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An approach to the asthma-protective farm effect by geocoding: Good farms and better farms

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Abstract

Background: The highly consistent association of growing up on a farm with a reduced asthma risk has so far been attributed to direct farm exposure. In contrast, geographic determinants of the larger environment have never been assessed. In this study, the effects of proximity to farms and environmental variables in relation to the residential address on asthma and atopy were assessed.

Methods: Addresses of 2265 children of the Bavarian arm of the GABRIELA study were converted into geocodes. Proximity to the nearest cow farm was calculated, and environmental characteristics were derived from satellite data or terrestrial monitoring. Bacterial diversity in mattress dust samples was assessed in 501 children by sequencing of the 16S rRNA amplicons. Logistic regression models were used to calculate associations between outcomes and exposure variables.

Results: Asthma and atopy were inversely associated with the presence of a farm within a radius of maximum 100 m. The environmental variables greenness, tree cover, soil sealing, altitude, air pollution differed not only between farm and non-farm children but also between farm children with and without another farm nearby. The latter distinction revealed strong associations with characteristics of traditional farms including a broader diversity of microbial exposure, which mainly contributed to the protective effect on asthma. In non-farm children, the protective effect of a farm nearby was completely explained by consumption of farm milk.

Conclusions: Clustering of farms within a neighborhood of 100 m is strongly associated with the protective effect on asthma and may represent a more traditional style of farming with broader microbial exposure.

KEYWORDS

asthma, bacterial diversity, farming, geocoding, greenness, PM_{10}, soil sealing

1 | INTRODUCTION

Fresh air, wide green areas at the foot of the mountains, lakes, and trees around are our first associations with farm life in the alpine areas, where the strong and highly consistent asthma- and atopy-protective effect of growing up on a farm has been studied for years.[1] But why have these exposures never been in the focus of research into the "farm effect"?

Obviously, scarcity of environmental data may explain this. In the current era of profound environmental changes, however, climate, vegetation, weather, air pollution, and land use are closely monitored by satellites and networks of terrestrial measurement stations. These provide data on, for example, ozone (O_3), nitrogen dioxide (NO_2), particulate matter ≤ 10 μm (PM_{10}), greenness, tree cover, soil sealing, altitude above sea level, and population density, thereby suitably modeling the above invoked picture.

Many of these environmental exposures have been implied in disease causation, exacerbation, and vice versa in primary and secondary prevention. Examples for risk factors are pollution and traffic proximity,[2] whereas beneficial effects are discussed for greenness,[3,4] forest bathing,[5] altitude therapy,[6] and soil contact.[7] Geocodes, that is, a finely meshed virtual network of coordinates coating the entire globe, now provide a link between satellite and terrestrial data to population-based studies and thus to disease occurrence.

So far, the main farm-related exposures involved in the protective farm effect on asthma and allergies have been found in consumption of farm milk[8,9] and exposure to cattle and animal sheds,[10,11] or more precisely endotoxin and microorganisms.[12,13] These findings were also replicated in the large GABRIEL Advanced (GABRIELA) studies.[14-16]

Admittedly, farming practices are regionally very different (eg, traditional farming in alpine areas vs North American ranching) and farm exposure does not only exert beneficial effects; rather proximity to a farm has been reported repeatedly as a risk factor for respiratory health.[17-19] Therefore, we hypothesized that physical proximity to a farm might impact the protective effect of growing up on a farm on asthma and allergies.

The aim of this analysis was to determine differences in residential exposures of farm children and their classmates and to quantify the protective effects of these exposures on asthma and atopy.

2 | METHODS

2.1 | Study design and selection of analysis population

The GABRIELA study was a multicenter survey conducted in rural areas of 4 different European countries.[20] Of the 11 183 children in the Bavarian arm, 2573 were invited for environmental exposure assessment. In 501 and 429 children, respectively, microbial diversity and endotoxin levels were assessed in mattress dust samples.

The Bavarian arm of the GABRIELA study was approved by the institutional review boards of the Bavarian Medical Association, and informed consent was obtained from the parents. The usage of address data was approved by the data protection officers of the University Hospitals Munich and the Bavarian State Ministry for Food, Agriculture, and Forestry.

2.2 | Definitions of outcomes and variables

Asthma was defined as a physician's diagnosis of asthma, an obstructive bronchitis, use of an asthma inhaler ever, or wheezing during the last 12 months. Farm exposure was categorized based on questionnaire data into 3 strata: (i) children living on a farm currently run by the family, (ii) children not living on a farm, but with regular contact to farms, meaning at least once a week for a period of 6 months minimum, and (iii) children without any contact to farms. The main protective determinants of asthma in the GABRIELA study were farm milk consumption and exposure to cows and straw.[16] These determinants were coded by variables on intensity (never, monthly, weekly, daily, twice a day) at several time periods, that is, 1st, 2nd/3rd, 4th/5th year and during the last 12 months at school age. We defined regular exposure as at least weekly and integrated the time periods by disjunction ("or") as families usually do not change their habits.[16]

Allergen-specific immunoglobulin E (IgE) was measured by UNICAP 1000 (Phadia AB, Uppsala, Sweden),[16] and atopic sensitization was defined as specific IgE ≥ 0.7 kU/L to any of the following allergens: *Dermatophagoides pteronyssimus* (d1), cat dander (e1), timothy grass (g6), cultivated rye (g12), common silver birch (t3), mugwort (w6), food mix (fx5: egg white, milk, fish, wheat, peanut, and soybean) and grass mix (gx3: sweet vernal grass, rye grass, timothy grass, cultivated rye, and velvet grass).

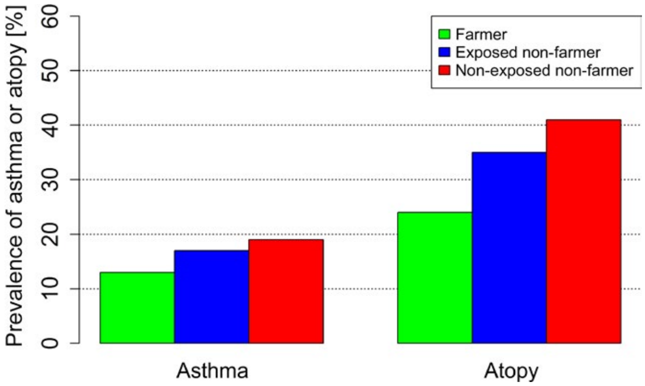

FIGURE 1 Prevalence of asthma and atopy over exposure strata [Colour figure can be viewed at wileyonlinelibrary.com]

2.3 | Geocoding and exposure variables

A dataset containing all 3 million addresses of Bavaria and their respective geocodes was provided by the Landesamt für Digitalisierung, Breitband und Vermessung; the Bavarian State Ministry for Food, Agriculture, and Forestry made the addresses of all Bavarian farms run in 2015 available. The residential addresses of the study children and the addresses of all Bavarian farms were converted into geocodes, that is, data pairs containing geographic longitude and latitude in the Universal Transverse Mercator (UTM) system. The presence of a cattle farm (in farm children besides their own farm) was determined for areas with radiuses from 25 m to 10 000 m. Population density was substituted by the number of addresses within a radius of 500 m.

Corresponding to GABRIELA fieldwork during 2005-2007, environmental variables were derived from different databases based on satellite images or from land-use regression models and covered levels of NO_2 and O_3, altitude above sea level, tree cover as defined by vegetation >5 m, and greenness during cloud-free summer months as determined by normalized difference vegetation index (NDVI).[21,22] Altitude of residence (meters above sea level) was calculated using the Shuttle Radar Topography Mission (SRTM) dataset.[22] Levels of NO_2, O_3, and PM_{10} were obtained from raster maps as part of the Air Pollution Modelling for Support to Policy on Health and Environmental Risks in Europe project.[23] Degree of soil sealing was calculated in a 1000 m buffer around residence, and data were derived from a raster dataset from the European Environment Agency.[24] Tree cover data in a 500 m buffer around residence were obtained from Landsat Vegetation Continuous Fields maps.[25,26]

For microbial diversity, 16s rRNA was amplified in DNA extracted from mattress dust and sequenced by Illumina. The resulting reads were deblurred, rarefied to 42 132 reads, and clustered within sub-operational taxonomic units (sub-OTUs), which were summed up as measure of richness.[27] Endotoxin was measured using a kinetic chromogenic Limulus amebocyte lysate assay after extraction of mattress dust by pyrogen-free water added with 0.05% Tween-20[28,29]; levels are expressed as endotoxin units (EU) per square meter of sampled mattress surface.

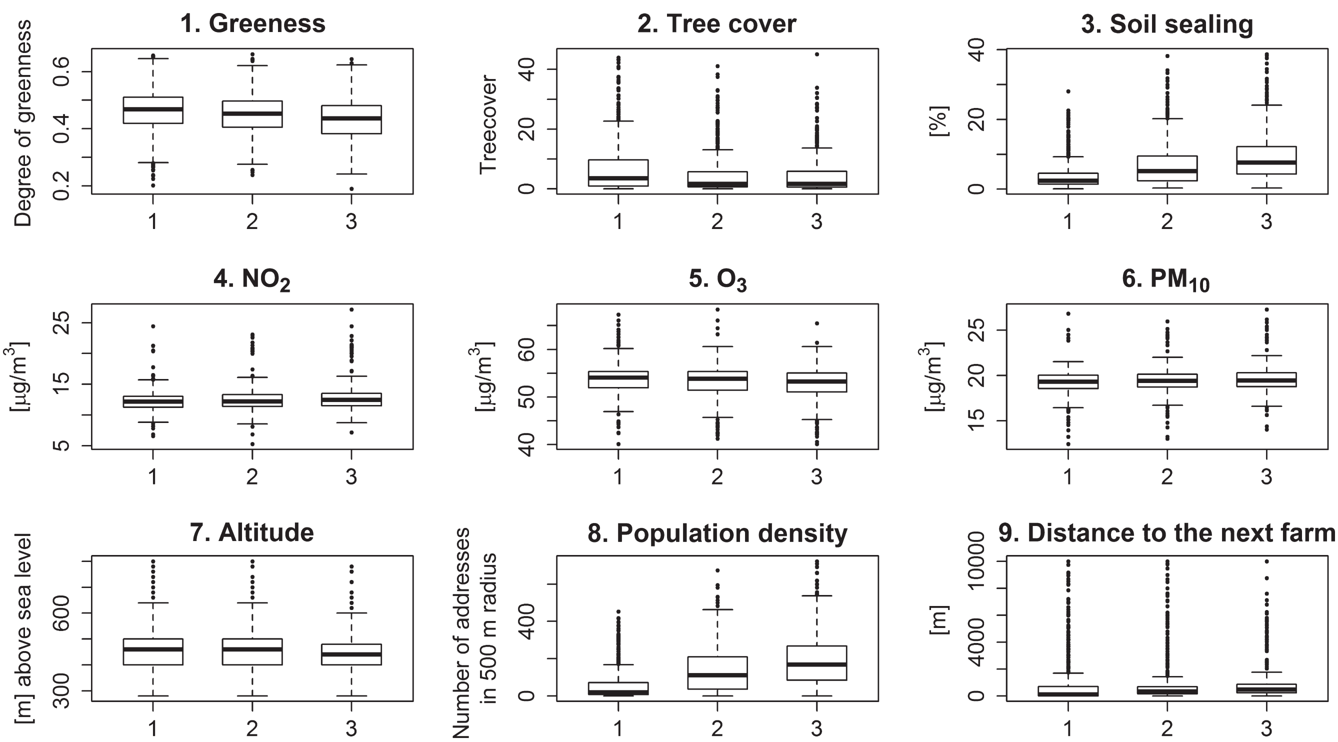

FIGURE 2 Distribution of environmental variables across exposure strata. 1 = farm children; 2 = exposed non-farm children; 3 = non-exposed non-farm children; differences between the subgroups were statistically significant ($P < .01$) except for ozone, altitude, and distance to the next farm

2.4 | Statistical methods

Associations of outcome and exposures were assessed by logistic regression using a stratified weighted design when considering microbiome data.[15] Continuous variables were standardized to interquartile ranges. An effective *P*-value of $P < .05$ was considered statistically significant in all reported models. All statistical analyses were performed using R version 3.2.3 software package (The R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

Of the Bavarian children invited to phase 2 of the GABRIELA study, 2276 (88%) participated (Figure S1). This population was somewhat enriched for farm children with a lower asthma and atopy risk (Table S1). Geocoding of addresses was successful in 2265 (99.5%) children.

Prevalence of asthma and atopy increased across the 3 exposure strata, that is, farm, exposed, and unexposed non-farm children (Figure 1). Similarly, all environmental exposures except ozone levels and altitude differed between the 3 exposure strata (Figure 2) but were unrelated to asthma or atopy (Table S2). The borderline association of atopy and NO_2 was only seen when adjusting for the farm exposure strata thereby implying negative confounding.

Only the presence of a farm in the surrounding revealed clear inverse associations both with asthma and atopy though only when in close proximity, that is, up to 50 or 100 m (Figure 3). From 500 m onwards, the presence of a farm was a risk factor for atopy.

For subsequent analyses on the presence of a farm in close vicinity ("farm nearby"), we chose a radius of 50 m as the effect size already declined at 100 m and we considered 25 m too narrow given the size of an average farm. When stratifying for farm and non-farm children (Table 1), weaker effects by the strata-wise estimates were observed thereby indicating partial confounding by farming and additional effect modification for asthma with a stronger effect in farm children. A sensitivity analysis considering family structures confirmed the results (data not shown).

When adjusting the effects of a farm nearby on asthma and atopy by the previously identified major protective determinants, the effects were mainly explained by consumption of farm milk in non-farm children (Table 1). In farm children, however, the effect of a farm nearby on asthma and atopy was only partially explained by farm milk.

Farm children with another farm nearby differed from other farm children in all residential exposures (Figure 4) except O_3 and PM_{10} and were exposed to a broader spectrum of environmental bacteria (Figure 5A) but similar endotoxin levels (Figure 5B).

None of the characteristics differing between farm children with and without another farm nearby (Table S3) explained the protective effect on asthma; however, bacterial richness explained the effect in farm children completely (Figure 5C-D) though not on atopy (data not shown).

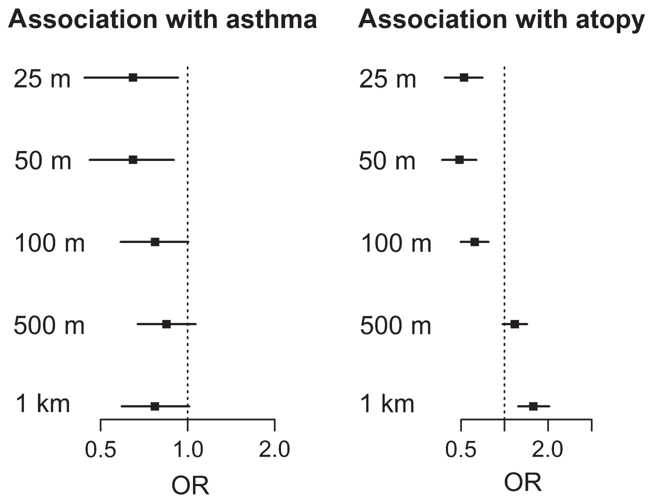

FIGURE 3 Association of asthma and atopy with the presence of farms in the area. Number of farms within a given radius was dichotomized for at least 1 farm in the radius vs no farms. Associations are calculated by logistic regression resulting in odds ratios (OR) with 95%-confidence intervals

4 | DISCUSSION

Physical proximity to a farm was inversely associated with childhood asthma and atopic sensitization. In non-farm children, this was explained by regular consumption of unprocessed milk directly obtained from a farm, whereas in farm children, a relevant proportion of the effect remained unexplained. Residential exposures such as greenness, population density, and air quality differed between the exposure strata but also between farm children with and without another farm nearby. However, these residential exposures were barely related to asthma or atopy. Only bacterial richness explained the remaining effect of farm proximity on asthma but not atopy.

In the field of environmental epidemiology, the recent years brought a paradigm shift from risk factor research toward exploration of resources that increase resilience against disease and foster health. The usefulness of research into classical risk factors such as particulate matter is beyond doubt. Not only excess in noxious agents but also shortage in beneficial resources affects human health negatively.

In this context, access to green spaces has been identified as beneficial with respect to mental health[30] and overall mortality.[31] For childhood asthma and atopy, there is some evidence though possibly restricted to specific settings with regional variation.[32-34]

In our analysis, there was a clear gradient in population density, greenness, tree cover, and their counterpart soil sealing over the exposure strata (Figure 2). Apparently, the above pictured scenery for the farm children studies does not just seem a cliché, but was substantiated by objectively measured data. These environmental factors, however, were not involved in the protective farm effect on asthma and atopy and may operate only in urban areas with inequality in access to green spaces.

Actually, the discovery of the farm effect was a by-product of air quality research. When relating indoor air quality to respiratory health,

TABLE 1 Explanation of the effect of a farm within 50 m of the residential address on asthma and atopy for all children and stratified by farming

	Crude association	Adjusted for straw	Adjusted for cow contact	Adjusted for farm milk
Asthma				
All children (n = 2265)	0.65 [0.46;0.90]	0.72 [0.50;1.02]	0.74 [0.51;1.06]	0.81 [0.53;1.21]
Farm children (n = 916)	0.75 [0.49;1.13]	0.76 [0.49;1.16]	0.85 [0.54;1.33]	0.83 [0.49;1.37]
Non-farm children (n = 1349)	0.86 [0.40;1.64]	0.77 [0.33;1.56]	0.80 [0.36;1.59]	1.05 [0.35;2.60]
Atopy				
All children (n = 2265)	0.49 [0.37;0.64]	0.56 [0.42;0.74]	0.57 [0.42;0.76]	0.59 [0.42;0.83]
Farm children (n = 916)	0.64 [0.45;0.90]	0.68 [0.47;0.97]	0.65 [0.45;0.94]	0.65 [0.43;0.99]
Non-farm children (n = 1349)	0.67 [0.37;1.15]	0.66 [0.35;1.17]	0.69 [0.38;1.22]	0.90 [0.40;1.90]

OR are given with 95% confidence intervals.

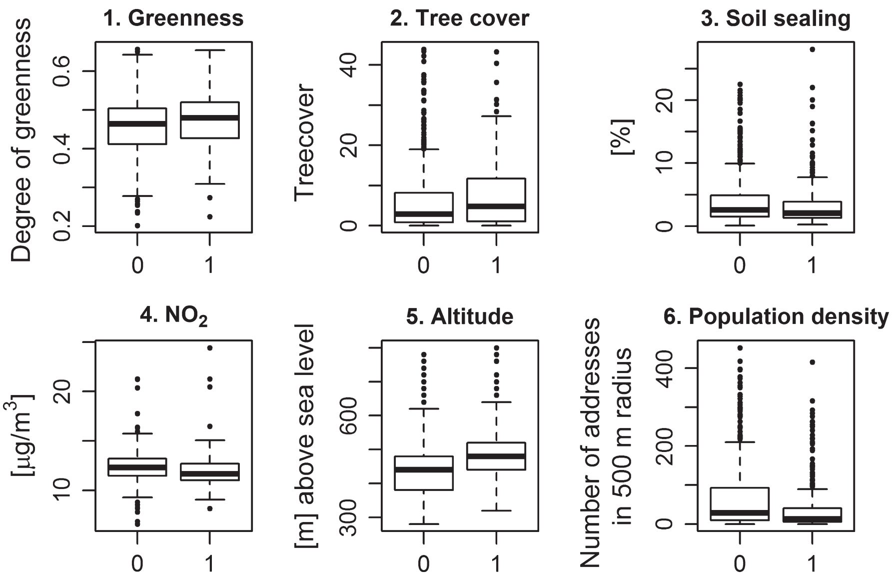

FIGURE 4 Comparison of farm children with and without another farm in close proximity. 0 = farm children without a farm within 50 m (n = 588); 1 = farm children with a farm within 50 m (n = 328); differences between the subgroups were statistically significant (*P* < .005)

a counterintuitive protective effect of heating with wood and coal on asthma and atopy was found.[35] With respect to outdoor air quality, associations of NO_2 and PM_{10} were found with non-seasonal rhino-conjunctivitis, nocturnal and chronic cough though not for asthma and atopy.[36] Also in the current study, O_3 and PM_{10} levels were not related to asthma and atopy. The borderline association of NO_2 and atopy remained obscure; residual confounding could not be excluded.

The absent risk effects by pollution in our study as well as in previous studies in rural areas are in contrast to a recent meta-analysis.[37] Studies on air quality, however, often focus on areas with traffic-related air pollution. These are not necessarily confined to urban areas; however, the levels of NO_2, O_3, and PM_{10} in the GABRIELA study (Figure 2) were lower as compared to most studies listed in the meta-analysis.[37]

Considering geographic characteristics, the present analyses do not suggest a direct contribution of the larger environment to the farm effect on asthma and atopy. Thus, the farm effect seems to operate through other exposures than vegetation density and air quality. Indeed, the protective effects of a farm in the neighborhood on both asthma and atopy ceased with distance thereby indicating a local phenomenon. The radius of the effect was hardly more than 100 m, which is far less than the usual walking distance of school children.

The explanation of the effect of a farm nearby on asthma in non-farm children by regular consumption of farm milk suggests that families buy unprocessed milk mostly from their neighbors. Besides, the explanation of the effect of a farm nearby does not invalidate other protective effects such as an exposure to cows, their feed, bedding, or housing, as these effects are largely independent of the milk effect.[16]

In most European farms, animal houses are built in close vicinity to the homes of the farming families. In our analysis, the distance from residential buildings to animal houses could not be determined as we used the residential addresses for geocoding. Therefore, we did not consider the children's own farm when assessing the distance to the next farm. However, a farm nearby differentiated well between 2 groups of farm children. Those with a farm nearby lived in an area

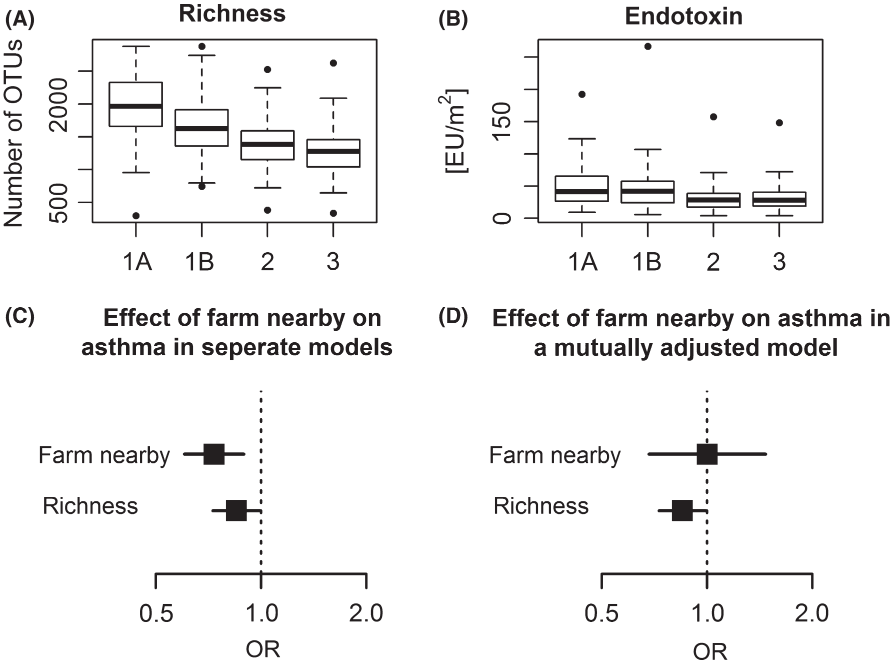

FIGURE 5 Bacterial richness and endotoxin levels in mattress dust. A-B, Bacterial richness as number of detectable operational taxonomic units (OTUs) and endotoxin levels over the following 4 exposure strata: 1A = farm children with another farm nearby; 1B = farm children without another farm nearby; 2 = exposed non-farm children; 3 = non-exposed non-farm children. C-D, Associations with asthma are shown for farm children with microbiome data (n = 191). Odds ratios (OR) for richness are based on 100 OTUs as unit and are weighted back to all farm children. When entering both farm nearby and richness in the same model mutually adjusted, the effect of farm nearby is completely explained by bacterial richness

with lower population density, on a higher altitude, with higher vegetation density around, less soil sealing, and lower NO_2 values. As large farms do not have a neighboring farm within 50 m, the variable "farm nearby" may be a proxy for small traditional farms.

We have long postulated that the main farm effect was attributed to traditional farms and that not all farms offered protection[10]; however, the definition of a traditional farm has been elusive. Intriguingly, the presence of another farm within 50 m just defined by geocodes fulfilled many of the above criteria. Possibly, the neighboring farm is run by a member of the extended family.

For atopy, the protective effect of a farm nearby turned into a risk effect, when the next farm was beyond 500 m. This implies that only a direct contact to a farm within the radius of a school child or the consumption of raw milk purchased from the neighbor may protect. In contrast, a farm in the wider area may represent a risk factor. Such a farm might be larger and emit airborne pollutants such as ammonia. Possibly, the discrepancies between protective [38] and detrimental [17-19] effects by farm proximity might be resolved by considering the short- and long-distance effects separately. Between 100 m and 500 m, the opposite effects might cancel out.

Yet, the concept of traditional, family run farms does not in itself elucidate the unexplained effect of a farm nearby. A promising trace was found in the profound difference in bacterial diversity between children from presumably traditional farms and their peers from possibly more industrialized farms in analogy to findings from the Amish and Hutterite studies,[39] where type of farming made a big difference in health outcomes.

We have previously attributed a relevant proportion of the asthma-protective farm effect to indoor bacterial diversity,[13] which also reflects children's outdoor exposure, including exposure to animal sheds.[40] In addition, there is considerable agreement of bacterial diversity in mattress dust and nasal samples indicating that many bacteria are inhaled and get into contact with the nasal mucosa, where they may exert their effects on airway disease.[14,15] Many of the bacterial taxa detected in farm children's mattresses are derived from soil and feces of ruminants such as cows.[14] These bacteria may also produce volatile substances such as short-chain fatty acids, which can be inhaled when in close contact with animals but are instantly diluted with distance from a farm.

5 | CONCLUSIONS

Looking down from the sky on the rural areas of Bavaria with the eyes of a satellite, this investigation ended up with a very earthly explanation for the farm effect on asthma and atopy, that is, microbial exposure besides the independent effect of farm milk. Both sources of exposure are confined to rather narrow areas of about 100 m in diameter. The novel finding of this study, however, is the identification of farms with an additionally elevated potential for asthma protection, that is, farms in remote areas clustering with other small farms in hamlets. On these farms, particularly high bacterial diversity may determine whether to be or not to be asthmatic.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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