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Contacts with environmental biodiversity affect human health: links revealed during the initial waves of the COVID-19 pandemic

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The gradual decrease in the prevalence of serious infectious diseases over the last century has been followed by increase in so called "modern" diseases, including allergies, chronic inflammatory conditions, psychiatric, and metabolic disorders. Between 2019 and 2022, public awareness of the threat of infectious diseases in humans was renewed by the global pandemic of a new type of a coronavirus, the SARS-COV-2. This public interest opened improved possibilities to test hypotheses on the factors associated with inter-individual variation in susceptibility to infectious and "modern" diseases. Based on the Hygiene hypothesis and Biodiversity hypothesis, we predicted that contacts with natural environment and wildlife in childhood and/or in adulthood can improve general health and decrease the risks of severe COVID-19 progression or prevalence of the "modern" diseases, namely the allergies. Here we report the results of an online, self-evaluating questionnaire survey conducted in the Czech Republic, where we contrasted selected health issues, and linked them to the living environment, including the level of contacts with biodiversity. In a sample of 1188 respondents, we revealed a significant association of time spent in nature or contacts with biodiversity with physical and mental health, or incidence of allergies. This is unlike the COVID-19 progression, which was related to age, physical health, smoking, allergies, and interaction of age with smoking, but not to contacts with the natural environmental diversity. Our findings regarding to physical and mental health and allergies are in agreement with the Biodiversity hypothesis of allergy and, linking human and environmental health, they urge for One Health approach application.

Keywords Allergies, Biodiversity antigen richness, Civilization diseases, Contacts with nature, Infectious diseases, Wildlife

Dramatic changes in the human lifestyle over the past century significantly shifted various physiological regulations from their optima earlier selected throughout evolution[1]. Recently, especially in high-income countries we have observed a massive increase in health disorders that can be linked to inflammation, such as increased susceptibility to immunopathologies and higher incidence of allergies[2,3]. These current health challenges are multifactorial, complex and global[4]. Although not yet clearly recognised, these issues may be related to decreased environmental health.

Derived from the Hygiene hypothesis[5], the Biodiversity hypothesis predicts the importance of contacts of individuals with heterogeneity of antigens derived from the natural environment, including pathogens and symbionts[6]. During ontogenetic development, immune system harnesses the richness of environmental antigens to set an optimal regulation of immune tolerance, balancing the affordable protection against the pathogens with costs resulting from immunopathology in a given environmental context[7–9]. Combined effects of the contacts with microbes and parasites naturally colonising host bodies during childhood and also later during life are expected to contribute to immunomodulation[10]. Absence of various immunomodulatory compounds in the modern urban environment can alter tolerogenic immune responses to common antigens into exaggerative pro-inflammatory responses[11]. A shift has been suggested in the immune regulation balance from Treg/Th2-IgA-pruducing responses towards Th1 responses combined with IgE production responsible for exaggerated tissue damage in reaction to recognition of natural antigens[12,13]. Such changes in human–environment balance

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modulating immune regulation can also be tracked through the health trends indicated in population surveys[14]. Despite to certain level subjective, self-administered questionnaires used for epidemiologic surveys show good reproducibility[15] and offer important insights into the environmental associations with diseases[16], although their ability to reveal direct causality is limited.

Although proposed primarily for allergies, the impact of such regulation can be much wider and affect also other diseases, including infections, where pathology often results from the inflammatory over-responsiveness[17]. Similar to regulation of allergies, also regulation of immune responses to pathogens can be modulated by environmental changes that are associated with altered composition of the host's symbiotic microbiota[18,19]. Current results show that different people responded differently to a novel coronavirus infection caused by the SARS-CoV-2 virus, assumingly dependent on their genetic background[20], but also lifestyle and living environment[21,22].

Until recently, advances in medical care diminished the public awareness of the health threats resulting from infectious diseases[23]. However, the global pandemic of SARS-CoV-2 between 2019 and 2022, causing respiratory disease COVID-19, renewed the general interest in infectious diseases and facilitated public health questionnaire studies. Here we hypothesise that through decreased tolerogenic immune regulation, the lack of contacts with natural environmental diversity (biodiversity-related antigen richness) could increase the risk of COVID-19 infection and/or its severity, having in parallel analogous impact on selected "modern" diseases including allergies. We predict that controlling for age, sex, body mass, health (i.e. composite state of physical and mental well-being), sport activities and socio-economic background, on a population level the self-reported COVID-19 disease progression will be milder, allergies less frequent and perception of health improved in people experiencing increased direct contacts with wildlife, domestic animals, and plants that serve as sources of natural biodiversity of antigens.

Methods

Data structure and respondents

This survey study was pre-registered on OSF (created: 2021-05-18; https://osf.io/x4zyv/?view_only=f22560412c55449daa22a6266b2cb842). We used the tool Qulatrics (https://www.qualtrics.com/) to create an online questionnaire. This questionnaire was available from 27 May 2021 through our website (https://web.natur.cuni.cz/zoology/eei/) and the site link was sent to various organisations involved in nature protection, animal and plant care (zoological and botanical gardens), schools and universities, and shared on social media used throughout the Czech Republic. Before commencing the questionnaire, participants received clear information that the study was performed for research purposes, and that the participation is voluntary and anonymous. To participate in the study, respondents had to provide informed consent by clicking the respective button. The questionnaire took approximately one hour to complete. The Institutional Review Board of the Faculty of Science, Charles University approved the project and the process of obtaining informed consent (No. 2020/25). The study was performed in accordance with relevant guidelines and regulations.

In the questionnaire's anamnestic section, respondents were asked about their age, sex (assigned at birth), height, weight, and selection from multiple-choice lists on previous infections, vaccination, and allergies. They also answered three questions evaluating their current, usual and before-COVID general physical health condition and three analogous questions on their general mental health condition. Both variables describe composite health expressed as self-perceived condition of wellbeing of the respondents. Further, the respondents answered 10 questions regarding their living, work, and childhood environment (7-item scale from the countryside to metropolis), commuting, smoking, and daily hygiene. Next, the respondents were asked about their outdoor activities, contacts with plants and animals, as well as overall environmental diversity. Respondents used Likert scales for their answers, or they wrote in the exact number or chose an exact option. Crucially, they had to answer whether they were tested positively for SARS-CoV-2 and what was the disease progression (subjective severity assessment of the disease course on scale from asymptomatic to hospitalization on intensive care unit). The questionnaire containing the original questions and all answers obtained (in Czech) are available in Supplementary Material 1. After seven months we closed the survey and downloaded the available data. We tested selected health parameters (physical and mental health, SARS-CoV-2 infection, COVID-19 progression and presence of allergies) as the variables dependent on selected environmental and lifestyle factors. All variables with multiple levels in scale were transformed to a numeral scale and all yes/no answers were treated as factors. Parameters indicating diversity, such as diversity of environmental activities, or animals and plants kept in households, or pathogen-borne diseases throughout life, were summed as the total number of realised options and further used as a continuous variables. All variables used for the statistical analysis are explained in detail in Table S2.1 in the Supplementary material 2. All pre-processed data used for the statistics are listed in Table S2.2. Original data are provided in Table S2.3. We used a correlation matrix and Principal Component Analysis (PCA) to reduce the number of individual variables adopted in our statistical models (see Table S2.4). Importantly, the variable "contact with environmental diversity" was constructed as PC1 scores obtained from the PCA of all surveyed variables connected with activities conducted in nature or concerning animals, plants or wildlife. The PC1 score provides a more accurate estimate of the environmental diversity than any variable surveyed alone.

Dataset and statistics

In total, we collected 1811 survey responses which is comparable to datasets obtained from other similar questionnaire-based health surveys[24,25]. We first filtered out any answers from unfinished survey responses, retaining 1188 complete responses for the analysis. We created two datasets, first one with all the valid responses and a second one containing only the subset of self-reported SARS-CoV-2 positive individuals (327 responses).

First, to understand which clinical and environmental parameters drive the general perception of health of the responders in our dataset, we tested how the self-reported usual physical health state was associated with incidence of allergies, number of infectious diseases during life, and selected lifestyle factors, including the contacts with various environmental diversity parameters (model structure shown in Table S2.5). In case of the significance of the composite variable contact with environmental diversity in a model, the statistics was repeated, using the original individual variables: intensity of the contacts with natural environment, intensity of the contacts with animals, diversity of animals in contact, diversity of plants in contact, time spent in nature, diversity of activities in nature at presence and diversity of activities in nature during childhood (Table S2.4). Then, using similar approach, we tested analogous associations also for the self-reported mental health, SARS-CoV-2 infection and COVID-19 progression. Finally, we tested the model with incidence of allergies adopted as a response variable, testing directly the Biodiversity hypothesis (see all the full models listed in Table S2.5). In all cases the relationships were tested using linear models (LMs) and in the case of a categorical variable (0/1) by the general linear models (GLM) in the 'Ime4 package' in R studio version 3.6.2[26]. Minimum adequate models (MAMs; here defined as models with all terms significant at $p \le 0.05$) were identified by backward elimination of non-significant terms from the full models. All backward elimination steps in the models were verified by changes in deviance with an accompanying change in degrees of freedom (ANOVA) and Akaike information criterion (AIC), using F-statistics.

Results

The analysed dataset contained 768 women (mean age = 37.99, sd = 12.80) and 420 men (mean age = 38.97, sd = 13.14). SARS-CoV-2 infection (codes: negative = 861, positive = 327) was reported by both women (205, i.e. 26.69% were positive) and men (122, i.e. 29.05% were positive). The effect of sex on self-reported SARS-CoV-2 positivity was not significant (OR = 0.889, CI 95 = 0.683–1.160, $p < 0.386$).

The feeling of self-reported physical healthiness (Physical health) was significantly negatively associated with the number of different infection diseases during life, ($p < < 0.001$, Fig. S1) and positively with commuting ($p = 0.010$, Fig. S2), sports ($p = 0.009$, Fig. S3), number of hours of sleep ($p = 0.033$, Fig. S4) and time spent in nature ($p < < 0.001$, MAM1, Table 1; Table S3.1; Fig. 1).

Similar to physical health, also the self-evaluated mental health, that was sex-dependent ($p = 0.003$, Fig. S5), was negatively associated with the number of different infections during life ($p = 0.033$, Fig. S6). Surprisingly, we identified a weak negative association of the Mental health with the diversity of activities performed in nature ($p = 0.021$, Fig. S7). This is contrasting the significant positive relationships of the Mental health with age ($p < < 0.001$, Fig. S8), commuting ($p = 0.039$, Fig. S9), number of hours of sleep ($p = 0.005$, Fig. S10), time spent in nature ($p < < 0.001$, Fig. S11) and intensity of the contacts with natural environment ($p = 0.013$, MAM2, Table 1; Table S3.2; Fig. 2).

The infection of SARS-CoV-2 was in negative relationship with physical health ($p < < 0.001$, Fig. 3) and in positive relationship with number of people in the household ($p = 0.001$, Fig. S12), and weakly also with the regular sport activities ($p = 0.033$, Fig. S13) and number of infectious diseases during lifetime ($p = 0.046$, MAM3, Table 1; Table S3.3; Fig. S14).

Next, in the subset of the SARS-CoV-2-positive individuals (n = 327), we tested for the effect of the selected health and environmental parameters on the progression of the COVID-19 disease, expressed as occurrence of self-reported symptoms on a scale from no to severe. The results show negative association of the COVID-19 severity with physical health ($p < < 0.001$, Fig. S15) and its positive association with smoking ($p = 0.038$, Fig. S16), incidence of allergies ($p = 0.003$, Fig. S17) and age ($p < 0.001$, Fig. 4). Furthermore, we detected significant interaction of age with smoking ($p = 0.009$). Our analysis did not show any link between the COVID-19 progression and contacts of the individual with natural environment or its diversity (MAM4, Table 1; Table S3.4).

Finally, we focused on the relationship between the natural environment diversity and incidence of allergies. Our analysis revealed significant positive effects of the number of infectious diseases during life ($p < < 0.001$, Fig. S18), childhood environment (scaled from countryside to metropolis, $p = 0.005$, Fig. 5) and hygiene ($p = 0.005$, Fig. S19) and significant negative effect of the contacts with natural environment diversity ($p = 0.024$, MAM 5, Table 1; Table S3.5; Fig. 6) on the incidence of allergies.

Discussion

Our results indicate that the general self-reported health status of an individual (including physical and mental health and allergies incidence), which further affects the outcomes of infectious diseases, including COVID-19 progression, is linked with the time spent in nature, intensity of the contacts with nature and their diversity. We evidenced positive associations between the time spent in nature and physical health, and between the intensity of the contacts with natural environment and mental health. Furthermore, we reveal negative association between the diversity in the contacts with natural environment and incidence of allergies. Our data also show negative association of the SARS-CoV-2 infection with physical health and several lifestyle parameters and dependence of the COVID-19 progression on age, physical health, allergies, and smoking. However, in our dataset we were not able to directly link the SARS-CoV-2 infection or the COVID-19 severity with any parameter describing the level of contacts with nature or environmental diversity.

During the last century, human population worldwide experienced important shifts in prevalence and effects of diseases of various types. While improved hygiene and medical care decreased mortality due to microbial infections, the modern societies are experiencing a continuous increase in prevalence of allergies, autoimmune and chronic inflammatory diseases, as well as psychiatric and metabolic disorders[27–30]. Number of studies indicated the importance of contacts with nature on health and condition[31]. The same pattern was observed in our current results. Multiple lines of evidence support the fact that living in an environment enriched with biodiversity is associated with decrease in overall early mortality in adults[32]. Apart from the benefits gained through exercise related to time spent in nature that improves body condition, biodiversity itself can provide positive

Minimum adequate model	Estimate	SE	Df	F	P
MAM1: physical health ~ number of different infection diseases + commuting + sport + sleep + time spent in nature			6/1058	3654.4	< < 0.001
Number of different infection diseases	− 3.127	0.572	1/1058	29.941	< < 0.001
Commuting	0.538	0.209	1/1059	6.610	0.010
Sport	1.089	0.421	1/1059	6.687	0.009
Number of hours of sleep	1.079	0.506	1/1059	4.541	0.033
Time spent in nature	2.120	0.383	1/1059	30.652	< < 0.001
MAM2: mental health ~ sex + age + number of different infection diseases + commuting + number of hours of sleep + intensity of contacts with natural environment + time spent in nature + diversity of activities in nature			9/1064	1466.5	< < 0.001
Sex (males)	4.071	6.751	1/1056	8.703	0.003
Age	0.265	1.380	1/1056	23.146	< < 0.001
Number of different infection diseases	− 1.512	0.711	1/1056	4.530	0.034
Commuting	1.793	0.262	1/1056	4.292	0.039
Number of hours of sleep	3.331	0.632	1/1056	8.038	0.005
Intensity of contacts with natural environment	3.027	1.336	1/1056	6.2143	0.013
Time spent in nature	3.027	0.535	1/1056	32.006	< < 0.001
Diversity of activities in nature	− 1.294	0.560	1/1056	5.354	0.021
MAM3: SARS-CoV-2 ~ physical health + number of different infection diseases + number of people in household + sport			5/1070	96.294	< < 0.001
Physical health	− 0.004	0.001	1/1066	30.635	< < 0.001
Number of people in household	0.030	0.009	1/1066	10.597	0.001
Sport	0.022	0.010	1/1066	4.551	0.033
Number of different infection diseases	0.029	0.015	1/1066	3.991	0.046
MAM4: COVID progression ~ age + smoking + physical health + allergies + age:smoking			5/293	8.842	< < 0.001
Physical health	− 0.011	0.003	1/289	18.049	< < 0.001
Age	0.028	0.008	1/289	11.649	< 0.001
Allergies	0.323	0.108	1/289	8.947	0.003
Age: smoking	− 0.014	0.005	1/289	6.909	0.009
Smoking	0.420	0.202	1/289	4.332	0.038
MAM5: allergies ~ number of different infection diseases + childhood environment + hygiene + contact with environmental diversity			5/1071	188.7	< < 0.001
Number of different infection diseases	0.0528	0.016	1/1060	10.722	0.001
Childhood environment	0.023	0.008	1/1067	8.158	0.005
Hygiene	0.042	0.015	1/1067	7.926	0.005
Contact with environmental diversity	− 0.008	0.004	1/1067	4.974	0.026

Table 1. Complete list of the Minimum adequate models (MAMs). *Df* degrees of freedom (expressed as number of parameters/residual Df), *MAM* minimal adequate model, *SE* standard error.

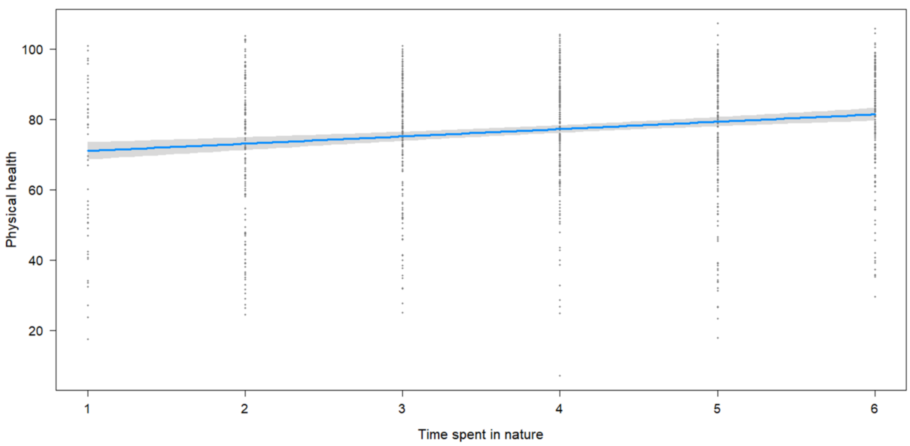

Figure 1. Positive association between the physical health and time spent in nature. Physical health is scaled from 0 (worst physical health), to 100 (best physical health). Time spent in nature is scaled from 1 (no regular time spent in nature), to 6 (every day activity in nature). The graph was created using the *visreg* function, which visualises the response variable treated on the effects of other significant variables represented in the minimum adequate model (MAM 1, Table 1).

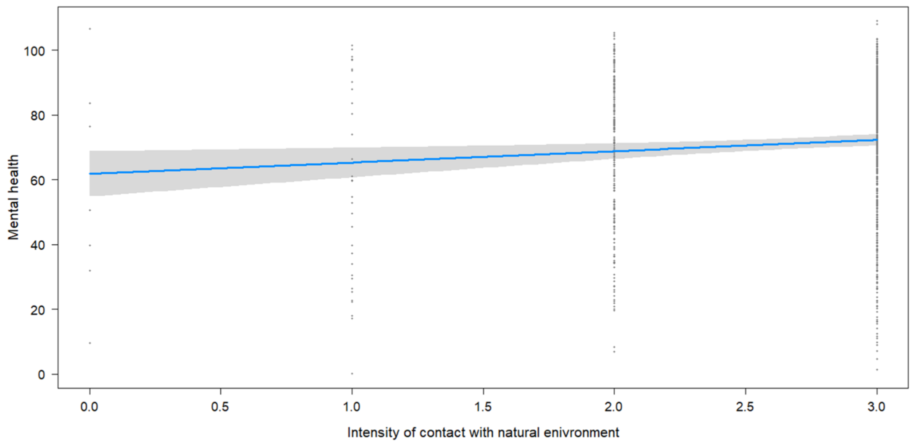

Figure 2. Positive association of mental health and contact with nature. Mental health is scaled from 0 (bad mental health) to 100 (best mental health). Contact with nature is scaled from 0 (minimal or no contact) to 3 (intensive contact). The graph was created using the *visreg* function which visualises the response variable treated on the effects of other significant variables in the minimum adequate model (MAM 2, Table 1).

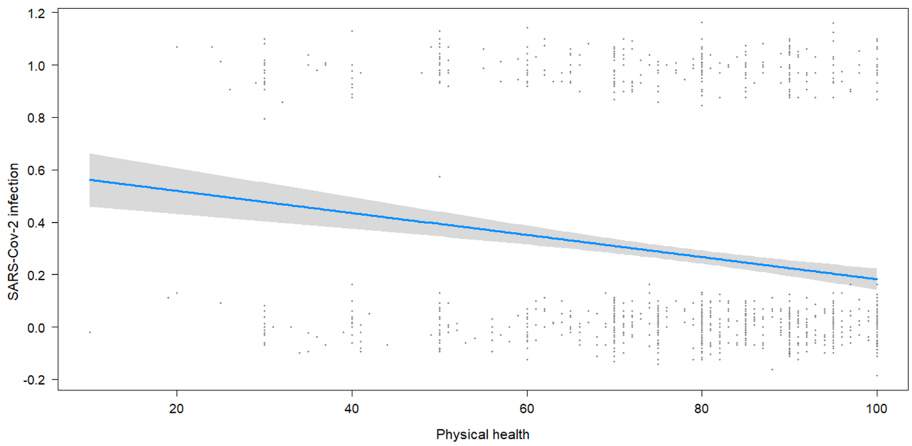

Figure 3. Negative association of SARS-Cov-2 infection with physical health. Self-reported physical health is expressed on a scale from 0 (worst physical health) to 100 (best physical health). The graph was created using the *visreg* function which visualises the response variable treated on the effects of other significant variables in the minimum adequate model (MAM 3, Table 1).

effects. Intensity of the contacts with natural environments and time spent in nature were reported to positively affect the mental health[4,33,34]. Even early life exposure to nature has been repeatedly shown to contribute to mental health later in life[35]. In line with that, our data suggest the link between intensity of the contacts with natural environmental diversity and mental health. This relationship could result from psychological effects of natural environmental structures or from the variation in access to sunlight[36–38]. Surprisingly, we detected also the positive association between the commuting time and both physical and mental health. This might support the Sunlight hypothesis[39–41] suggesting benefits resulting from increased vitamin D synthesis in individuals spending more time outdoors. Alternatively, it has been previously suggested that commuting might represent a mild eustress which improves the physical and mental resilience of an organism[42]. Another possibility is a positive effect of mild pathogen exposure during commuting (resulting from increased contacts with other people in public transportation), consistent with the Hygiene hypothesis[43].

The Hygiene hypothesis[2,44] and the related Biodiversity hypothesis[6] can also directly explain the association between health and the intensity of the contacts with nature revealed in our study. It has been suggested that human immune system is evolutionarily adapted to maintain its optimal regulatory balance between pro-inflammatory and tolerogenic responsiveness when stimulated by the antigenic diversity of the original human living environments[6,11]. Human immunity evolved in close contacts with diversified wildlife, but also many natural commensals and pathogens. Antigenic diversity presented to immune cells guides the immune system development and regulation[7–9,12]. Yet, it is a trend of modern human lifestyle to inhabit urban environments that are poor in antigenic diversity and providing diminished contacts with natural microbial communities[13]. The

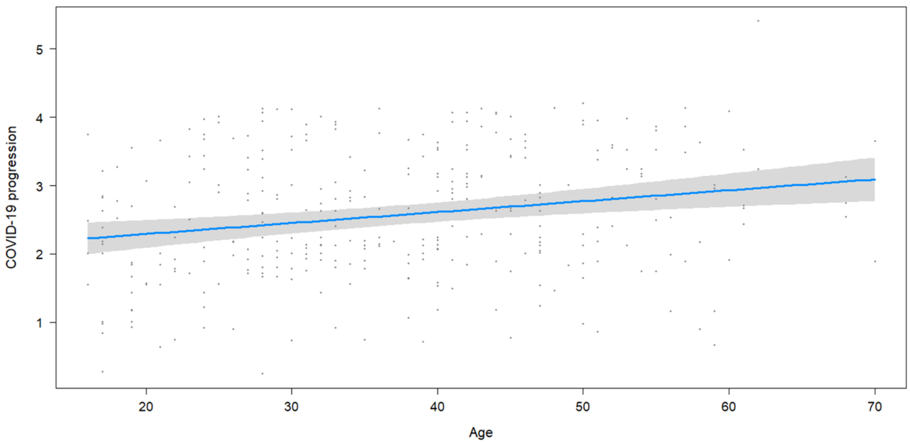

Figure 4. Positive association of the COVID-19 progression symptoms with age (years). Self-reported COVID-19 infection symptoms on a scale from 0 (no symptoms) to 5 (very severe symptoms) were more severe progression was reported in individuals of advanced age. The graph was created using the *visreg* function which visualises the response variable treated on the effects of other significant variables in the minimum adequate model (MAM 4, Table 1).

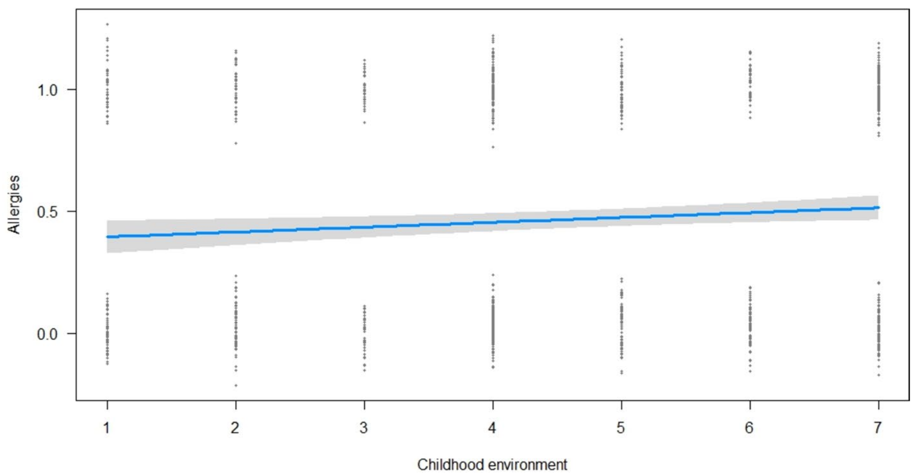

Figure 5. Positive association of allergies incidence with childhood environment. The variable childhood environment is scaled from 1 (countryside) to 7 (metropolis). The graph was created using the *visreg* function which visualises the response variable treated on the effects of other significant variables in the minimum adequate model (MAM 5, Table 1).

decrease in antigenic diversity can impair immunological tolerance and promote inflammatory pathways that eventually contribute to progression of infectious diseases and health disorders[6]. This may be masked by other environmental factors, such as for example smoking[45,46], which had also significant effect in our analysis. In our dataset, we were not able to directly link the SARS-CoV-2 infection or the COVID-19 severity with any parameter describing the level of contact with nature or environmental diversity. However, an indirect connection can be still assumed through the links of the COVID progression to nature-associated physical health.

The antigenic diversity loss is a multi-factorial process that includes excessive hygiene, life in artificial environment inside the buildings, and change in diet, further coupled with global biodiversity loss and stressful lifestyle disrupting the physiological balance[47,48]. Natural composition of microbiome sets tolerogenic immune responses mediated though Treg cells and IgA antibodies[12]. Shifts in microbial diversity can trigger pro-inflammatory responses against common natural antigens, activating Th1 cells and IgE production. This may elicit chronic inflammation which acts as the causative agent in many “modern” diseases. This view is supported by evidence linking environmental variation to immune-related disorders. For example, children growing up on farms were reported to suffer less frequently from allergies[24,49]. In line with the assumed physiological mechanism, enrichment of the individual microbiome with commensal symbionts can attenuate chronic inflammatory disorders[9,50]. In our data, adults that grew up during their childhood in bigger cities suffered more commonly with allergies. Furthermore, individuals experiencing closer contacts with natural environments that are rich in biodiversity suffered less frequently from allergies than individuals lacking these contacts. Therefore, our results support the

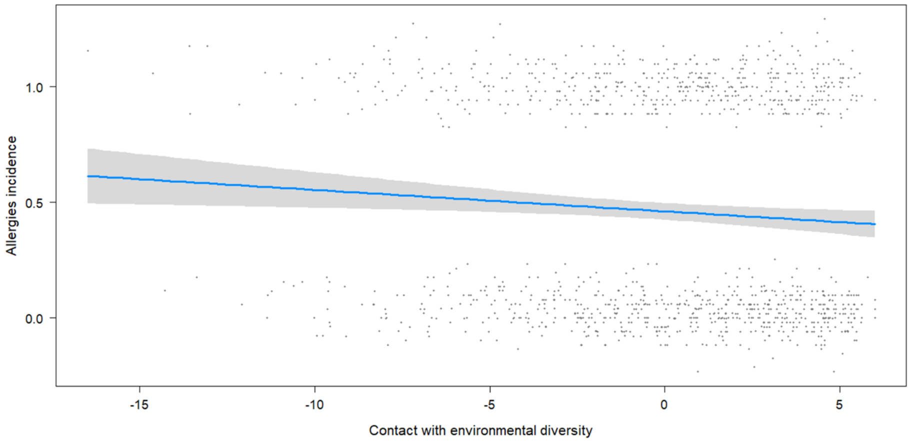

Figure 6. Negative association of the incidence of allergies and contact with environmental diversity. The variable "Contact with environmental diversity" represents PC1 score obtained from the PCA of variables: intensity of the contacts with natural environment, intensity of the contacts with animals, diversity of animals in contact, diversity of plants in contact, time spent in nature, diversity of activities in nature now and diversity of activities in nature during childhood. The graph was created using the *visreg* function which visualises the response variable treated on the effects of other significant variables in the minimum adequate model (MAM 5, Table 1).

Hygiene hypothesis and Biodiversity hypothesis of allergies and highlight the adverse effects of biodiversity loss in the anthropogenic environments on human health.

It has been suggested that the pattern linking the contacts with environmental diversity with health could be driven by the direct positive effects of sports-related physical training[51]. However, this is unlikely in our data because our analysis controlled for the direct effects of sports. Sports were revealed as positively contributing only to physical health and SARS-CoV-2 infection incidence which is in accordance with the previous study by Flegr et al.[46]. Yet, it has to be admitted that our dataset and results suffer from several limitations. First, the survey is based on auto-selection of the respondents, which could bias the frequencies of certain trait combination in the dataset. Second, the respondents' subjective assessment of their own health or mental state could mismatch their objective clinical state. Third, when the respondents' past experience is concerned, a self-reported survey may be biased also by variation in the individual memory among the respondents. These issues are common to all public surveys based on self-reported records. In addition to this, a persistent challenge in cross-sectional studies, including ours, is that they cannot answer the causality of the observed associations. Previous research has shown that in addition to correlative results, there is also causal, physiological and immunological, evidence supporting the beneficial effects of living in natural environments and having contacts with biodiversity[52,53]. Nevertheless, such evidence is still limited and conclusively addressing this question would require a different study design. Finally, it should be noted that a more detailed analysis of contribution of individual factors was hampered by a lower than expected number of respondents. We had anticipated the participation of approximately 10,000 subjects in the preregistration. However, this milestone was not achieved, possibly due to a prevailing weariness regarding COVID-related research within the Czech population during the latter stages of the pandemic. Nevertheless, the number of responses obtained was still sufficient for testing the main hypotheses and comparable to other similar questionnaire studies targeting public health[24,25].

Conclusions

Our results suggest that self-reported health condition, including incidence of allergies, physical and mental health, is associated with intensity and diversity of the contacts with natural environmental diversity. While multiple explanations can be offered, these findings are in agreement with the Biodiversity hypothesis, linking environmental antigenic composition with modulation of immune function and resistance to immunopathologies. Modern lifestyle related to environmental biodiversity loss leads to disruption of the long-evolved homeostasis in physiological processes, allowing the outbreak of "modern" diseases including chronic inflammatory diseases, allergies, metabolic and psychiatric disorders. Our research thus indicates the value of the human contacts with nature and natural diversity of antigens in the environment. Since the frequency and quality of the human contacts with nature and wildlife are conditioned by the environmental health, this study aids to reveal the importance of biodiversity conservation in the human living environment for the good health maintenance, consistent with the concept of One Health.

Data availability

Data is provided within the manuscript or supplementary information files.

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Competing interests

The authors declare no competing interests.

Additional information

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