Effect of Radon Exposure on Asthma Morbidity in the School Inner-City Asthma Study

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Abstract

Background: Radon may have a role in obstructive lung disease outside its known carcinogenicity. Little is known about radon's effects on asthma morbidity.

Objective: To determine the effect of radon on fractional exhaled nitric oxide (F_ENO), asthma symptom-days, and lung function in inner-city asthmatic school-children.

Methods: Two hundred ninety-nine school-aged asthmatic children enrolled in the School Inner-City Asthma Study (SICAS-1) were followed. One and two-month averaged radon was

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assessed using a spatiotemporal model predicting zip code-specific monthly exposures. $F_E NO$ and spirometry were measured twice during the academic year. Asthma symptoms were assessed four times during the academic year. The interaction between indoor radon exposure (Bq/m^3) and seasonality predicting log-transformed $F_E NO$, FEV_1% predicted, FVC% predicted, FEV_1/FVC, and asthma symptom-days was evaluated.

Results: Participants with high radon exposure had greater change in $F_E NO$ from warm to cold periods compared to low radon exposure (interaction p=0.0013). Participants with >50th percentile radon exposure experience significant $F_E NO$ increase from warm to cold weather (β=0.29 [95% CI: 0.04,0.54], p=0.0240). We report a positive association between radon 1-month moving average (IRR=1.01, p=0.0273) and 2-month moving average (IRR=1.01, p=0.0286) with maximum asthma symptom-days (n=299, obs=1,167).

Conclusions: In asthmatic children, radon may be associated with increased asthma morbidity, suggesting radon may be a modifiable environmental risk factor for airway inflammation.

Keywords

Asthma; radon; environmental exposure; exhaled nitric oxide; obstructive lung disease

INTRODUCTION

Asthma is the most common non-communicable chronic disease in children worldwide,[1] affecting approximately 14% of children globally[2] and one of 11 (7.1 million) children in the United States.[3] Environmental factors, such as allergen and air pollution exposure, are known to cause morbidity, disability, and healthcare utilization in children with asthma. Identifying potential environmental exposures and testing remediation strategies that improve asthma morbidity in children remains an unmet need.

Radon, an ubiquitous radioactive gas formed by the decay of uranium radionuclides naturally present in rocks in the earth's crust,[4] is well-known for its carcinogenic effects but more recent data suggests it is associated with chronic obstructive pulmonary disease (COPD) non-cancer morbidity and mortality, as well.[5, 6] In buildings with inadequate ventilation, radon can accumulate to harmful concentrations indoors. Driven by pressure differences, radon gas traverses from the soil into homes through porous block walls, cracks, joints, or utility openings. The radioactive products of radon are known to bind fine particles, gain entry to the respiratory tract, and can deposit on the bronchial epithelium, exposing neighboring lung cells to radiation.[7] Radon and radon progeny, the radioactive decay products of radon, yield oxygen free radicals and hydrogen peroxide in airway samples at doses within the range of acceptable home radon levels.

We recently found that residential radon concentrations were associated with asthma diagnosis and school absenteeism in an unselected cohort of urban school-aged children screened for enrollment in the School Inner City Asthma Study (SICAS).[8] There are no studies to date examining the effects of radon exposure on children with asthma. Based on recent data demonstrating radon exposure is associated with non-cancer related COPD morbidity and mortality,[5, 6] we hypothesized that residential radon exposure would

be associated with asthma morbidity and increased airway inflammation. We tested this hypothesis in the well-characterized asthma population enrolled in the School Inner-City Asthma Study by determining the effect of environmental radon on airway inflammation, measured by fractional exhaled nitric oxide (F_ENO), asthma symptoms, and lung function.

METHODS

Study population and Design

SICAS was a prospective cohort study of the effect of school classroom environmental exposures on asthma morbidity conducted in children (ages 4–15 years) with persistent asthma attending inner-city schools in the northeast United States from 2008–2013. Full details of the study design and selection of the SICAS-1 study cohort have been described elsewhere.[9] Briefly, children with asthma attending participating schools were included if they had children with physician diagnosis of asthma with either symptoms of exacerbation in the last year or controller medication (Figure 1). In the Spring prior to the study year, screening surveys were distributed to participating schools. Asthma symptoms were assessed by phone survey every 3 months through the following academic year, and spirometry and F_ENO measurements were obtained in the school twice during the academic year and linked to the Fall/Spring environmental sampling. Prior to enrollment, written informed consent was provided from the participant's guardian, and assent was obtained from the participant. The SICAS study was approved by the Boston Children's Hospital institutional review board.

Study procedures

Baseline study participant characteristics, which assessed medical history, sociodemographic information, and baseline symptoms, were obtained at a research clinic visit during the summer prior to the academic year by questionnaire. Aeroallergen sensitization testing was assessed by serum specific IgE (ImmunoCAP, PhadiaAB, Uppsala, Sweden) or allergy skin testing (MultiTest device, Lincoln Diagnostics, Decatur, IL) to the following aeroallergens: cat, dog, mouse pelt, rat pelt, house dust mite (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), German cockroach (*Blatella germanica*), Alternaria tenius, Aspergillus, Penicillium, Cladosporium, ragweed mix, oak tree pollen, and timothy grass pollen (Greer, Lenoir, North Carolina). Sensitization was defined by specific-IgE level of 0.35 kU/L or a wheal size 3 mm or larger than the negative saline control on skin prick testing. "Any sensitization" was a term to specify participants with 1 sensitization to an allergen.

F_ENO assessment was not part of the initial parent study design and only collected in years 4 and 5 of the study. F_ENO was measured by the Niox Mino device (Aerocrine, Solna, Sweden). Spirometry (Koko spirometer, nSpire Health, Inc., Longmont, CO, USA) was performed according to ATS guidelines.[10]

Exposure assessment

Residential radon exposure was assessed using a spatiotemporal model predicting monthly radon levels (Bq/m^3) for each ZIP Code Tabulation Area (ZCTA) based on home zip code

where children in the SICAS study lived.[7] Radon exposure data was contemporaneous with other study measurements. Full details of the model design have been described elsewhere.[7] In brief, the prediction model was based on 363,783 field measurements in the Greater Boston area and used a two-stage ensemble-based machine learning method to estimate monthly ZIP Code-level average basement radon concentrations based on meteorological, geological, architectural, and socioeconomic factors. The temporal resolution of the model is monthly and the spatial resolution of the model was by zip code.[7] Monthly $PM_{2.5}$, NO_2, and O_3 measurements from contemporaneously collected samples from the local EPA central monitoring site were utilized in multipollutant models.

Outcome measures

F_ENO measurement (ppb) was performed per standardized methodology according to ATS guidelines.[11] Asthma symptom outcomes were measured as maximum symptom-days, a validated asthma epidemiologic outcome[12] which has been used in previous urban home- and school-based studies.[13–16] It is defined by the greatest result of (1) number of days with wheezing, cough, or chest tightness, (2) number of days on which the child had to discontinue play activities or slow down due to wheezing, cough, or chest tightness, or (3) number of nights with wheezing, cough, or chest tightness leading to disturbed sleep in the 2 weeks prior to survey. The primary spirometry outcome was the ratio of forced expiratory volume in 1 second (FEV_1) per forced vital capacity ratio (FEV_1/FVC), which is the most sensitive marker of airflow obstruction in children with asthma.[17, 18] Forced expiratory volume in one second (FEV_1) percent predicted and forced vital capacity (FVC) percent predicted were calculated with NHANES III reference equations,[19] the standard at the time of the SICAS study.

Statistical analysis

Subject characteristics at baseline were assessed with descriptive statistics. Moving averages of indoor radon exposure (Bq/m^3) at the home zip code were calculated relative to the health outcome visit date as 1-month moving radon average and 2-month moving radon average. The 1-month moving average was defined as: (radon concentration during month of outcome visit + previous month)/2, and the radon 2-month moving average was defined as (radon concentration during month of outcome visit + previous 2 months)/3. For each moving average, we performed a repeated measures linear mixed effects model to evaluate the relationship between indoor radon exposure (Bq/m^3) and log-transformed (to approximate normal distribution) F_ENO, FEV_1/FVC, FEV_1 percent predicted, and FVC percent predicted. For each model, we tested effect modification of seasonal period (defined as Fall/Winter for September-February and Spring/Summer for March-August) and "any sensitization," and kept the interaction term in the model if it was significant ($p<0.05$). Evaluation of opposite seasons (fall/winter vs spring/summer), linked to the enrolled child, allowed assessment of seasonal epidemiology of asthma exacerbations which tend to follow the viral infection prevalence in the community. In all statistical models we adjusted for age, BMI, sex, ICS controller medication use, any sensitization, race, and household income <$25,000. A repeated measures generalized linear mixed model with a Quasi-Poisson distribution to account for overdispersion in count data was used to examine the association between residential radon exposure and asthma symptom-days. In our models,

we specify a random effect for subject to account for repeated outcome measures. Statistical computations were performed using SAS software, version 9.4 (SAS Institutes). All tests were 2-tailed, and findings considered significant for p <0.05.

We conducted several sensitivity analyses to assess potential confounding of ambient $PM_{2.5}$, NO_2 and O_3 on radon's effect. We tested the association between each pollutant and health outcome separately, adjusting for all covariates included in the original models. Pollutants significantly associated with each outcome were included with radon in a final adjusted model. We tested the correlation between radon and pollutants to assess potential for multicollinearity in adjusted models.

RESULTS

The analysis included 299 elementary school-aged children with asthma enrolled in the School Inner-City Asthma Study (SICAS-1). Participants were largely Black or Hispanic and had fairly high poverty levels, with 43% reporting household income <$25,000 (Table 1). Of our cohort, 70% reported allergic sensitization, and 30% were on ICS controller medication. Mean F_ENO was 21 ppb, mean FEV_1 % predicted 101%, FVC % predicted 100%, mean FEV_1/FVC ratio 0.9, and mean max asthma symptom-days 2.9. One hundred forty-five participants had complete data for radon exposure and F_ENO measurements for analysis (198 observations) due to later addition of F_ENO to study assessments.

Levels of indoor radon exposure (Bq/m^3) are shown in Table 2 as a distribution of quantiles of radon percentile based on geospatial modeling at participants' home zip code. Median radon level was 49.75 Bq/m^3, with interquartile range of 33.67 to 83.50 Bq/m^3.

In adjusted analysis, we found a significant interaction of season in the relationship between radon and F_ENO (p-value for interaction <0.01) when radon was dichotomized at the 50th percentile of exposure. Higher radon was significantly associated with greater change in F_ENO from warm to cold seasonal periods compared to low radon exposure (n=145, obs=198, p=0.0099; Above 50th percentile radon exposure: β=0.29 [95% CI: 0.04,0.54], p=0.0240; Below 50th percentile radon exposure: β=−0.19 [95% CI: −0.43,0.06], p=0.1313) (Figure 2, Table S1 in Supplementary Material).

All 299 participants had complete data for radon exposure and asthma symptom-days. In adjusted analysis, radon exposure was significantly associated with increase in maximum symptom-days, the main symptom-based outcome for both the 1-month moving average (IRR=1.014, 95% CI [1.002,1.027], p=0.0273) and 2-month moving average (IRR=1.015, 95% CI [1.002,1.028], p=0.0286) of radon exposure (n=299, obs=1,167) (Table 3).

For maximum symptom-days and lung function outcomes, there was no effect modification by season or allergic sensitization. Radon exposure was not significantly associated with any spirometry outcomes.

We found a strong correlation between 1-month moving averages of radon, $PM_{2.5}$, NO_2, and O_3, which was similar for 1- and 2-month moving averages (Tables S2 **and** S3 in Supplementary Material). In sensitivity analysis assessing confounding of the radon effect

by $PM_{2.5}$, NO_2, and O_3 on outcomes, we found that results were consistent for almost all models with the exception of O_3 and maximum symptom-days in which O_3 mitigated the effect of radon (Table S4 in Supplementary Material). However, the high collinearity of the exposures should be noted (Table S2 in Supplementary Material).

DISCUSSION

Radon is a modifiable environmental exposure with recent evidence suggesting a relationship to COPD and asthma. For the first time, we demonstrate a relationship between residential radon exposure and airway inflammation and asthma symptoms among school-aged children with asthma. We demonstrate a temporal association of indoor radon exposure with increase in asthma symptoms and a seasonal relationship with F_ENO. Participants with higher radon exposure had greater change in F_ENO from warm to cold periods compared to low radon exposure. These findings suggest radon exposure may be an important environmental risk factor for airway inflammation, identifying a novel, modifiable environmental risk factor for asthma morbidity in children.

This study has several strengths. Our sample size included 299 children in a well-characterized asthma population and represented a diverse group of subjects, particularly with regard to race and ethnicity. Several notable findings are highlighted by these analyses. First, levels of radon exposure in our study were all greater than the natural outdoor level of radon (14.8 Bq/m^3), which is the level U.S. Congress has set as the target indoor radon level per the Indoor Radon Abatement Act of 1988,[20] though lower compared to the EPA recommended action level of 148 Bq/m^3 advised for indoor radon mitigation.[21, 22] Despite this, we found a clear relationship between higher radon exposure with increased asthma symptom-days and higher F_ENO levels. Our findings suggest radon is an important contributor to asthma morbidity at levels below existing EPA guidelines, which were developed specifically based on lung cancer risk associated with radon.[23] In addition, due to lower proximity to the ground, smaller lungs, and faster breathing rates in children, which may draw radon and other air pollutants deeper into children's lungs, young children may experience even higher levels of radon exposure.[23, 24]

Second, we report elevated F_ENO with cold compared to warm seasons for participants with higher indoor radon exposure and found increased asthma symptoms associated with radon exposure. F_ENO measures airway inflammation, with higher levels associated with asthma exacerbations and lung function decline. In chronic inflammatory airway disease, including asthma, standard tests such as FEV_1 reversibility or provocation tests are only indirectly associated with airway inflammation, with spirometry measuring airflow limitation, while F_ENO offers an advantage of directly reflecting the extent of airway inflammation.[25] Therefore, the absence of finding an association with spirometry may be a reflection of the sensitivity of the measure rather than lack of airway disease.

It is known radon levels may fluctuate seasonally, with indoor levels typically higher during winter months,[26] at a time when windows and doors are more often shut limiting natural ventilation. Additionally, use of heaters leads to warm air which can drive pressure differences in the home causing radon gas from soil in the ground to be entrained from

beneath homes.[27] At the same time, cold weather can cause the ground to become more compact and create pressure for radon to escape from the ground beneath homes through cracks, holes, or porous entry points in the foundation. With the combination of increased exposure levels and increased time spent indoors in cold weather, it is not surprising we found radon was associated with seasonal change in F_ENO, where participants with higher radon exposure (>50th percentile radon, Figure 2) had greater change in F_ENO from warm to cold periods compared to low radon exposure (<50th percentile radon). While the levels of F_ENO in our study were generally within what may be considered normal range [Mean ppb (SD) 21.0 (22.5), range 5.0–143 ppb], the highly significant difference in levels indicates a true biological and clinically relevant effect that is further supported by symptomatic relationships in asthma found in our study.

While we found a significant association of radon exposure with airway inflammation and asthma symptoms, there was lack of a significant association of radon with lung function via spirometry in our study, which may be due to several factors. Previous studies assessing spirometric measurements and bronchodilator response in children have described poor sensitivity in the pediatric population, thus highlighting challenges in pediatric asthma to measure clinically significant change in lung function.[28–30] Additional studies have also found that in children with asthma, lung function tends to be normal even among those with severe asthma.[31] Furthermore, asthma is assessed by multiple measures, with phenotypic research in asthma highlighting various domains of asthma presentation and treatment responses, with variable emphasis on lung function abnormalities, exacerbations, inflammatory biomarkers, and symptoms.[32, 33]

We did not find effect modification by allergic sensitization in the relationship between radon exposure and any of our asthma outcomes suggesting that the presence of atopy is not an important part of the mechanism by which radon exerts its health effects. This is supported by other data that has demonstrated radon to cause oxidative stress in cell culture[34,35] and in vivo murine models.[36] In this study, oxidative stress induction was evidenced by increased protein expression of Nrf-2 and its down-stream antioxidant proteins, which are consistent with changes in oxidative stress indices and likely to play a significant role.[36] Additionally, human exposure studies examining the associations between particle radioactivity and biomarkers of oxidative stress and inflammation have demonstrated increase in biomarkers of oxidative stress and inflammation, such as increases in interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and P-selectin.[37] These findings, together with our current study results, suggest radon's respiratory effects are not mediated by conventional TH_2 inflammatory mechanisms which are primarily implicated in pediatric asthma. This study utilized the clinically relevant measures of atopy. Measures of non-TH_2 biomarkers was beyond the scope of this analysis but will be important to evaluate in future analyses.

There are a few limitations that should be noted. We were limited in our ability to assess the effect of co-pollutants as the parent study did not collect in-home dust or personal pollution samples. Our residential radon models are based on zipcode-based geospatial models. We performed sensitivity analyses to assess potential confounding by ambient $PM_{2.5}$, NO_2, and O_3 and found largely consistent relationships between radon and our health outcomes,

even despite a high degree of collinearity of the exposures. We recognize that direct measurement of radioactivity inside the classrooms using scintillation, ionization chamber or solid-state detection methods would offer more specific personalized measures of exposure. However, these measurements were not included in the SICAS protocol. Nevertheless, ZCTA offers validated spatiotemporal estimates for residential radon. Future studies should include directly measured radon, and co-pollutants to fully understand how these personal exposures affect respiratory health. As with any epidemiologic exposure study, the effect of unmeasured confounders is a risk.

We acknowledge we did not have complete data for the $F_E NO$ outcome due to its late addition to the study protocol. However, these limited data do not suggest bias, as it would be considered missing completely at random due to study design rather than related to participant characteristics; the associations that we were able to find despite limited number of observations is indicative of the strength of the findings. Finally, we used modeled radon exposure in the absence of directly measured exposure; however, the model is derived from measured in-home values and has been validated.[7] Future studies directly measuring radon may serve to complement our findings and further illuminate radon's effects on asthma.

CONCLUSIONS

Residential radon has not previously been described as an environmental risk factor for asthma morbidity.[5] Our work demonstrates radon is associated with increased asthma symptoms and elevated $F_E NO$ in inner-city children with asthma, suggesting radon exposure may be an important novel and modifiable environmental risk factor for asthma morbidity in children. While the levels of $F_E NO$ in our study were generally within what may be considered normal range [Mean ppb (SD) 21.0 (22.5), range 5.0–143 ppb], the highly significant difference in levels indicates a true biological and clinically relevant effect that is further supported by symptomatic relationships in asthma found in our study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Data Availability Statement:

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Abbreviations:

Bq/m^3	Becquerels per cubic meter
BMI	body mass index
F_ENO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
FEV_1/FVC	percent of forced expiratory volume in 1 second over forced vital capacity
ICS	inhaled corticosteroid
IRR	incidence rate ratio
NO_2	nitrogen dioxide
O_3	ozone
PFT	pulmonary function test
$PM_{2.5}$	particulate matter 2.5 μm in diameter

| **SICAS** | School Inner-City Asthma Study |
| **ZCTA** | ZIP Code Tabulation Area |

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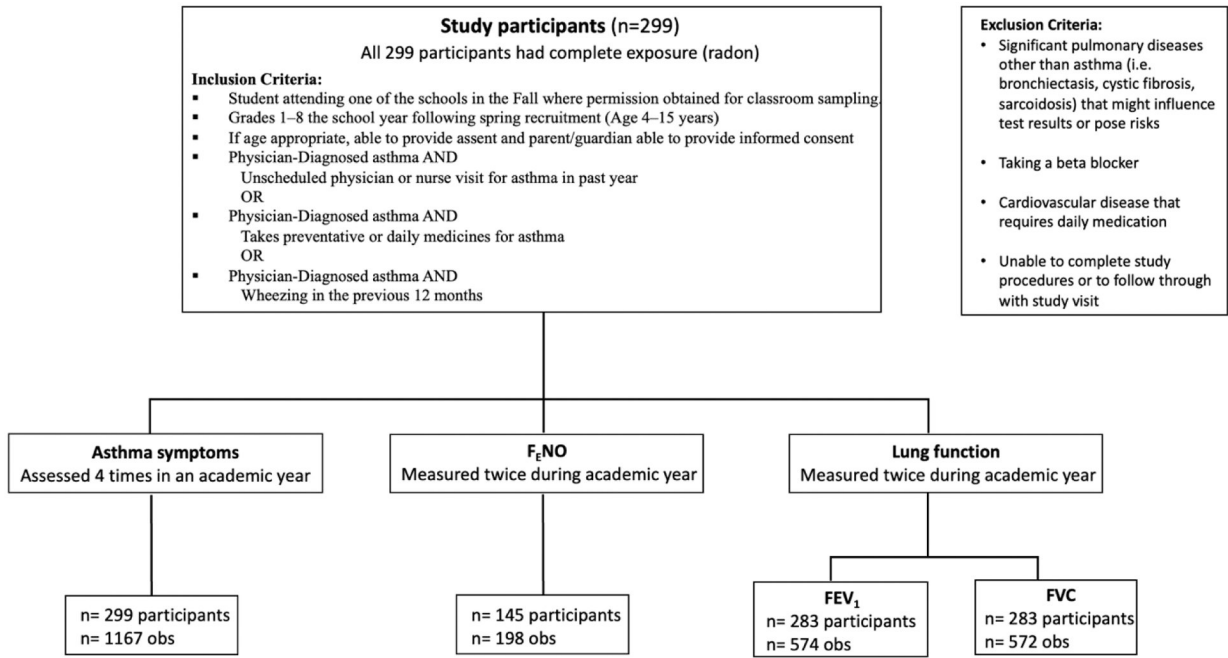
Figure 1.

Inclusion and Exclusion Criteria with Number of participants and observations for variables (Exposure and Outcomes)

Flowchart shows the inclusion and exclusion criteria for the study and the number of study participants and observations, highlighting that all study participants (n=299) had complete exposure (radon). The outcomes with number of observations and study participants are also shown.
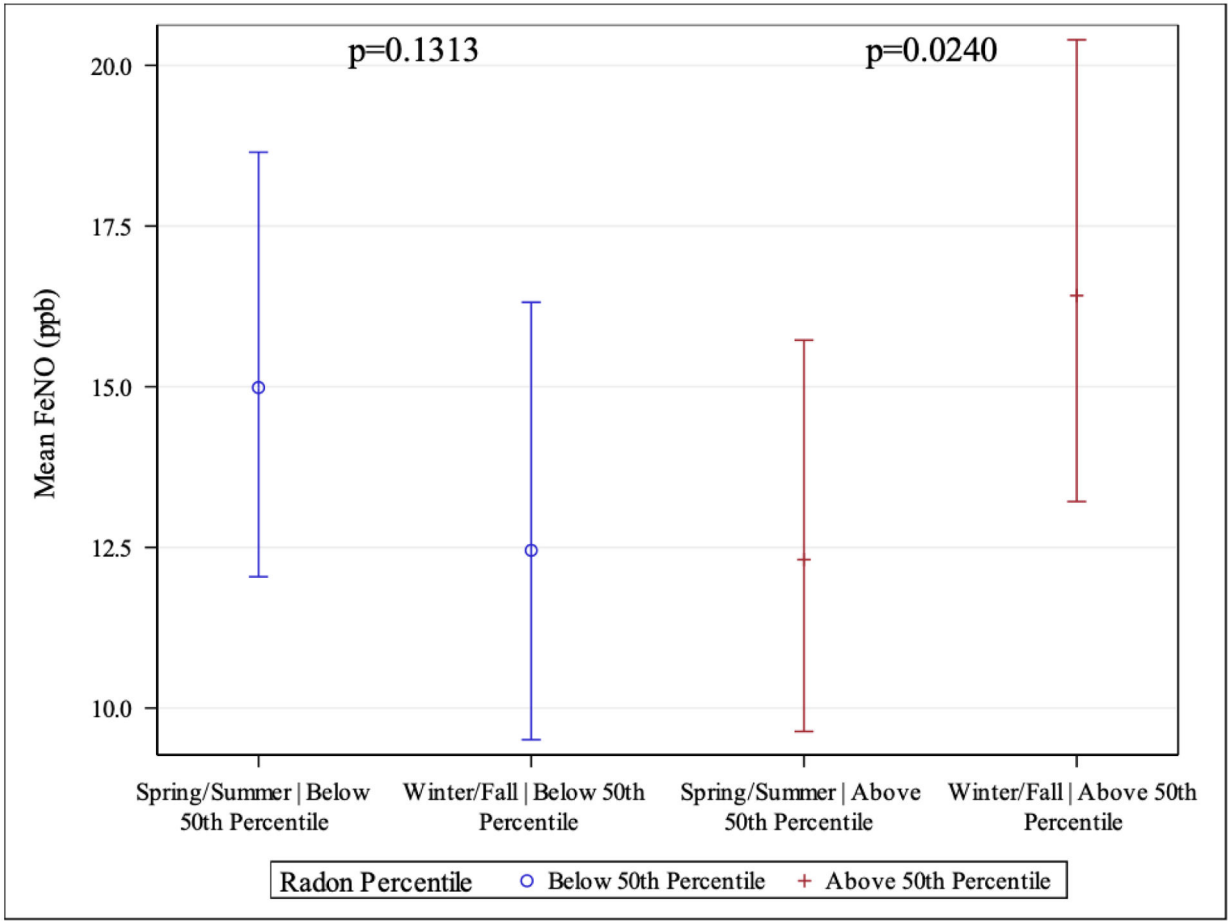
Figure 2. Radon is associated with seasonal change in F_ENO in school-age children with asthma.
Interaction between indoor radon exposure and seasonal period predicting log-transformed F_ENO for 1-month moving average. Participants with high radon exposure (>50th percentile radon; red bars) had greater change in F_ENO from warm (Spring/Summer) to cold periods (Winter/Fall) compared to low radon exposure (<50th percentile radon; blue bars) (interaction p=0.0013). Interaction between >50th percentile radon exposure over 1-month moving average and seasonal period (n=198, p=0.0099). Above 50th percentile (β= 0.29 [95% CI: 0.04, 0.54], p=0.0240). Below 50th percentile (β= −0.19 [95% CI: −0.43, 0.06], p=0.1313).

Table 1.

Study participant characteristics at baseline (n=299)

Variable	Description	N=299
Age	*Mean (SD)*	8.5 (1.8)
Female, n (%)		142 (47.5%)
Race or ethnic group, n (%)	*Black*	111 (37.1%)
	Mixed	52 (17.4%)
	Other	124 (41.5%)
	White	12 (4.0%)
Hispanic, n (%)		104 (34.8%)
Household Income <$25,000, n (%)	*No*	126 (42.1%)
	Yes	128 (42.8%)
	Unknown	45 (15.1%)
BMI Percentile	*Mean (SD)*	74.6 (27.1)
BMI Category, n (%)	*Underweight*	4 (1.3%)
	Normal	150 (50.2%)
	Overweight	39 (13.0%)
	Obese	106 (35.5%)
Allergic Sensitization 1 allergen, n (%)		214 (71.6%)
ICS Controller Medication Use, n (%)		91 (30.4%)
$F_E NO$ (ppb) [†]	*Mean (SD)*	21.0 (22.5)
FEV_1% predicted [‡]	*Mean (SD)*	101.1 (19.2)
FVC % predicted [§]	*Mean (SD)*	100.0 (17.6)
FEV_1/FVC [¶]	*Mean (SD)*	0.9 (0.1)
Maximum asthma symptom-days [#]	*Mean (SD)*	2.9 (4.1)

FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; $F_E NO$: fractional exhaled Nitric Oxide.

Maximum asthma symptom-days = in the 2 weeks prior to each follow-up survey, the greatest result of the following three variables: 1) number of days with wheezing, cough, or chest tightness, 2) number of days on which child had to slow down or discontinue play activities due to wheezing, chest tightness, or cough, 3) number of nights with wheezing, cough, or chest tightness leading to disturbed sleep due to child's asthma

[†] total n included (%): 95 (31.8%),

[‡] total n included (%): 261 (87.6%),

[§] total n included (%): 261 (87.6%),

[¶] total n included (%): 261 (87.6%),

[#] total n included (%): 284 (99.3%)

Table 2.

Quantiles of indoor radon exposure (Bq/m^3) for 1-month moving average

Level	Quantile
100% Max	83.50
75% Q3	54.69
50% Median	49.75
25% Q1	45.42
0% Min	33.67

Table 3.

Multivariate regression modeling predicting maximum asthma symptom-days by radon 1-month and 2-month moving average.

	Radon 1-month moving average		Radon 2-month moving average	
	IRR	p-value, 95% CI	IRR	p-value, 95% CI
Maximum Asthma Symptom-Days[a]	1.014	p=0.0273, 1.002 to 1.027	1.015	p=0.0286, 1.002 to 1.028

Main effects of indoor radon exposure predicting maximum asthma symptom-days in school-age children with asthma show a positive association between radon 1-month moving average (IRR=1.014, 95% CI [1.002,1.027], p=0.0273) and radon 2-month moving average (IRR=1.015, 95% CI [1.002,1.028], p=0.0286) with maximum symptom-days (n=299, obs=1,167). Multivariate model: Maximum symptoms-days adjusted for Age, Race, Gender, BMI, ICS controller medication use, allergic sensitization, and household income <$25,000.

IRR = Incidence rate ratio, CI = Confidence interval

[a]Maximum asthma symptom-days = in the 2 weeks prior to each follow-up survey, the greatest result of the following three variables: 1) number of days with wheezing, cough, or chest tightness, 2) number of days on which child had to slow down or discontinue play activities due to wheezing, chest tightness, or cough, 3) number of nights with wheezing, cough, or chest tightness leading to disturbed sleep due to child's asthma