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A PheWAS Analysis of the Risks and Benefits of Growing Up on a Farm

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ABSTRACT

Objective: Growing up on a farm presents a health paradox, with increased risks of injuries but some purported benefits. This study estimated differences in the burden of medical comorbidities between youth who live versus do not live on farms. No a priori hypotheses were tested.

Methods: A phenome-wide association study (PheWAS) was used in a cohort of youth in north-central Wisconsin. Those who lived on farms were matched (1:3) to a non-farm comparison group. Outcomes included a comprehensive set of diagnoses (Phecodes) that occurred between 2017 and 2021. PheWAS analyses included logistic regression models of Phecode associations with farm residency.

Results: There were 36 Phecodes that significantly differentiated the two groups. Youth who lived on farms had significantly higher odds of agricultural injury, dermatophytosis, spinal neuritis, and strabismus compared to non-farm youth. Remaining Phecodes indicated protection in the farm group. Notably, relative to the non-farm group, farm youth had a 20%–30% lower odds of respiratory illnesses, as well as 30%–40% lower odds of mental health and neurological conditions.

Conclusion: This was the first known study to utilize a PheWAS approach to comprehensively compare medical comorbidities in farm versus non-farm youth. Findings confirmed the known injury hazards in farm youth, but there appeared to be more health benefits of living on farms. Some of these apparent protections were novel, particularly those related to affective disorders, but require future confirmatory testing to understand how care seeking behaviors may also influence farm and non-farm households.

KEYWORDS
Farm; health; PheWAS; Wisconsin; ; youth

Introduction

Agriculture consistently ranks among the deadliest U.S. occupational sectors.[1,2] Given the typical integration of agricultural work alongside home residency, agriculture is also unique insofar as it is one of the few industries that routinely exposes children, both through direct work participation and indirect interactions, to workplace hazards. There are an estimated 260,000 youth employed on U.S. farms, and another 893,000 individuals aged 0–19 years who live on farms (at least half of whom directly participate in farm work).[3] Living and/or working on a farm puts children at increased risk for severe injury from machinery, heavy equipment, livestock, and other agricultural dangers (e.g., pesticide poisoning).[4–6] Young workers, for example, are nearly eight times more likely to experience a fatal injury while working in agriculture as compared to all other industries combined.[2]

But there are also some known health benefits of regular farm exposures. Most notably, asthma and atopic diseases are less common in children and adolescents who grow up on farms.[7,8] In addition, allergies that persist into adulthood are less common in farm youth.[9,10] Specific mechanisms for these health protections are just beginning to emerge, but mounting evidence suggests early life and in utero exposures to various livestock, microbes, and other farm-related airborne vectors can more efficiently prime immune system pathways.[11,12]

Growing up on a farm may present a health paradox,[13] with increases in some injuries and decreases in some allergic/respiratory conditions. Prior research on this topic is very limited though in that most published studies focus narrowly on farm safety and rarely include a non-farm

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comparison group. No studies have broadly examined the burden of possible medical comorbidities faced by both farm and non-farm youth. More research is needed to identify the emerging breadth of health risks, as well as health benefits, of child rearing on farms. This may help prioritize future childhood agricultural health and safety initiatives and identify protective mechanisms that are potentially generalizable to other pediatric populations. Using a phenome-wide association study (PheWAS) design,[14] the purpose of this study was to estimate differences in the comprehensive burden of medical comorbidities between youth who live vs. do not live on farms in north-central Wisconsin.

Methods

Design and setting

A PheWAS design was used,[14] which included a series of matched retrospective cohort studies conducted simultaneously for each medical comorbidity. The target population is described in more detail elsewhere,[15] but included members of the (Wisconsin) National Children's Center for Rural and Agricultural Health and Safety Surveillance system (WINS). WINS is an ongoing cohort study designed to track agricultural injuries in child/adolescent patients of the Marshfield Clinic Health System (MCHS) and/or members of the MCHS-affiliated health plan, Security Health Plan of Wisconsin (both headquartered in Marshfield, WI), who reside in a 20-county region of north-central Wisconsin. Study data were extracted from administrative and medical information in MCHS electronic health records (EHR) and health insurance claims. All study procedures were approved in advance by the MCHS Institutional Review Board, with a waiver of informed consent and HIPAA authorization.

Farm residence and matching

The sample included individuals in the WINS cohort who were age 0–17 years for ≥90 days between 2017 and 2021, and who had reasonably complete capture of their medical care within MCHS data systems, as evidenced by: (1) "medically-homed" status at an MCHS medical center (i.e., an assigned MCHS primary care provider or ≥2 preventive or well-child visits over the previous 3 years); (2) resident of the Marshfield Epidemiologic Study Area (MESA)[16,17]; or (3) member of the MCHS-affiliated Security Health Plan of Wisconsin (headquartered in Marshfield, WI). As described previously in the WINS cohort,[15] youth were stratified by those who lived vs. did not live on a farm, based on residential address and linked farm production information during the 2017–2021 study timeframe. For each child/adolescent in the farm group, up to three randomly selected individuals in the non-farm group were also included in the sample, matched on age (±1 year), sex, medically homed status, race/ethnicity, Medicaid status, time under observation in the WINS cohort (±3 months), and residential ZIP code.

Medical comorbidities

Outcomes included a comprehensive set of medical diagnoses from the EHR and health insurance claims, specifically the "roll-up" categories of health conditions, or Phecodes, developed by Vanderbilt University. As described in more detail elsewhere,[18,19] this approach takes most of the International Classification of Diseases 10th revision (ICD-10) diagnostic codes available from EHR billing data and assigns them to nearly 2,000 different Phecodes. Each Phecode is a unique medical comorbidity, capturing various ICD-10 diagnostic codes indicative of acute disease states, chronic conditions, and/or injuries related to said Phecode. This approach is more intuitive than using all of the tens of thousands of ICD-10 codes individually, as each Phecode combines relevant ICD-10 codes to form a conceptual health condition. In addition, using logic from prior WINS analyses of farm-related injuries,[15] we also screened for a locally developed Phecode that specifically captured agricultural injuries (unavailable in the Vanderbilt Phecode set). Individuals in the analytical sample were under observation for Phecodes occurring between 2017 and 2021, while they met all WINS cohort study eligibility criteria. Two separate approaches were used to analyze Phecode outcomes, including a rule-of-2

and rule-of-1 approach. The rule-of-2 approach required that, for any given Phecode, multiple instances (i.e., appearing on more than 1 day) were required to be categorized as a participant with the illness/injury, whereas participants with no indication of that given Phecode were categorized as not having said illness/injury (and those with a single instance were excluded). The rule-of-1 approach only required a given Phecode to have occurred in a single instance to be categorized as having the illness/injury, and again, participants with no indication of that Phecode were categorized as not having said illness/injury. These two approaches to outcome ascertainment were used to capture more transient or acute (or otherwise less routinely documented) health conditions under the rule-of-1 approach, and contrast those findings to the rule-of-2 approach, which is generally a more valid method of capturing chronic or recurrent Phecodes that need ongoing care (and avoids rule-out diagnoses).

Analyses

A PheWAS analytical approach was used similar to a recent study by Barnado and colleagues[20] and informed by prior guidelines from Caroll et al.[21] PheWAS analyses were carried out separately under the rule-of-1 and rule-of-2 methods. For each Phecode where there were at least 20 individuals with the given illness/injury in the analytical sample, logistic regression was used to model the association with farm residency. These were rank-ordered by the significance of their associated differences between the farm vs. non-farm group using conditional logistic regression, with adjustment for matching variables. No *a priori* hypotheses were tested and, to correct for multiple testing concerns, we used a false discovery rate/threshold of 0.05.[22] This method adjusts p-values to yield q-values, which are the minimum threshold at which a particular association is considered significant based on the estimated probability of it being a false positive finding.[23] For medical comorbidities that most clearly differentiated the farm vs. non-farm groups, per the 0.05 false discovery rate criterion, follow-up analyses were performed to estimate odds ratios and 95% confidence intervals. Analyses were conducted using SAS Version 9.4 (Cary, NC).

Results

In the final analytical sample, there were 4,598 children/adolescents in the farm group and 13,524 in the matched, non-farm comparison group. As expected given the matching procedures, the two groups were well balanced on sociodemographic characteristics (Table 1). Across both groups, the mean age was 12 years, with 42% on Medicaid and 91% White non-Hispanic race/ethnicity.

Under the rule-of-1 approach, there were 649 unique Phecodes that had at least 20 participants.

Table 1. Sociodemographic characteristics of youth who live and do not live on farms in north-central Wisconsin.

Characteristic	Farm (n = 4,598)	Non-farm (n = 13,524)
Age (y)	12.4 (5.9)	12.6 (5.9)
Sex		
Female	2,190 (48%)	6,447 (48%)
Male	2,408 (52%)	7,077 (52%)
Race/ethnicity		
White, non-Hispanic	4,174 (91%)	12,383 (92%)
Not White or Hispanic	158 (3%)	403 (3%)
Unknown	266 (6%)	738 (5%)
Medicaid	1,946 (42%)	5,744 (43%)
Medically homed		
MCHS	3,697 (80%)	10,973 (81%)
Outside of MCHS	901 (20%)	2,551 (19%)
Number of ambulatory visits (last 5 years)	10.6 (13.1)	11.4 (13.5)
Cohort follow-up time (m)	43.6 (18.0)	43.7 (18.0)

MCHS, Marshfield Clinic Health System
Values are given as mean ±SD or frequency (% of column total).

As outlined in Figure 1, 36 Phecodes exceeded the 0.05 false discovery rate threshold, with five of those Phecodes having higher odds in children and adolescents who lived on farms. Specifically, relative to non-farm youth, farm youth had significantly higher odds of agricultural injuries (odds ratio [OR] ± 95% confidence interval [CI] = 2.17 [1.56, 3.01]), dermatophytosis of the body (e.g., tinea corporis, imbricata, cruris) (OR±CI = 1.92 [1.52, 2.41]) and dermatophytosis (e.g., tinea barbae, capitis, manuum) (OR±CI = 1.79 [1.25, 2.57]), thoracic or lumbosacral neuritis (OR±CI = 3.12 [1.59, 6.09]), and strabismus (OR±CI = 1.96 [1.30, 2.95]). The remaining 31 Phecodes indicated health protection for farm youth. With several thousand individuals with various respiratory infections and related symptoms, such respiratory conditions were the predominant medical comorbidity in both groups, but generally had 20%–30% lower odds in the farm group relative to the non-farm group. Similarly, mental health conditions, when viewed collectively, were also among the most common medical comorbidities, but generally had 30%–40% lower odds in the farm group relative to the non-farm group. Most notably, children and adolescents who lived on farms had significantly lower odds of phobia/panic disorder (OR±CI = 0.46 [0.32, 0.67]) and suicidal ideation (OR±CI = 0.48 [0.33, 0.71]) compared to non-farm children and adolescents.

Under the rule-of-2 approach, there were fewer unique Phecodes observed that had at least 20 participants ($n = 426$). This was expected given the requirement of multiple Phecode occurrences for each participant, as this approach is generally less sensitive to acute, transient, or rule out diagnoses. As described in Figure 2, 14 Phecodes exceeded the 0.05 false discovery rate threshold, all of which indicated a protective association in the farm group. Again respiratory infections and related symptoms, as well as mental health conditions, were the predominant Phecodes differentiating the farm and non-farm groups. Although there were fewer total number of Phecodes for

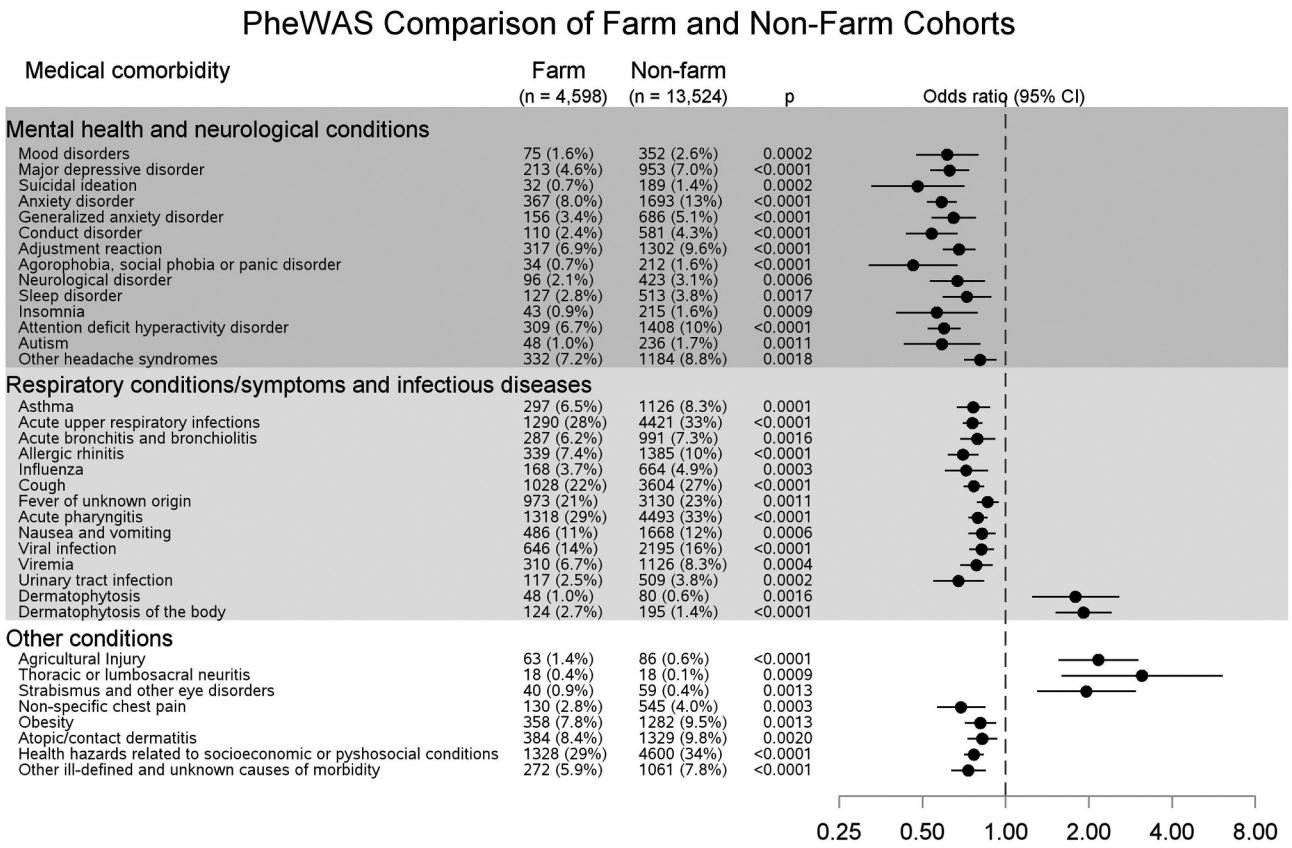

Figure 1. Medical comorbidities that significantly differentiated farm and non-farm youth in north-central Wisconsin, using a rule-of-1 analytical approach.

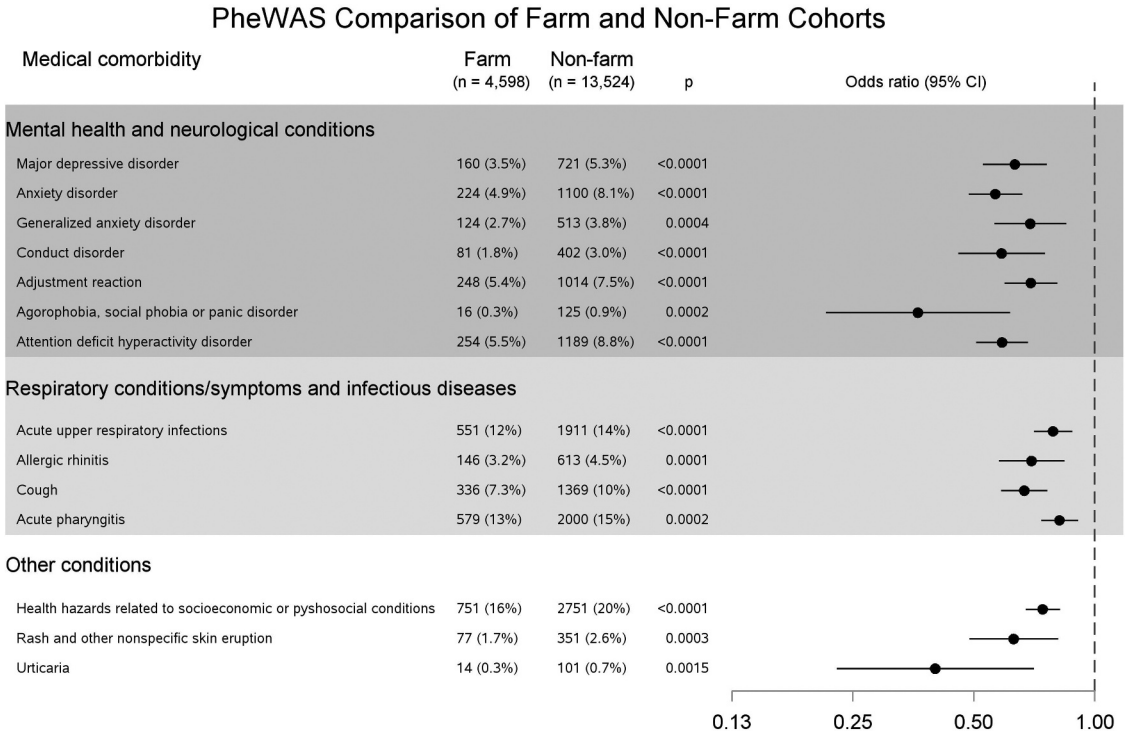

Figure 2. Medical comorbidities that significantly differentiated farm and non-farm youth in north-central Wisconsin, using a rule-of-2 analytical approach.

respiratory infections and mental health conditions as compared to the rule-of-1 analysis, the odds ratio ranges were similar. In addition, farm youth were significantly less likely to experience urticaria.

Discussion

This was the first known study to use PheWAS methodology to examine a comprehensive set of medical comorbidities in farm youth and simultaneously compare them to a matched group of youth who did not live on farms. Many of the most serious hazards associated with growing up on a farm, namely those related to injuries, were already known. This was largely confirmed in our study, where youth who lived on north-central Wisconsin farms clearly had a higher burden of agricultural injuries, occurring over twice as often than in youth who did not live on farms, similar to prior work in this same population.[15] Though far less common than agricultural injuries or dermatophytosis (i.e., ringworm), there were some other increased health hazards observed in farm youth, including ocular strabismus and spinal nerve inflammation, which occurred two and over three times more often, respectively, compared to non-farm youth. These conditions have received little or no known recognition in prior scientific literature on farm youth. Though not the focus of this study, such conditions could be related to a higher prevalence of other risk factors in farm households, including smoking[24,25] or sequelae from prior agricultural injuries.

There also appeared to be several health benefits of growing up on a farm. Some of these have been observed in previous studies, including protection against asthma and atopic disease,[8,9,26,27] as well as certain respiratory conditions (e.g., rhinitis),[28,29] though ours may be among the first known studies to show reduced influenza diagnoses (and related flu-like symptoms) and urinary tract infections in farm youth. Given recent increases in affective disorders in children and adolescents across the U.S.,[30] it was potentially encouraging that, as compared to their non-farm counterparts, youth who lived on farms were less apt to receive diagnoses of various mental health conditions. Such conditions were not rare in either group, but medically documented suicidal ideation and affective disorders

such as major depression, along with several forms of anxiety, were consistently lower in farm youth. In addition, farm youth had fewer indications of socioeconomic/psychosocial hazards, a broad set of diagnoses that indicate a negative influence on health status. The magnitude of the farm vs. non-farm differences in anxiety, depression, and socioeconomic/psychosocial hazards was similar under both the rule-of-1 and rule-of-2 analyses.

Most of the medical comorbidities that significantly differentiated farm youth were chronic conditions or infections with varying degrees of severity. For some of these, it remains unclear to what degree our findings reflect true differences in the farm environment, or differences in farm families' propensity to seek medical attention, or both. For example, the rule-of-1 analysis found the odds of an autism diagnosis was about 40% lower in youth who lived on farms. This was somewhat surprising, given prior literature that found increased odds of autism secondary to in utero pesticide exposures.[31] But given their close match to the non-farm sample on sociodemographic characteristics, our findings could reflect more underlying autism risk factors in non-farm households (e.g., air pollution, maternal autoimmune disorders),[32] or perhaps more encompassing, previously unknown benefits of early life exposures to farm animals and the natural environment[33] (as has been noted recently for childhood obesity[34]). It could also reflect different decision thresholds in farm parents to seek specific medical testing for (or disclose/discuss) mild autism symptoms in their children, perhaps due to competing demands on the farm or limited local access to specialized treatment facilities.

Similar care seeking avoidance/delay could also influence mental health conditions. Farm families routinely experience financial and access barriers to healthcare,[35] though head-to-head comparisons of such barriers between farm and non-farm groups are rare. Like the general population, most U.S. farmers have health insurance coverage through an employer (often via a spouse employed off the farm), the government, or private purchase.[36] Although our sample was matched on Medicaid status, there could be residual health insurance quality imbalances (e.g., higher deductibles) that discouraged more farm youth from seeking mental healthcare. Similarly, despite age-matching in our sample, there could also be age-specific effects, as a recent cross-sectional survey of farm adolescents in the Midwestern U.S. suggested a higher prevalence of anxiety and depression symptoms relative to historical comparisons to the general adolescent population.[37] From a cognitive-behavioral perspective, relative to non-farm comparison groups, two small studies in Australia found greater self-reliance needs as a personal barrier to (hypothetically) seeking mental health support,[38] as well as significantly lower odds of self-reported mental healthcare visits in adult farmers.[39] In contrast, alongside the broad emotionally protective effects of adequate green-space (presumed to be greater in farm settings) for youth,[40] at least one prior study has observed less psychological distress in girls who live on farms relative to those who do not,[41] and another found fewer depressive symptoms in adult farm women.[42] In addition, farm youth in this study, as well as those in the WINS cohort generally, see their physician just as often as non-farm youth.[15] As it has been investigated in more detail for agricultural injuries, asthma, and atopic diseases, future research should identify causal factors specific to the farm environment that drive differences in these apparent mental health benefits.

Strengths of this study included the large sample size and objective, broad capture of medical comorbidities from EHR and claims data sources. In addition, the matched design helped balance potential confounders between the farm and non-farm groups. PheWAS studies are limited, however, in that they broadly screen for a myriad of outcomes that could be subject to spurious associations. This is controlled to some degree with the use of a conservative false discovery rate threshold to help protect against Type I errors associated with multiple testing, but the retrospective use of Phecodes also poses some risk of outcome misclassification. Validation of all Phecodes is unavailable, thus we conducted two separate PheWAS analyses under a rule-of-1 and a rule-of-2 scenario to ascertain and compare outcomes. This was done to better capture more transient (e.g., bronchitis), acute (e.g., agricultural injuries), or otherwise non-routinely documented (e.g., obesity) health conditions under the rule-of-1

approach, and contrast those findings to the rule-of-2 approach, which likely improves the validity of observed chronic or recurrent health conditions that require follow-up monitoring (e.g., affective disorders) and avoids more rule-out diagnoses.[21] We consider our PheWAS findings as hypothesis-generating and subject to future, confirmatory testing using proper designs for each outcome. Finally, the target population was regional and had limited racial/ethnic diversity, thereby limiting generalizability.

Conclusion

Our findings seem to confirm the previously described "farm kid paradox".[13] The risk of serious injuries are ever-present for farm youth,[43,44] yet farm parents enthusiastically tout child rearing advantages such as time outdoors and instilling a strong work ethic, among other reasons.[45] More research is needed to identify specific causal pathways at individual and household levels, but despite the familial stressors of challenging labor, worksite hazards, unpredictable weather, and financial uncertainties, there appear to be several quantifiable health benefits for children and adolescents who grow up on farms and these may, in some sense, offset the risks of injuries and other medical perils. In particular, symptoms of anxiety, depression, and suicidal ideation are increasing in children and adolescents across the U.S.,[30] and even more so in underserved rural areas.[46] Youth who live on farms are clearly not immune to these and other mental health challenges, but they may have some level of protection against them as compared to their non-farm counterparts. The presence or absence of Phecodes are imperfect markers of (confirmed) disease burden and these apparent health benefits could partially reflect greater reluctance to seek some forms of medical care and/or disclose certain sensitive symptoms in farm families. As such, lower access to and/or utilization of specialty care for mental health symptoms in youth should be confirmed in larger, future studies that can help identify the most medically valuable elements of the farm environment that can be generalized to all children and adolescents.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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Contributors statement

RRB, RLB, RMG, BPW, and JJV conceptualized and designed the study, and critically reviewed and revised the manuscript. RRB drafted the initial manuscript. RLB and RMG led the statistical analyses. CGB and JMR critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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