeneity					Heterogeneity		
Land cover classes and greenness indices	**Tertiles/ classes**	**aOR**	**95% CI**	I^2	*p*	E	**aOR**	**95% CI**	I^2	*p*	E
Coniferous forest	lowest tertile	1					1				
	middle	1.02	0.87, 1.20	0%	.99	F	0.96	0.80, 1.14	0%	.69	F
	highest	1.13	0.95, 1.36	0%	.43	F	1.09	0.89, 1.34	0%	.60	F
Mixed forest	lowest tertile	1					1				
	middle	1.15	0.97, 1.36	30%	.21	F	1.01	0.85, 1.20	0%	.54	F
	highest	1.01	0.85, 1.20	28%	.23	F	0.96	0.81, 1.16	13%	.33	F
Broad-leaved forest†	None (0%)	1					1				
	low	1.01	0.85, 1.20	0%	.65	F	1.10	0.89, 1.37	0%	.48	F
	high	1.04	0.87, 1.25	28%	.23	F	1.21	0.97, 1.51	39%	.16	F
Agricultural areas†	None (0%)	1					1				
	low	**1.20**	**1.02, 1.41**	26%	.24	F	1.18	0.91, 1.51	56%	.05	R
	high	1.04	0.87, 1.26	0%	.56	F	1.04	0.86, 1.26	0%	.54	F
Transport†	None (0%)	1					1				
	low	0.96	0.83, 1.12	0%	.73	F	0.92	0.79, 1.07	0%	.69	F
	high	0.90	0.74, 1.10	30%	.21	F	0.96	0.81, 1.15	0%	.52	F
Herbaceous vegetation	lowest tertile	1					1				
	middle	1.05	0.89, 1.25	47%	.09	F	0.86	0.72, 1.03	24%	.26	F
	highest	0.90	0.74, 1.10	0%	.59	F	0.90	0.74, 1.11	32%	.20	F
NDVI	lowest tertile	1					1				
	middle	1.06	0.89, 1.26	0%	.93	F	1.03	0.86, 1.23	0%	.65	F
	highest	1.05	0.88, 1.26	3%	.40	F	1.12	0.93, 1.35	0%	.63	F
VCDI	lowest tertile	1					1				
	middle	1.09	0.93, 1.28	20%	.28	F	0.95	0.81, 1.12	0%	.66	F
	highest	0.96	0.81, 1.14	0%	.48	F	1.04	0.80, 1.34	55%	.05	R

Individual cohorts were adjusted for *a priori* selected confounders: gender, maternal history of allergic diseases, parental educational level, and the number of older siblings. In LUKAS also living on farm and cohort. Cut-offs for tertiles/classes, see Table S5. Significant ($p < .05$) results are in bold text.

†Tertiles were used as cut offs in broad-leaved forest and transport infrastructure in both larger grids and in agriculture areas in the grid of 1250 m x 1250 m.

aOR, adjusted odds ratio; CI, confidence interval; E, effect of heterogeneity; F, fixed effect; NDVI, the Normalized Difference Vegetation Index; R, random effect; VCDI, the Vegetation Cover Diversity Index.

TABLE 4. Results of the meta-analyses for the associations between land cover classes and greenness indices and the development of doctor-diagnosed eczema by the age of two years stratified by the season of birth in 250 m x 250 m grid in all cohorts.

Land cover classes and greenness indices	Tertiles/ classes	Doctor-diagnosed eczema by the age of two years																			
		Winter					Spring					Summer					Autumn				
		aOR	95% CI	Heterogeneity			aOR	95% CI	Heterogeneity			aOR	95% CI	Heterogeneity			aOR	95% CI	Heterogeneity		
				I^2	*p*	E			I^2	*p*	E			I^2	*p*	E			I^2	*p*	E
Coniferous forest	lowest tertile	1					1					1					1				
	middle	1.05	0.75, 1.47	0%	.79	F	**1.48**	**1.04, 2.11**	0%	.55	F	1.03	0.75, 1.42	0%	.27	F	1.32	0.96, 1.81	0%	.71	F
	highest	1.11	0.77, 1.62	0%	.54	F	1.42	0.97, 2.09	51%	.07	F	0.97	0.67, 1.39	26%	.24	F	1.29	0.92, 1.80	0%	.61	F
Mixed forest	lowest tertile	1					1					1					1				
	middle	1.12	0.78, 1.62	54%	.06	F	1.37	0.95, 1.99	0%	.61	F	1.14	0.83, 1.58	0%	.67	F	1.24	0.90, 1.70	0%	.91	F
	highest	0.83	0.42, 1.64	65%	.01	R	1.40	0.97, 2.02	0%	.67	F	0.88	0.62, 1.26	6%	.38	F	1.21	0.84, 1.72	49%	.08	F
Broad-leaved forest	None (0%)	1					1					1					1				
	low	0.71	0.37, 1.37	6E3 %	.02	R	1.38	0.94, 2.04	24%	.25	F	0.87	0.59, 1.29	0%	.42	F	**1.46**	**1.02, 2.08**	0%	.94	F
	high	**0.68**	**0.47, 0.99**	25%	.25	F	1.30	0.93, 1.92	0%	.64	F	0.86	0.60, 1.24	0%	.75	F	1.13	0.79, 1.61	48%	.08	F
Agricultural areas	None (0%)	1					1					1					1				
	low	1.11	0.72, 1.68	15%	.32	F	1.31	0.84, 2.04	0%	.49	F	0.77	0.48, 1.24	39%	.15	F	1.21	0.82, 1.77	0%	.92	F
	high	0.82	0.50, 1.37	0%	.65	F	**1.56**	**1.03, 2.36**	0%	.63	F	0.93	0.61, 1.42	0%	.55	F	1.22	0.81, 1.84	1%	.41	F
NDVI	lowest tertile	1					1					1					1				
	middle	**0.64**	**0.45, 0.92**	0%	.84	F	1.20	0.82, 1.76	21%	.28	F	0.78	0.56, 1.08	0%	.82	F	1.09	0.78, 1.53	0 %	.85	F
	highest	0.73	0.50, 1.06	28%	.23	F	1.35	0.72, 2.52	58%	.05	R	0.88	0.60, 1.28	43%	.12	F	1.22	0.85, 1.75	0 %	.82	F
VCDI	lowest tertile	1					1					1					1				
	middle	0.81	0.56, 1.17	0%	.88	F	0.97	0.67, 1.40	7%	.37	F	0.99	0.71, 1.39	0%	.69	F	1.01	0.73, 1.39	11%	.34	F
	highest	0.98	0.68, 1.41	46%	.10	F	**1.57**	**1.11, 2.23**	0%	.64	F	0.89	0.64, 1.25	0%	.71	F	1.09	0.78, 1.52	50%	.08	F

Individual cohorts were adjusted for *a priori* selected confounders: sex, maternal history of allergic diseases, parental educational level, and the number of older siblings. In LUKAS also living on farm and cohort. Cut-offs for tertiles/classes, see Table S5. For land cover classes which were not present (0%) from more than 33.3% of the observations, the 0% category was used as reference category, and values above 0% were evenly divided into two groups (low and high). Significant ($p < .05$) results are in bold text. *aOR*, adjusted odds ratio; *CI*, confidence interval; *E*, effect of heterogeneity; *F*, fixed effect; I^2: percentage of variation across studies that is due to heterogeneity rather than chance or an intuitive and simple expression of the inconsistency of studies' results; *NDVI*, the Normalized Difference Vegetation Index; *R*, random effect; *VCDI*, the Vegetation Cover Diversity Index.

FIGURE LEGENDS

FIGURE 1. Geographical distribution of the birth cohorts and the number of children at the outcome age of two years and at birth (n/N). *HELMi*, Health and Early Life Microbiota; *KuBiCo*, Kuopio Birth Cohort.

FIGURE 2. Meta-analyses for the associations between four significant land cover classes and development of doctor-diagnosed eczema by the age of two years in 250 m x 250 m grid in all cohorts. *aOR*, adjusted odds ratio; *CI*, confidence interval; *HELMi*, Health and Early Life Microbiota; I^2: percentage of variation across studies that is due to heterogeneity rather than chance or an intuitive and simple expression of the inconsistency of studies' results; *KuBiCo*, Kuopio Birth Cohort.

Supporting Information

Early-life environment and the risk of eczema at 2 years – meta-analyses of six Finnish birth cohorts

Short running title: Early-life environment and the risk of eczema at 2 years

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Abbreviations:

CI	Confidence interval
CLC	CORINE Land Cover
CORINE	The Coordination of Information on the Environment
ISAAC	The International Study of Asthma and Allergies in Childhood
IQR	Interquartile range
NDVI	The Normalized Difference Vegetation Index
OR	Odds ratio
SD	Standard deviation
Th2	T-helper-2
VCDI	The Vegetation Cover Diversity Index

Methods

All, except high atopy risk cohort FLORA Study, were population-based cohorts. Also, the birth cohort of LUKAS consists of two parts: first part is called LUKAS1 and is the Finnish arm of the European PASTURE birth cohort, where half the families lived on farms with livestock and other half in rural areas. LUKAS2 is its additional cohort, which was not limited to any occupations or places of residence but recruited all who came to give birth to a particular hospital within one year. The study cohorts used the same research methods. The cooperation of these birth cohorts has generated an active, long-term collaborative data and sampling network between the major birth cohorts across Finland. Extensive background information on children has been collected from gestation to present day, including data on health, immunological, neurological and early microbiome development, clinical factors, nutrition, environmental exposures, life style determinants, and biological samples.

The study outcome was the doctor-diagnosed eczema. In four cohorts, the outcome of eczema was defined as parental report of lifetime prevalence of doctor-diagnosed eczema ever by the child age of two years using the standardized questions from the International Study of Asthma and Allergies in Childhood (ISAAC).[1] In FLORA Study, the outcome was doctor-diagnosed eczema based on the Williams's criteria.[2] In HELMi, the eczema definition was based on two questions on doctor-diagnosed and/or parent-reported rash (Tables S1 and S2).

The European-wide Coordination of Information on the Environment (CORINE) Land Cover (CLC) combines geo-spatial environmental information from national databases and satellite images into 44 land cover classes describing various types of artificial surfaces, agricultural land, forests, wetlands and water bodies.[3] The latest versions of CLC controlled close to the birth years were utilized as the land use cover maps usually use data from at least two years earlier than the final map is delivered so that the data is as accurately as possible representing land cover in the participants' birth years, where we expect not significant land use change in the previous or subsequent years (Table 1).

For this study, fourteen exposures of land cover classes and greenness indices were used due to rest of the land cover classes were too rare or completely absent from our data sets (Tables S3-S5). Percentages of twelve land cover classes were calculated from the original CLC classes: coniferous forest; mixed forest; broad-leaved forest; agricultural areas; transport infrastructure; residential areas; industrial/commercial; herbaceous vegetation; sport/leisure; bare surface; wetlands; and water bodies. More detailed definitions of the land cover classes are shown in Table S3. Each land cover class and greenness index were calculated within predefined grid sizes of 250 m x 250 m, 750 m x 750 m and 1250 m x 1250 m for all initially recruited children in each cohort (Figure S2).

The greenness indices were defined as the Normalized Difference Vegetation Index (NDVI)[4] and the Vegetation Cover Diversity Index (VCDI)[5] based on the Simpson’s Diversity Index formula. NDVI indicates the intensity of living vegetation and biomass (green color), and thus it is not associated directly to any classified land cover class, but rather brings broader dimension to the interpretation of geographical variation of living vegetation.[4] NDVI was calculated using the Landsat 5 satellite, carrying the Thematic Mapper for continuous image collection for the study period, and based on land surface reflectance of visible red and near-infrared wavelengths; chlorophyll in healthy vegetation absorbs radiation in the visible red region (630-690 nm) of the electromagnetic spectrum and reflects radiation in the near-infrared region (760-900 nm). The NDVI values were derived from multispectral satellite images series, with a 30m x 30m of spatial resolution. After removing out water bodies, NDVI ranges from 0 to 1. We used the median of the NDVI values of the studied grid areas as a measure of NDVI. VCDI indicates the amount of different vegetation types based on the percentage of CLC land cover classes. VDCI is a single estimated value ranging from 0 to 1; the index value is 0 when the area/grid contains only one vegetation type, whereas the value approaches 1 when there are several vegetation types and the proportion of vegetation types is equally distributed in the area/grid.[5]

Land cover classes and greenness indices were classified into three-class variables (with the lowest class as the reference category) using the same cut-off values in individual cohorts (Table S5) within in total of 9 311 observations. For land cover classes which were not present (0%) from more than 33.3% of the observations, the 0% category was used as reference category, and values above 0% were evenly divided into two groups (low and high) (Table S5).

Firstly, the associations between exposures and outcome were conducted within each cohort individually. In addition, the first phase was reanalyzed without adjusting for the parental educational level (the family socio-economic status) and respectively adjusting for birth season to study their independent effects. Secondly, to calculate the combined effect across cohorts, the meta-analyses were performed using the estimates of individual cohorts in 250 m x 250 m grid, where the effect size estimates and their standard errors were first calculated separately for all cohorts, and then, the meta-analysis was performed using the fixed effects method with the DerSimonian-Laird estimator for the between-study variance: if heterogeneity was observed (I^2 index $p < .05$), the random effect method was used.[6] Thirdly, in sensitivity analyses were investigated 1) the role of larger surroundings using two different distances in the grids (750m x 750m and 1250m x 1250m), 2) the homogeneity of the outcome: HELMi cohort was excluded from the analyses, 3) the role of long-term exposure: only children who had lived entire two years in the birth address were included in the analyses, and 4) the effect of birth season by using stratified analyses. HELMi cohort included only the children who lived entire two-years period in the birth address.

All analyses were adjusted for *a priori* selected confounders of child sex, maternal history of atopic diseases (asthma, hay fever and/or eczema), the number of older siblings (0, 1, ≥2), and the highest parental (either mother or father) educational level used as the proxy of family socio-economic status (Tables S1 and S2). Two additional adjustments were used in LUKAS due to the study design (living on a farm and cohort; LUKAS1 or LUKAS2).[7] From 387 children in LUKAS, 108 (27.9%) children were living on a farm, 187 (48.3%) were from LUKAS1 and 200 (51.7%) were from LUKAS2 cohorts. The analyses of individual cohorts were performed using Enterprise Guide SAS (SAS Institute, Cary, NC) version 9.4 in LUKAS, FLORA, and STEPS, IBM SPSS 26.0 software (SPSS Inc, Chicago, Ill, USA) in FinnBrain and KuBiCo, and R (R Foundation for Statistical Computing) version 4.0.3 in HELMi. Meta-analyses, box-plot graphics and heat maps were performed using the R Studio version 4.1.2.

References

1. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International study of asthma and allergies in childhood (ISAAC): Rationale and methods. In: European Respiratory Journal. 1995. p. 483–91.
2. Williams H, Jburney P, Pembroke A, Hay R. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. III. Independent hospital validation. British Journal of Dermatology. 1994;131:406–16.
3. Kosztra B, Büttner G, Hazeu G, Arnold S. Updated CLC illustrated nomenclature guidelines. . Wien, Austria; 2017 Sep.
4. Markevych I, Schoierer J, Hartig T, Chudnovsky A, Hystad P, Dzhambov AM, et al. Exploring pathways linking greenspace to health: Theoretical and methodological guidance. Vol. 158, Environmental Research. 2017. p. 301–17.
5. Ritsema van Eck J, Koomen E. Characterising urban concentration and land-use diversity in simulations of future land use. Annals of Regional Science. 2008;42:123–40.
6. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177–88.

7. Karvonen AM, Hyvärinen A, Roponen M, Hoffmann M, Korppi M, Remes S, et al. Confirmed moisture damage at home, respiratory symptoms and atopy in early life: A birth-cohort study. Pediatrics. 2009;124:329–38.

TABLE S1. Characteristics of the study populations.

		FLORA Study (N = 914)		LUKAS (N = 387)		STEPS Study (N = 839)		FinnBrain (N = 1 177)		KuBiCo (N = 1 037)		HELMi (N = 731)	
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Sex	Girl	465	50.9	193	49.9	420	50.0	540	45.9	478	46.1	357	48.8
	Boy	449	49.1	194	50.1	419	50.0	637	54.1	559	53.9	374	51.2
Maternal atopic diseases	Yes	737	80.6	221	57.1	373	44.5	523	44.4	443	42.7	309	42.3
	No	177	19.4	166	42.9	466	55.5	654	55.6	594	57.3	422	57.7
Parental educational level	Low	109	11.9	97	25.1	109	13.0	276	23.4	54	5.2	33	3.3
	Middle	376	41.1	185	47.8	402	47.9	423	35.9	222	21.4	190	18.8
	High	429	46.9	105	27.1	328	39.1	478	40.6	761	73.4	508	70.2
Number of older siblings	None	504	55.1	137	35.4	455	54.2	680	57.8	427	41.2	321	31.7
	1	281	30.7	132	34.1	249	29.7	365	31.0	293	28.3	311	30.7
	≥ 2	129	14.1	118	30.5	135	16.1	132	11.2	317	30.6	99	9.8
Moved by age of two years	Yes	412	45.1	67	17.3	286	34.1	318	27.0	283	27.3	0	0
	No	502	54.9	320	82.7	553	65.9	859	73.0	754	72.7	731	100
Eczema by age of two years	Yes	262	28.7	108	27.9	198	23.6	258	21.9	265	25.6	142	19.4
	No	652	71.3	279	72.1	641	76.4	919	78.1	772	74.4	589	80.6

TABLE S2. The harmonized outcome and confounder data; questions used in six cohorts

Cohort	The outcome questions	Follow-up point
FLORA Study	Has a doctor diagnosed any of the following diseases in your child? Atopic eczema ever: Yes/No, when?	Asked at the age of 2 years (ever)
LUKAS	Has a doctor diagnosed any of the following diseases in your child in the last... months? Atopic eczema: Yes/No	Asked at the age of 12 months (past 10 months), at 18 months (past 6 months) and at the age of 2 years (past 6 months): if any yes
STEPS Study	Has a doctor ever diagnosed atopic eczema in your child? Yes/No	Asked at the age of 12 months (ever) and 2 years (ever)
FinnBrain	Has a doctor ever diagnosed atopic eczema in your child? Yes/No	Asked at the age of 2 years (ever)
KuBiCo	Has your child ever had atopic eczema? AND Is the atopic eczema in your child diagnosed by a doctor?	Asked at the age of 12 months (ever), and at the age of 2 years (ever)
HELMi	1) Has a doctor given your child a long-term diagnosis during the previous 3 months? If yes, which diagnosis? AND/OR 2) Does your child have atopic eczema? Yes/No	Asked repeatedly after every 3 months from the age of 3 months to 2 years
	Sex: boy/girl	
FLORA Study	Questionnaire	Filled at study entry during pregnancy (mother) and at the delivery
LUKAS	Questionnaires	Filled in by a midwife during delivery and the questionnaire at 2 months
STEPS Study	Birth registry	After birth
FinnBrain	Questionnaires and birth registry	Filled in by a midwife during delivery and the questionnaires
KuBiCo	Birth registry	After birth
HELMi	Parental questionnaire	After birth
	The number of older siblings (0, 1, ≥2)	
FLORA Study	Number of children and adults in the same household?	Questionnaire at 3 months
LUKAS	Do you have children of your own yet? Yes/No, if yes, how many children do you have? The number of children.	Questionnaire during pregnancy
STEPS Study	Number of children in the same household?	Questionnaire at 10 gestational weeks and at 2 years
FinnBrain	Number of older siblings (birth years)?	Maternal questionnaires at 14 gestational weeks and at 3 months
KuBiCo	Number of previous births?	Birth registry
HELMi	Number of previous births? Number of children in the same household?	Questionnaire after birth
	Highest level of parental education (either mom or dad): 1= low (basic), 2=middle, 3=high (academic)	
FLORA Study	Parental questionnaires *(asked separately from mom and dad)*: The level of education of parents: Elementary/ comprehensive school, vocational/trade school, college, university of applied sciences, university	Questionnaire 3 months after birth
LUKAS	Parental questionnaires *(asked separately from mom and dad)*: What is your highest school or college degree? Elementary/ comprehensive school, vocational/trade school (low), high school/college (middle), university (high)	Maternal questionnaire during pregnancy and paternal questionnaire 2 months after birth
STEPS Study	Parental questionnaires *(asked separately from mom and dad)*: Educational background? Elementary/comprehensive school, high school, vocational/trade school (low), college, university of applied sciences (middle), university studies or diploma) (high)	During pregnancy at gestational weeks 10
FinnBrain	Parental questionnaires *(asked separately from mom and dad)*: Education in years? Low (elementary/comprehensive school, high school, vocational/trade school = up to 12 years); middle (college, university of applied sciences = 13-15 years); high (university studier or diploma = over 15 years).	During pregnancy at gestational weeks 14
KuBiCo	Parental questionnaires *(asked separately from mom and dad)*: How many years have you gone to school and studied full-time *(full years)*? Elementary/comprehensive school is counted: low (up to 12 years); middle (13-15 years); high (over 15 years).	During pregnancy
HELMi	Parental questionnaires *(asked separately from mom and dad):* Educational background? Low (elementary/comprehensive school, high school, vocational/trade school); middle (university of applied sciences); high (university studies or diploma).	During pregnancy
	History of maternal allergic diseases: asthma, hay fever and/or eczema (Yes [if any] /No [none])	
FLORA Study	Maternal history of allergic diseases (asthma, hay fever and atopic dermatitis)? Maternal history of doctor diagnosed asthma?	Asked when recruiting because maternal or paternal history of doctor-diagnosed allergic diseases (asthma, hay fever and atopic dermatitis) was one inclusion criterion in the cohort
LUKAS	Maternal questionnaire: 3 questions: Have you ever had asthma? Yes/No; Have you ever had allergic rhinitis (hay fever)? Yes/No; Have you ever had atopic eczema? Yes/No	During pregnancy
STEPS Study	Maternal questionnaire: 1) Doctor-diagnosed allergic rhinitis (due to pollen, room dust and/or animals)? 2) Doctor-diagnosed allergic rhinitis? 3) Doctor-diagnosed asthma? 4) Doctor-diagnosed food allergy? 5) Doctor-diagnosed atopic eczema?	During pregnancy at gestational weeks 30
FinnBrain	Maternal questionnaire: 2 questions: Have you ever had allergy, allergic rhinitis or atopic eczema? Yes/No; Have you ever had asthma? Yes/No	During pregnancy at gestational weeks 14
KuBiCo	Maternal questionnaire: 3 questions: Have you ever had doctor-diagnosed asthma? Yes/No; Have you ever had allergic rhinitis (hay fever)? Yes/No; Have you ever had atopic eczema? Yes/No	During pregnancy
HELMi	Maternal questionnaire: Have you any disease or allergy? Yes/No, if yes, what allergy/-ies? Allergy for pollen, food, animal, insect, medicin, mold, contact?	During pregnancy

TABLE S3. The definitions of the land cover classes based on the CORINE classifications and what they represent in this study.

Land cover classes	CLC Level 1	CLC Level 2	CLC Level 3	Represents in this study
Coniferous forest	3 Forest and semi natural areas	31 Forests	312 Coniferous forest	
Mixed forest	3 Forest and semi natural areas	31 Forests	313 Mixed forest	
Broad-leaved forest	3 Forest and semi natural areas	31 Forests	311 Broad-leaved forest	
Agricultural areas	2 Agricultural areas	21 Arable land 22 Permanent crops 23 Pastures 24 Heterogeneous agricultural areas		Primarily arable land of winter and spring wheat, barley, oat, rye, potato and other tubers, and grass for fodder
Transport infrastructure	1 Artificial surfaces	12 Industrial, commercial and transport units	122 Road and rail networks and associated land	
Residential areas	1 Artificial surfaces	11 Urban fabric	111 Continuous urban fabric 112 Discontinuous urban fabric	
Commercial/ Industrial	1 Artificial surfaces	12 Industrial, commercial and transport units	121 Industrial or commercial units	
Herbaceous vegetation	3 Forest and semi natural areas	32 Scruband/orherbaceous vegetation associations	321Naturalgrasslands 322 Moors and heathland 323 Sclerophyllous vegetation 324 Transitional woodland-shrub	Mainly natural / semi-natural grassland, moors and heathland and transitional woodland-shrub
Sport/ leisure	1 Artificial surfaces	14 Artificial, non-agricultural vegetated areas	142 Sport and leisure facilities	Includes urban parks, stadiums and golf course
Bare surface	3 Forest and semi natural areas	33 Open spaces with little or no vegetation	331 Beaches, dunes, sands 332 Bare rocks 333 Sparsely vegetated areas 334 Burnt areas 335 Glaciers and perpetual snow	
Wetlands	4 Wetlands	41 Inland wetlands 42 Maritime wetlands	411 Inland marshes 412 Peat bogs 421 Salt marshes 422 Salines 423 Intertidal flats	
Water bodies	5 Water bodies	51 Inland waters 52 Marine waters	511 Water courses 512 Water bodies 521 Coastal lagoons 522 Estuaries 523 Sea and ocean	

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TABLE S4. The number of observations in six cohorts in different land cover classes and greenness indices in 250 m x 250 m grid.

	FLORA Study			HELMi			STEPS Study			FinnBrain			LUKAS			KuBiCo		
Land cover classes and greenness indices	**N**	**%†**	**mean‡**	**N**	**%†**	**mean‡**	**N**	**%†**	**mean‡**	**N**	**%†**	**mean‡**	**N**	**%†**	**mean‡**	**N**	**%†**	**mean‡**
Coniferous forest	914	65.1	5.29	731	77.4	6.65	839	80.1	11.41	1177	81.1	11.3	387	82.7	10.84	1037	92.7	14.10
Mixed forest	914	63.1	4.37	731	77.7	4.64	839	75.9	3.55	1177	73.9	3.7	387	73.1	5.71	1037	91.8	8.70
Broad-leaved forest	914	26.4	0.82	731	48.2	1.6	839	25.0	0.56	1177	52.3	0.68	387	45.7	1.79	1037	58.5	3.10
Agricultural areas	914	8.6	1.26	731	10.5	1.92	839	37.9	9.90	1177	39.0	9.1	387	54.0	19.87	1037	23.6	6.70
Transport infrastructure	914	73.2	11.45	731	69.8	9.14	839	52.2	6.02	1177	52.5	5.8	387	49.1	5.54	1037	42.8	4.40
Residential areas	914	99.9	62.66	731	100.0	56.58	839	99.9	48.44	1177	99.0	48.5	387	99.2	37.44	1037	97.8	42.10
Commercial/ Industrial	914	67.7	9.53	731	75.0	11.04	839	67.0	8.48	1177	67.2	8.6	387	54.8	5.21	1037	60.3	7.50
Herbaceous vegetation	914	57.2	2.66	731	76.7	4.01	839	97.4	9.42	1177	95.9	9.7	387	81.9	7.14	1037	89.2	7.40
Sport/ leisure	914	11.8	0.76	731	35.3	3.18	839	12.8	1.13	1177	14.9	0.99	387	16.3	1.19	1037	18.8	1.30
Bare surface	914	10.2	0.31	731	7.5	0.11	839	3.9	0.05	1177	5.9	0.11	387	1.8	0.02	1037	0.7	0.01
Wetlands	914	0.2	0.01	731	4.0	0.15	839	1.3	0.08	1177	1.4	0.15	387	5.4	0.52	1037	6.0	0.42
Water bodies	914	3.7	0.86	731	7.8	0.96	839	6.3	0.96	1177	5.9	1.3	387	19.6	4.72	1037	20.7	3.80
NDVI	914	100.0	0.46	731	100.0	0.47	839	100.0	0.54	1177	100.0	0.54	387	100.0	0.68	1037	100.0	0.58
VCDI	753	82.3	0.41	691	91.0	0.52	824	91.6	0.44	1151	90.3	0.46	378	91.8	0.46	1030	97.1	0.54

N, number of observations in the 250 m x 250 m grid.
† percentage of observations in which a land cover class or greenness index is above 0.
‡ Mean proportion of the given land cover class within a cohort.

TABLE S5. Cut-offs for the tertiles/classes in three grids.

	Cut-offs of tertiles/classes								
	250 m x 250 m			750 m x 750 m			1 250 m x 1 250 m		
Land cover classes and greenness indices	lowest tertile/ class (none)	middle tertile/ low class	highest tertile/ high class	lowest tertile/ class (none)	middle tertile/ low class	highest tertile/ high class	lowest tertile/ class (none)	middle tertile/ low class	highest tertile/ high class
Coniferous forest	0-1.98%	1.981-10.95%	10.96-91.7%	0-6.49%	6.50-17.33%	17.34-74.4%	0.05-8.50%	8.51-19.07%	19.08-69.7%
Mixed forest	0-1.10%	1.11-5.00%	5.01-56.2%	0-3.331%	3.332-6.65%	6.66-39.9%	0.08-4.319%	4.320-7.21%	7.22-41.2%
Broad-leaved forest	None (0%)	0.59-1.921%	1.922-50.7%	0-0.43%	0.44-1.36%	1.37-27.5%	0-0.6%	0.61-1.67%	1.68-29.2%
Agricultural areas	None (0%)	0.59-15.99%	16.0-100%	None (0%)	0.069-9.49%	9.49-96.2%	0-0.72%	0.73-12.76%	12.77-91.8%
Transport infrastructure	None (0%)	0.59-10.471%	10.472-45.6%	0-3.75%	3.76-7.89%	7.90-54.2%	0-3.74%	3.75-7.36%	7.37-42.9%
Residential areas	0-35.85%	35.86-63.54%	63.55-100%	0-28.16%	28.17-45.75%	45.76-90.4%	0-24.40%	24.41-38.90%	38.91-83.4%
Commercial/ Industrial	None (0%)	0.59-8.971%	8.792-96.2%	0-4.13%	4.14-11.69%	11.70-60.4%	0-5.15%	5.16-12.61%	12.62-52.3%
Herbaceous vegetation	0-3.04%	3.05-9.00%	9.01-92.3%	0-5.85%	5.86-10.5%	10.6-46.5%	0.03-6.41%	6.42-10.50%	10.51-35.6%
Sport/ leisure	None (0%)	0.59-4.860%	4.861-73.7%	None (0%)	0.069-1.66%	1.67-69.6%	0-0.46%	0.47-1.77%	1.78-37.0%
Bare surface	None (0%)	0.59-1.00%	1.01-18.0%	None (0%)	0.069-0.21%	0.22-39.3%	None (0%)	0.0251-0.12%	0.13-33.1%
Wetlands	None (0%)	0.59-2.778%	2.779-54.0%	None (0%)	0.069-0.88%	0.89-35.1%	None (0%)	0.0251-0.62%	0.63-25.3%
Water bodies	None (0%)	0.59-12.90%	12.90-100%	None (0%)	0.07-5.76%	5.77-79.0%	None (0%)	0.0251-5.49%	5.50-81.2%
NDVI	0.05-0.510	0.511-0.607	0.6071-0.86	0.076-0.603	0.604-0.70	0.71-0.83	0.089-0.64	0.65-0.72	0.73-0.82
VCDI	0-0.440	0.441-0.6100	0.6101-0.82	0-0.55	0.551-0.62	0.63-0.85	0.03-0.560	0.5061-0.629	0.63-0.84

Land cover classes and greenness indices were classified into three-class variables (with the lowest class as the reference category) using joint tertiles as cut-offs. For land cover classes which were not present (0%) from more than 33.3% of the observations, the 0% category was used as reference category, and values above 0% were evenly divided into two groups (low and high). *NDVI*, the Normalized Difference Vegetation Index; *VCDI*, the Vegetation Cover Diversity Index.

Table S6. Comparisons between eligible and non-eligible study populations.

		FLORA (N=1018)					HELMi (N=1065)					STEPS study (N=1805)				
		Eligible		**Non-eligible**			**Eligible**		**Non-eligible**			**Eligible**		**Non-eligible**		
		N=914		N=104			N=731		N=334			N=839		N=966		
		n	%	n	%	*p*	n	%	n	%	*p*	n	%	n	%	*p*
Gender	Girl	465	50.9	25	51.0	*.98*	357	48.8	162	46.7	*.58*	420	50.0	443	46.1	*.09*
	Boy	449	49.1	24	49.0		374	51.2	156	48.5		419	50.0	519	53.9	
	missing	0		55			0		16			0		4		
Maternal history of allergic diseases	Yes	737	80.6	88	84.6	*.33*	309	42.3	141	42.2	*.64*	373	44.5	132	40.7	*.25*
	No	177	19.4	16	15.4		422	57.7	179	53.6		466	55.5	192	59.3	
	missing	0		0			0		14			0		642		
Parental education level	Low	109	11.9	2	9.5	*.65*	33	4.5	13	3.9	*.25*	109	13.0	175	19.5	*<.001*
	Middle	376	41.1	7	33.3		190	26.0	99	29.6		402	47.9	417	46.5	
	High	429	46.9	12	57.1		508	69.5	206	62.3		328	39.1	305	34.0	
	missing	0		83			0		14			0		69		
The number of older siblings	None	504	55.1	50	52.1	*.63*	321	43.9	182	54.5	*<.001*	455	54.2	502	52.0	*.32*
	One	281	30.7	29	30.2		311	42.5	100	29.9		249	29.7	283	29.3	
	≥ 2	129	14.1	17	17.7		99	13.5	38	11.4		135	16.1	181	18.7	
	missing	0		8			0		14			0		0		

		FinnBrain (N=3837)					LUKAS (N=442)					KuBiCo (N=5752)				
		Eligible		**Non-eligible**			**Eligible**		**Non-eligible**			**Eligible**		**Non-eligible**		
		N=1177		N=2660			N=387		N=55			N=1037		N=4715		
		n	%	n	%	*p*	n	%	n	%	*p*	n	%	n	%	*p*
Gender	Girl	540	45.9	1253	48.6	*.12*	193	49.9	22	40.0	*.17*	478	46.1	2366	50.2	*.02*
	Boy	637	54.1	1325	51.4		194	50.1	33	60.0		559	53.9	2343	49.8	
	missing	0		82			0		0			0		0		
Maternal history of allergic diseases	Yes	523	44.4	831	43.3	*.54*	221	57.1	29	53.7	*.13*	443	42.7	946	42.4	*.87*
	No	654	55.6	1088	56.7		166	42.9	25	46.3		594	57.3	1286	57.6	
	missing	0		741			0		1			0		2484		
Parental education level	Low	276	23.4	794	40.0	*<.001*	97	25.1	21	38.2	*.01*	54	5.2	155	7.0	*.07*
	Middle	423	35.9	654	32.9		185	47.8	29	52.7		222	21.4	509	23.0	
	High	478	40.6	538	27.1		105	27.1	5	9.1		761	73.4	1552	70.0	
	missing	0		674			0		0			0		2499		
The number of older siblings	None	680	57.8	599	55.6	*.47*	137	35.4	14	25.5	*.19*	427	41.2	1888	44.1	*<.001*
	One	365	31.0	360	33.4		132	34.1	18	32.7		293	28.3	1378	32.2	
	≥ 2	132	11.2	118	11.0		118	30.5	23	41.8		317	30.6	1019	23.8	
	missing	0		1583			0		0			0		430		

Table S7. Associations between land cover classes and greenness indices and the development of doctor-diagnosed eczema by the age of two years.

		All cohorts		Doctor diagnosed eczema by the age of 2 years																	
				FLORA Study			HELMi			STEPS Study			FinnBrain			LUKAS			KuBiCo		
Land cover classes and greenness indices	Tertiles/ classes	5 085		(262/914†, 28.7%‡)			(141/731†, 19.3%‡)			(198/839†, 23.6%‡)			(258/1 177†, 21.9%‡)			(108/387†, 27.9%‡)			(265/1 037†, 25.6%‡)		
		N	%	n	%‡	**aOR (95% CI)**	n	%‡	**aOR (95% CI)**	n	%‡	**aOR (95% CI)**	n	%‡	**aOR (95% CI)**	n	%‡	**aOR (95% CI)**	n	%‡	**aOR (95% CI)**
Coniferous forest	lowest tertile	1752	34.5	415	27.7	1	313	19.8	1	310	20.3	1	391	19.4	1	113	25.7	1	210	23.3	1
	middle	1764	34.6	355	29.9	1.12 (0.82, 1.54)	266	19.8	1.02 (0.68, 1.55)	230	27.0	1.46 (0.97, 2.19)	379	22.4	1.21 (0.85, 1.73)	133	27.8	1.05 (0.58, 1.91)	401	27.7	1.27 (0.86, 1.89)
	highest	1569	30.9	144	28.5	1.07 (0.70, 1.64)	152	17.7	0.85 (0.50, 1.40)	299	24.4	1.29 (0.88, 1.90)	407	23.8	1.29 (0.92, 1.83)	141	29.8	1.24 (0.70, 2.21)	426	24.7	1.14 (0.77, 1.71)
Mixed forest	lowest tertile	1729	34.0	452	28.1	1	236	18.2	1	292	19.9	1	440	20.5	1	164	29.3	1	145	24.1	1
	middle	1643	32.3	212	28.3	1.01 (0.70, 1.46)	248	23.0	1.35 (0.86, 2.12)	358	24.3	1.28 (0.87, 1.86)	442	25.3	**1.32 (0.96, 1.82)**	84	29.8	1.03 (0.57, 1.87)	299	25.8	1.18 (0.73, 1.89)
	highest	1713	33.7	250	30.0	1.13 (0.80, 1.59)	247	17.0	0.92 (0.57, 1.48)	189	28.0	**1.55 (1.01, 2.39)**	295	19.0	0.936 (0.64, 1.37)	139	25.2	0.76 (0.44, 1.29)	593	25.8	1.17 (0.75, 1.81)
Broad-leaved forest	None (0%)	3164	62.2	673	27.9	1	379	18.5	1	629	22.9	1	843	21.7	1	210	30.5	1	430	27.2	1
	low	863	17.0	93	30.1	1.16 (0.72, 1.87)	160	20.6	1.17 (0.73, 1.87)	127	29.9	1.47 (0.96, 2.25)	186	21.5	0.91 (0.61, 1.35)	69	30.4	0.96 (0.52, 1.77)	228	23.7	0.85 (0.58, 1.25)
	high	1058	20.8	148	31.1	1.16 (0.78, 1.71)	192	20.3	1.11 (0.70, 1.72)	83	19.3	0.82 (0.46, 1.47)	148	23.6	1.17 (0.77, 1.77)	108	21.3	**0.57 (0.32, 1.00)**	379	24.8	0.89 (0.64, 1.23)
Residential areas	lowest tertile	1599	31.4	120	29.2	1	143	16.0	1	287	27.5	1	391	23.5	1	218	25.7	1	440	23.6	1
	middle	1667	32.8	337	28.5	0.95 (0.60, 1.51)	270	20.4	1.35 (0.80, 2.37)	276	25.7	0.91 (0.62, 1.32)	385	23.6	1.02 (0.73, 1.43)	79	34.2	1.38 (0.73, 2.62)	320	26.3	1.15 (0.82, 1.62)
	highest	1819	35.8	457	28.7	0.94 (0.60, 1.47)	318	20.1	1.37 (0.82, 2.36)	276	17.4	**0.56 (0.37, 0.84)**	401	18.7	0.75 (0.53, 1.07)	90	27.8	1.09 (0.57, 2.07)	277	27.8	1.19 (0.84, 1.7)
Agricultural areas	None (0%)	3698	72.7	835	29.0	1	654	18.9	1	521	20.9	1	718	20.9	1	178	31.5	1	792	26.5	1
	low	671	13.2	51	21.6	0.68 (0.34, 1.36)	49	26.5	1.54 (0.76, 2.95)	158	27.9	1.50 (0.99, 2.26)	248	23.0	1.10 (0.78, 1.57)	59	17.0	**0.44 (0.20, 0.95)**	106	17.9	0.64 (0.38, 1.09)
	high	716	14.1	28	32.1	1.13 (0.50, 2.55)	28	17.9	0.88 (0.29, 2.22)	160	28.1	**1.52 (1.00, 2.29)**	211	24.2	1.23 (0.85, 1.78)	150	28.0	1.19 (0.63, 2.26)	139	25.9	0.98 (0.64, 1.5o)
Transport infrastructure	None (0%)	2216	43.6	245	34.3	1	221	20.7	1	401	21.2	1	559	21.8	1	197	30.0	1	593	28.2	1
	low	1364	26.8	230	25.7	0.68 (0.45, 1.01)	228	17.5	0.80 (0.50, 1.29)	216	26.9	0.92 (0.64, 1.34)	336	20.8	0.94 (0.67, 1.32)	88	31.8	1.08 (0.62, 1.89)	266	24.8	0.83 (0.59, 1.17)
	high	1505	29.6	119	27.1	0.74 (0.53, 1.04)	282	19.8	0.93 (0.6, 1.45)	222	24.8	0.66 (0.43, 1.01)	282	23.4	1.06 (0.75, 1.50)	102	20.6	0.60 (0.33, 1.08)	178	18.0	**0.54 (0.35, 0.84)**
Commercial/ Industrial	None (0%)	1728	34.0	295	28.1		183	23.5	1	277	24.9	1	386	23.6	1	175	26.3	1	412	25.2	1
	low	1674	32.9	293	28.3	0.99 (0.69, 1.43)	242	16.9	0.66 (0.41, 1.10)	290	22.1	0.86 (0.58, 1.27)	390	21.5	0.91 (0.65, 1.28)	121	29.8	1.37 (0.79, 2.38)	338	24.9	0.91 (0.64, 1.28)
	high	1683	33.1	326	29.5	1.06 (0.74, 1.50)	306	19.0	0.75 (0.47, 1.19)	272	23.9	0.96 (0.64, 1.42)	401	20.7	0.83 (0.59, 1.17)	91	28.6	1.28 (0.70, 2.35)	287	26.8	1.04 (0.73, 1.48)
Herbaceous vegetation	lowest tertile	2150	42.3	675	28.4	1	424	20.3	1	172	25.0	1	260	21.2	1	185	30.3	1	434	27.9	1
	middle	1584	31.2	188	28.2	0.99 (0.68, 1.42)	216	18.0	0.82 (0.53, 1.25)	335	25.1	1.01 (0.66, 1.55)	434	21.2	0.98 (0.67, 1.43)	103	23.2	0.69 (0.39, 1.21)	308	23.4	0.79 (0.56, 1.11)
	highest	1351	26.5	51	33.3	1.24 (0.67, 2.29)	91	18.6	0.94 (0.51, 1.65)	332	21.4	0.80 (0.52, 1.25)	483	23.0	1.11 (0.77, 1.61)	99	28.3	0.87 (0.50, 1.52)	295	24.4	0.85 (0.60, 1.20)
Sport / leisure	None (0%)	4179	82.2	806	27.9	1	473	20.7	1	732	22.8	1	1002	22.5	1	324	28.7	1	842	25.5	1
	low	473	9.3	57	29.8	1.13 (0.62, 2.05)	123	22.0	1.06 (0.64, 1.71)	61	34.4	**1.77 (1.01, 3.09)**	102	12.7	**0.48 (0.26, 0.89)**	27	22.2	0.61 (0.23, 1.61)	103	31.1	1.38 (0.87, 2.18)
	high	433	8.5	51	39.2	**1.83 (1.01, 3.30)**	135	12.6	**0.54 (0.3, 0.93)**	46	21.7	0.97 (0.47, 2.01)	73	27.4	1.28 (0.74, 2.19)	36	25.0	0.76 (0.34, 1.71)	92	19.6	0.70 (0.40, 1.21)
Bare surface	None (0%)	4820	94.8	821	28.4	1	676	20.0	1	806	23.3	1	1107	22.0	1	380	28.2	1	1030	25.5	1
	low	133	2.6	45	31.1	1.13 (0.59, 2.18)	25	16.0	0.73 (0.21, 2.01)	18	27.8	1.20 (0.42, 3.42)	35	17.1	0.73 (0.30, 1.80)	6	16.7	0.45 (0.05, 4.19)	4	50.0	3.43 (0.47, 25.21)
	high	132	2.6	48	31.3	1.12 (0.59, 2.13)	30	10.0	0.48 (0.11, 1.40)	15	33.3	1.77 (0.59, 5.30)	35	25.7	1.17 (0.54, 2.56)	1	0.0	N/A	3	0.0	N/A
Wetlands	None (0%)	4943	97.2	912	28.6	1	702	19.0	1	828	23.3	1	1160	22.2	1	366	28.1	1	975	25.7	1
	low	72	1.4	1	100.0	N/A	18	27.8	1.57 (0.49, 4.35)	4	50.0	2.69 (0.37, 19.53)	10	10.0	0.43 (0.05, 3.48)	7	28.6	1.09 (0.20, 6.08)	32	21.9	0.80 (0.34, 1.91)
	high	70	1.4	1	0.0	N/A	11	27.2	1.76 (0.37, 6.40)	7	42.9	2.14 (0.47, 9.73)	7	0.0	N/A	14	21.4	0.59 (0.16, 2.20)	30	23.3	0.87 (0.36, 2.08)
Water bodies	None (0%)	4581	90.0	880	28.2	1	674	19.7	1	786	23.3	1	1108	22.2	1	311	27.3	1	822	25.6	1
	low	257	5.1	16	31.3	1.08 (0.37, 3.15)	38	18.4	0.85 (0.34, 1.91)	29	31.0	1.40 (0.62, 3.16)	26	15.4	0.64 (0.22, 1.90)	29	37.9	1.56 (0.70, 3.50)	119	31.1	1.42 (0.92, 2.18)
	high	247	4.9	18	50.0	2.27 (0.88, 5.83)	19	10.5	0.49 (0.08, 1.76)	24	25.0	1.12 (0.43, 2.88)	43	18.6	0.77 (0.35, 1.69)	47	25.5	0.84 (0.41, 1.72)	96	18.8	0.71 (0.41, 1.23)
NDVI	lowest tertile	1838	36.2	526	28.1	1	439	19.4	1	248	23.0	1	356	21.9	1	15	26.0	1	254	29.9	1
	middle	1568	30.8	239	28.9	1.04 (0.74, 1.47)	209	19.1	1.03 (0.67, 1.56)	300	21.7	0.91 (0.60, 1.38)	471	20.6	0.90 (0.64, 1.27)	60	35.0	1.43 (0.39, 5.20)	289	25.6	0.78 (0.53, 1.16)
	highest	1679	33.0	149	30.2	1.10 (0.74, 1.65)	83	20.5	1.00 (0.53, 1.77)	291	26.1	1.20 (0.80, 1.79)	350	23.7	1.14 (0.79, 1.64)	312	26.6	1.01 (0.30, 3.33)	494	23.3	**0.70 (0.49, 0.99)**
VCDI	lowest tertile	1638	32.2	299	27.1	1	212	16.0	1	345	21.5	1	420	23.8	1	135	31.9	1	227	27.3	1
	middle	1555	30.6	278	29.5	1.12 (0.77, 1.61)	201	18.9	1.25 (0.74, 2.1)	295	21.0	0.99 (0.67, 1.44)	371	20.2	0.78 (0.56, 1.11)	109	31.2	0.86 (0.49, 1.53)	301	26.3	0.96 (0.65, 1.43)
	highest	1674	32.9	176	33.0	1.34 (0.89, 2.02)	318	22.0	1.50 (0.96, 2.4)	184	31.5	**1.64 (1.09, 2.47)**	360	22.5	0.93 (0.66, 1.31)	134	23.1	**0.57 (0.33, 1.01)**	502	24.3	0.86 (0.60, 1.24)

aOR: adjusted odds ratio; CI: confidence interval; N/A: not applicable due to 0 cells.; NDVI: the Normalized Difference Vegetation Index; VCDI: the Simpson's Diversity Index of Vegetation Cover.

N includes subjects with information of all a priori selected confounders: gender, maternal history of allergic diseases, parental educational level, and the number of older siblings. In LUKAS also living on farm and cohort. Analyses adjusted for a priori selected confounders.

† Percentage of eczema in tertiles.

TABLE S8. Results of the meta-analyses for the associations between land cover classes and greenness indices and the development of doctor-diagnosed eczema by the age of two in children from five cohorts with the objective outcome of doctor-diagnosed eczema (excluding HELMi cohort) in 250 m x 250 m grid.

		Doctor-diagnosed eczema by the age of two years				
				Heterogeneity		
Land cover classes and greenness indices	**Tertiles/classes**	**aOR**	**95%CI**	I^2	*p*	E
Coniferous forest	lowest tertile	1				
	middle	**1.22**	**1.03, 1.45**	0%	.86	F
	highest	**1.21**	**1.01, 1.45**	0%	.96	F
Mixed forest	lowest tertile	1				
	middle	1.18	0.99 1.42	0%	.82	F
	highest	1.10	0.91, 1.32	21%	.28	F
Broad-leaved forest	None (0%)	1				
	low	1.04	0.85, 1.26	7%	.37	F
	high	0.95	0.78, 1.14	27%	.24	F
Agricultural areas	None (0%)	1				
	low	0.85	0.56, 1.30	67%	.02	R
	high	1.22	0.99, 1.50	0%	.71	F
Transport infrastructure	None (0%)	1				
	low	0.87	0.73, 1.03	0%	.67	F
	high	**0.74**	**0.62, 0.89**	42%	.14	F
Residential areas	lowest tertile	1				
	middle	0.86	0.71, 1.03	54%	.07	F
	highest	1.04	0.87, 1.24	0%	.79	F
Commercial/ Industrial	None (0%)	1				
	low	0.95	0.80, 1.13	0%	.72	F
	high	0.99	0.83, 1.17	0%	.74	F
Herbaceous vegetation	lowest tertile	1				
	middle	0.90	0.75, 1.08	0%	.71	F
	highest	0.94	0.78, 1.14	0%	.65	F
Sport/ leisure	None (0%)	1				
	low	1.01	0.62, 1.64	67%	.02	R
	high	1.07	0.81, 1.42	39%	.16	F
Bare surface	None (0%)	1				
	low	1.04	0.67, 1.63	0%	.62	F
	high	1.23	0.78, 1.93	0%	.77	F
Wetlands	None (0%)	1				
	low	0.91	0.46, 1.79	0%	.62	F
	high	0.93	0.48, 1.80	0%	.44	F
Water bodies	None (0%)	1				
	low	1.31	0.96, 1.80	0%	.71	F
	high	0.91	0.65, 1.27	16%	.31	F
NDVI	lowest tertile	1				
	middle	0.92	0.77, 1.10	0%	.80	F
	highest	0.99	0.82, 1.20	27%	.24	F
VCDI	lowest tertile	1				
	middle	0.94	0.79, 1.12	0%	.70	F
	highest	1.02	0.73, 1.42	67%	.02	R

Individual cohorts were adjusted for *a priori* selected confounders: gender, maternal history of allergic diseases, parental educational level, and the number of older siblings. In LUKAS also living on farm and cohort. Cut-offs for tertiles/classes, see Table S5. Significant ($p < .05$) results are in bold text. *aOR,* adjusted odds ratio; *CI*, confidence interval; E, effect of heterogeneity; *F*, fixed effect; *NDVI,* the Normalized Difference Vegetation Index; *R*, random effect; *VCDI,* the Vegetation Cover Diversity Index.

TABLE S9. Meta-analyses for the associations between land cover classes and greenness indices and the development of doctor-diagnosed eczema by the age of two in children who had lived entire two years in the birth address in 250 m x 250 m grid in all cohorts.

		Doctor-diagnosed eczema by the age of two years									
		All six cohorts					Not moved until age of two years				
				Heterogeneity					Heterogeneity		
Land cover classes and greenness indices	**Tertiles/classes**	**aOR**	**95% CI**	I^2	*p*	E	**aOR**	**95% CI**	I^2	*p*	E
Coniferous forest	lowest tertile	1					1				
	Middle	**1.19**	**1.01, 1.39**	0%	.86	F	1.17	0.96, 1.42	0%	.54	F
	Highest	1,16	0.98, 1.38	0%	.81	F	1.16	0.94, 1.42	0%	.59	F
Mixed forest	lowest tertile	1					1				
	Middle	**1.21**	**1.02, 1.42**	0%	.87	F	**1.32**	**1.08, 1.61**	0%	.90	F
	Highest	1.07	0.90, 1.28	9%	.36	F	1.15	0.93, 1.41	10%	.35	F
Broad-leaved forest	None (0%)	1					1				
	Low	1.06	0.88, 1.27	0%	.48	F	1.10	0.89, 1.36	0%	.61	F
	High	0.97	0.81, 1.15	15%	.32	F	0.98	0.80, 1.20	0%	.44	F
Agricultural areas	None (0%)	1					1				
	Low	0.93	0.64, 1.36	64%	.02	R	0.99	0.67, 1.46	57%	.04	R
	High	1.20	0.98, 1.48	0%	.77	F	1.20	0.95, 1.51	0%	.52	F
Transport infrastructure	None (0%)	1					1				
	Low	0.86	0.73, 1.01	0%	.78	F	0.95	0.79, 1.15	47%	.09	F
	High	**0.77**	**0.65, 0.91**	35%	.17	F	**0.76**	**0.62, 0.93**	45%	.11	F
Herbaceous vegetation	lowest tertile	1					1				
	Middle	0.89	0.75, 1.05	0%	.81	F	0.84	0.69, 1.02	26%	.24	F
	Highest	0.94	0.78, 1.13	0%	.78	F	0.98	0.79, 1.21	0%	.52	F
NDVI	lowest tertile	1					1				
	Middle	0.94	0.79, 1.11	0%	.87	F	0.96	0.78, 1.17	0%	.88	F
	Highest	0.99	0.83, 1.19	8%	.36	F	1.06	0.85, 1.31	0%	.53	F
VCDI	lowest tertile	1					1				
	Middle	0.97	0.82, 1.14	0%	.66	F	0.95	0.78, 1.16	0%	.61	F
	Highest	1.09	0.81, 1.46	65%	.01	F	1.03	0.75, 1.43	61%	.02	R

Individual cohorts were adjusted for *a priori* selected confounders: gender, maternal history of allergic diseases, parental educational level, and the number of older siblings. In LUKAS also living on farm and cohort. Cut-offs for tertiles/classes, see Table S5. Significant ($p < .05$) results are in bold text. *aOR*, adjusted odds ratio; *CI*, confidence interval; E, effect of heterogeneity; *F*, fixed effect; *NDVI*, the Normalized Difference Vegetation Index; *R*, random effect; *VCDI*, the Vegetation Cover Diversity Index.

FIGURE LEGENDS

FIGURE S1. The directed acyclic graph (DAG) showing the rationale for confounders.

FIGURE S2. Grid sizes around the residential locations. Yellow points are residential locations of participants at birth (spatially anonymized). The white grid represents the predefined grid size of Statistics Finland. Yellow box represents 250 m x 250 m grid size, blue box 750 m x 750 m grid size and red box 1250 m x 1250 m grid size.

FIGURE S3. Box-plots of the **(A)** percentages of land cover classes, and **(B)** greenness indices of NDVI and VCDI in children with (grey) and without (white) doctor-diagnosed eczema by the age of two years (DD eczema by 2y) in six Finnish birth cohorts. The boxplots present 5th percentile, first quartile, median, third quartile, and 95th percentile of the values in 250 m x 250 m grid. *HELMi*, Health and Early Life Microbiota; *KuBiCo*, Kuopio Birth Cohort; *NDVI*, the Normalized Difference Vegetation Index; *VCDI*, the Vegetation Cover Diversity Index.

FIGURE S4. Heat maps illustrating the Spearman correlations between all land cover classes and greenness indices **(A)** in the grid of 250 m x 250 m, **(B)** in the grids of 250 m x 250 m (1) and 750 m x 750 m (2), and (**C**) in the grids of 250 m x 250 m (1) and 1250 m x 1250 m (3).

FIGURE S5. Meta-analyses for the associations between birth season and development of doctor-diagnosed eczema by the age of two years in 250 m x 250 m grid in all cohorts. For each study, the size of the box is proportional to the precision (inverse of variance) of the study. The combined estimate from the meta-analysis is indicated by the Random effects model (due to high heterogeneity between studies) at the bottom of each figure.

aOR, adjusted odds ratio; *CI*, confidence interval; *HELMi*, Health and Early Life Microbiota; I^2: percentage of variation across studies that is due to heterogeneity rather than chance or an intuitive and simple expression of the inconsistency of studies' results; *KuBiCo*, Kuopio Birth Cohort.

FIGURE S6. Meta-analyses for the associations between land cover classes and development of doctor-diagnosed eczema by the age of two years stratified by the season of birth in 250 m x 250 m grid in all cohorts; **(A)** coniferous forest, **(B)** mixed forest, **(C)** broad-leaved forest **(D)** agricultural areas, **(E)** the Normalized Difference Vegetation Index **(**NDVI), and **(F)** the Vegetation Cover Diversity Index (VCDI). *aOR*, adjusted odds ratio; *CI*, confidence interval; *HELMi*, Health and Early Life Microbiota; *KuBiCo*, Kuopio Birth Cohort. Common effect model represent pooled effects across cohorts using fixed effect models, except models where heterogeneity was significant ($p < .05$): those random effects are marked with ^ sign after values of aOR and 95%CI.