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Original Research

Modification of asthma treatment efficacy by healthcare access: A reanalysis of AsthmaNet Step-Up Yellow Zone Inhaled Corticosteroids to Prevent Exacerbations (STICS) clinical trial

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ABSTRACT

Background: While randomized controlled trials (RCTs) in asthma management are designed to balance known and unknown variables across treatment groups, including social and environmental co-exposures, it remains important to consider how these co-exposures influence disease progression and treatment outcomes. The importance of considering socio-environmental co-exposures in the context of asthma is twofold: 1) asthma disproportionately affects low-income urban communities, where air pollution and chronic stress are pervasive; and 2) despite the wide range of asthma treatments, inadequate disease control persists.

Methods: In the present ancillary study of the Step-Up Yellow Zone Inhaled Corticosteroids to Prevent Exacerbations (STICS) RCT, we investigated how socio-environmental factors, such as air pollution exposure and healthcare access, modify the effect of inhaled corticosteroid (ICS) therapy in children with asthma. The original STICS RCT evaluated the efficacy and safety of increasing the dose of inhaled glucocorticoids from a baseline daily low dose to five times the daily dose for 7 days in school-age children with mild -to-moderate persistent asthma who began to have short-term loss of asthma control (Jackson et al., 2018 Mar 8) [1]. Our study adds onto those findings by incorporating residential level particulate matter 2.5 μg/m3 (PM2.5) and geographic health provider shortage areas (HPSA) as potential modifiers.

Results: Consistent with the main trial results, we did not find a difference in the number of exacerbations between treatment arms. However, we found the effect of receiving 5xICS, as compared with 1xICS on the time to prednisone was significantly different for children living in areas a shortage of health professionals (HR: 2.09; 95 % CI: 0.74, 5.95) than for children living in no shortage areas (HR: 0.40; 95 % CI: 0.21, 0.77).

Conclusion: This finding underscores the importance of considering environmental and social factors in asthma treatment.

Trial registration: ClinicalTrials.gov ID NCT02066129 https://clinicaltrials.gov/study/NCT02066129.

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1. Introduction

Randomized controlled trials (RCTs) are regarded as the gold standard for studying causal relationships in medical research, however, their rigorous screening processes and stringent enrollment criteria circumscribe the characteristics of the populations represented within the trial and thus compromise external validity [2]. This is a particularly notable issue in the context of pediatric asthma, as an estimated 50.3 % of children with current asthma have uncontrolled asthma [3] We posit that although RCTs treatment arms are carefully balanced in clinical outcomes at randomization, other co-exposures may be differentially distributed between treatment arms, especially in a relatively small RCT; and that these social and environmental co-exposures may influence treatment efficacy. Therefore transporting results from RCTs to standard clinical care practices necessitates exploring whether internally valid results apply to target populations of interest [4,5].

Given the role of exacerbations on the etiology and economic burden of asthma [6], research attention is focused on treatment efficacy of asthma medications. These include efficacy of inhaled corticosteroids (ICS) to reduce asthma exacerbations while also preventing exposure to systemic steroids. One trial – the Step-up Yellow Zone Inhaled Corticosteroids to Prevent Exacerbations (STICS), implemented by the National Institutes of Health AsthmaNet network, examined the effect of quintupling the dose of inhaled corticosteroids at the early signs of loss of asthma control on asthma exacerbations. The main STICS study found no statistically significant reduction in the rate of severe asthma exacerbations, nor any statistically significant difference in other asthma outcomes, between treatment arms [1]. However, these null findings may result from a combination of differential responses across groups based on differential exposure to socio-environmental features known to impact asthma [7–9]. For instance asthma severity among children varies substantially by socioeconomic status, in part because participants with lower socioeconomic status often reside in areas with greater air pollution, chronic stressors and poorer-quality housing [10]. Additionally, access to healthcare plays a pivotal role in managing asthma effectively. Children residing in communities with limited healthcare access, such as Health Professional Shortage Areas (HPSAs) or Medically Underserved Areas (MUAs), face challenges in obtaining timely and appropriate asthma care. This limitation not only affects the immediate management of asthma exacerbations but also impacts long-term asthma control, potentially altering the efficacy of interventions like ICS.

Exposure to air pollutants, including particulate matter less than 2.5 $\mu g/m^3$ in diameter ($PM_{2.5}$), is associated with increased asthma exacerbations [11], increased emergency room visits [12], and decreased lung function [13]. When fine particles deposit in the alveoli, they can trigger lower airway and parenchymal inflammation [14] and impair lung function. The literature on whether treatment with ICS prevents or worsens air pollution-mediated-asthma morbidity is modest to date; however, cigarette smoke, which has parallels with air pollution, has been shown to induce ICS resistance in asthma and thus it is feasible that air pollution may have similar effects [15,16]. Further, a vast body of evidence shows that children who grow up socioeconomically disadvantaged experience greater levels of inflammation and worse asthma symptoms than children from more advantaged backgrounds, leading to potential glucocorticoid resistance [17].

In the present study we hypothesize that air pollution modifies the ICS intervention response in the STICS trial, by decreasing the *time-to-systemic-glucocorticoid-use* among those with higher pollution exposures. We further hypothesize that individuals living in impoverished neighborhoods, characterized by decreased access to medical care (HPSA) or in medically underserved areas (MUAs), will be less responsive to the ICS intervention than children living in areas with greater access to healthcare. To explore these hypotheses, our study has been approved by AsthmaNet as an ancillary study for its novelty and potential to address critical gaps in asthma treatment efficacy research. We leverage geospatial methods, particularly Geographic Information Systems (GIS) based analyses, to allow for the examination of social and environmental exposures that are differentially distributed across trial participants regions and communities. Given the well-documented impacts of air pollution [7–9,18,19] and social stressors [20–22] on asthma onset and exacerbations, utilizing GIS-based spatial analysis is particularly relevant to RCTs for asthma.

2. Methods

STICS was a population-based clinical trial previously described in detail [1]. Briefly, 254 children aged 5–11 years were randomized in a 1:1 fashion to receive double blinded therapy either at a low dose (1xICS) or high dose (5xICS). Enrollment occurred between 2014 and 2016, and of 444 children initially enrolled, 254 underwent randomization and were followed through March 2017. Upon early signs of loss of asthma control or "yellow zone events," participants randomized to 5xICS were prescribed two inhalations of 220 μg/inhalation of Fluticasone twice daily for seven days, while the group randomized to the low dose group continued with the 1xICS of Fluticasone at 44 μg/inhalation of Fluticasone twice daily for seven days. The current ancillary analysis includes 219 children who completed the STICS trial and whose parent/guardian consented to the use of their residential address for geocoding and spatial analyses.

2.1. Outcomes

The trial primary outcome of the trial was the rate of severe asthma exacerbations treated with systemic glucocorticoids (Prednisone) during the blinded study treatment period, prescribed irrespective of residential location. Systemic glucocorticoids use was started after participants reported >6 inhalations of albuterol, a short-acting beta agonist (SABA) in 6 h, ≥12 inhalations of albuterol in 24 h, night awakenings leading to albuterol use during 2 of 3 consecutive nights, or ≥8 inhalations of albuterol during 2 of 3 consecutive days. Secondary outcome measures included time-to-first-asthma exacerbation and treatment failure [defined as 2 asthma exacerbations in 6 months, 3 asthma exacerbations in 1 year, or 6 treated yellow zone episodes]. In this study, we examined the primary and secondary outcomes from the STICS trial.

2.2. Geocoding, social, and environmental exposure estimates

Geocoding: The address(es) of each participant's residential location throughout the 52-week trial (4-week run-in and 48-week treatment) were collected by clinical coordinators and geocoded to x,y coordinates using ArcGIS™ (ESRI 2019). A custom-generated address locator using off-line reference data was used to ensure patient confidentiality and maximize positional accuracy of address locations [23]. Addresses were geocoded with a 100 % match rate (n = 219).

Air Pollution Estimates: $PM_{2.5}$, NO_2 and O_3 exposures were estimated for each participant using a spatiotemporal regionalized national universal kriging model [24]. The model combines fine-scale spatial covariates, including roadway information, with daily $PM_{2.5}$, NO_2 and O_3 concentration measurements from EPA AQS, IMPROVE monitoring sites, and researcher-led monitoring campaigns. We estimated two-week average $PM_{2.5}$, NO_2 and O_3 concentrations (in $\mu g/m^3$, ppm and ppb respectively) for all participants based on the centroid of their residential census block. We then computed a simple moving average of the exposure for each participant over the trial follow-up period. For the 14 children whose residence changed during follow up, we computed two-week moving averages corresponding to their combined residential locations. Addresses were stripped from the analytic data set after geocoding and exposure assignments; subsequently, we mapped data positions randomly perturbed to maintain the confidentiality of geographic locations.

Poverty: Census Block Group level data on income-to-poverty ratio

were obtained from the 2012–2016 American Community Survey 5-Year summary tables. The income-to-poverty ratio is a percentage comparing income to the federal poverty threshold. We calculated the percentage population with a ratio of income-to-poverty of less than 1 (below 100 % of the poverty threshold) for each Block Group and overlaid STICS patient locations to assign poverty values.

Medically underserved areas and Health Professional Shortage Areas: The US. Health Resources and Services Administration defines Medically Underserved Areas (MUAs) as areas lacking access to primary health care services. An MUA designation depends on the Index of Medical Underservice (IMU) score (1–100), calculated based on the provider-to-population ratio, poverty percentage, population age, and infant mortality rate. Any area with an IMU of 62.0 or below qualifies as an MUA. Health professional shortage area (HPSA) designations are either a geographic area, population group, or health care facility designated by the Health Resources and Services Administration (HRSA) as having a shortage of health professionals. Here we use Primary Care Physician HPSA for census tracts.

Individual and area-level covariates: Adjusting for potential pre-randomization covariates, is considered a good and conservative approach to ancillary RCT analyses [25,26]. Including these pre-randomization covariates reduced the uncertainty associated with outcome measures, thereby increasing the power of the study but did not impact the magnitude of the association between treatment and outcome. Pre-randomization covariates, such as age at enrollment, number of pets, gender, poverty, and race/ethnicity, were selected based on their potential to predict the outcome rather than their influence on treatment assignment, as they are assessed prior to randomization. All co-exposures of interest were median dichotomized to deal with non-parametric statistical approaches and for interpretability.

2.3. Statistical methods

The main objective of our analysis was to assess whether socio-environmental variables modified the effect of ICS treatment, at a high versus low dose on the 1) rate of asthma exacerbations, 2) time to asthma exacerbation treated with oral corticosteroids and 3) time to treatment failure.

We conducted this analysis in three steps. First, we replicated the results of the original STICS trial. Original analysis code was provided by the Data Coordinating Center for the NHLBI Asthma Network (AsthmaNet). For this, we modeled the rate of severe asthma exacerbation using a generalized linear model, with a log link function and response following a negative binomial distribution. The model includes recruitment site as a covariate and follow up time as an offset. We summarized time to-event outcomes (outcomes 2 and 3) using Kaplan-Meier curves and compared treatments with the log-rank test [1].

Second, to test whether there was effect modification by socio-environmental variables, we added an interaction term between median dichotomized modifiers and treatment to the generalized linear model. We fitted the stratified Cox Proportional Hazards regression extension to time-to-event outcomes. The significance of interactions between the social/environmental modifier variables and the treatment was assessed using ANOVA Type III tests. We summarized time to event outcomes using Kaplan-Meier curves, and confounders were selected a priori. All tests performed were two-sided, and a P-value of less than 0.05 was considered statistically significant.

Third, we conducted sensitivity analyses to examine results robustness, including removal of outliers (participants with more than 6 exacerbation events over follow-up), not adjusting for potential pre-randomization covariates, requiring a minimum number of days in the study [i.e., at least 100 (n = 201) or at least 180 days (n = 187)], and categorization of effect modifiers in quartiles rather than binary groups. All analyses were performed using SAS software, version 9.4 (SAS Institute), and $PM_{2.5}$ exposure estimates were assigned using R version 3.6.3 (R Core Team 2021).

3. Results

3.1. Descriptive results

Table 1 presents the baseline characteristics of the STICS trial participants. Between March 2016 and March 2017, 254 participants were randomized and subsequently followed. Each treatment arm had 127 participants. Of these, 35 were excluded from the current analysis due to missing addresses or lack of consent for address use post-study completion. Details of the population are shown in Table 1 and the comparison between the full study population in the STICS trial (n = 254) versus the ancillary population utilized in the present study (n = 219) are presented in Table 2.

We observed differences in individual characteristics between the treatment arms, most notably the 5xICS arm had proportionately more White children (49.6 % v 32.4 %) than the 1xICS arm. A greater proportion of children randomized to the 1xICS reported "other" or multiple race categories more often than those randomized to the high ICS group (12.0 % v 4.5 %). No baseline differences were observed between treatment arms in percent forced respiratory volume in 1 s (FEV1%) or the number of emergency department visits in the last twelve months. Further, there were no differences observed between the two treatment arms in terms of census tract poverty levels (11.0 % v 13.1 %), but more children living in MUA (29.7 % v 24.1 %) were also randomized to the 5xICS arm, than those in 1xICS arm. Children randomized to the 5xICS group were more frequently exposed to secondhand smoke at home than those randomized to the 1xICS group (31.5 % v 26.9 %). There were no significant differences between the treatment groups in air pollution exposures, which ranged from 2.09 to 30.96 ppm for NO_2, 9.83–38.90 ppb for O_3 and 3.30–11.44 μg for $PM_{2.5}$.

3.2. Rate of asthma exacerbations

In the original STICS trial, the rate of exacerbation did not differ significantly between the two groups (5xICS = 0.48/year v 1xICS = 0.37/year, [p = 0.31]) [1]. In our reanalysis, when we examined socio-environmental modifiers, we found no significant effect modification of the treatment on asthma exacerbation rates by levels of $PM_{2.5}$, NO_2 and O_3 between the treatment groups (P for interaction 0.48, 0.43

Table 1
Analytic sample characteristics at baseline (n = 219).

Characteristic	1xICS, N = 107		5xICS, N = 111	
	N	N = 107[a]	N	N = 111
Age Group	107		111	
5–8 yrs		53 (50 %)		57 (51 %)
8–11 yrs		54 (50 %)		54 (49 %)
Body Mass Index	107	17.0 (15.6, 19.2)	111	16.8 (15.6, 20.0)
Sex	107		111	
Male		66 (62 %)		74 (67 %)
Female		41 (38 %)		37 (33 %)
Race	107		111	
White		31 (29 %)		46 (41 %)
Black		23 (21 %)		22 (20 %)
Hispanic		32 (30 %)		32 (29 %)
Other		21 (20 %)		11 (9.9 %)
Mean NO_2	107	9.4 (6.1, 13.4)	111	8.6 (5.8, 13.2)
Mean $PM_{2.5}$	107	7.49 (6.58, 8.51)	111	7.33 (6.68, 8.40)
Mean O_3	107	25.7 (23.5, 28.9)	111	25.4 (23.5, 28.7)
HPSA[b]	107		111	
No		61 (57 %)		69 (62 %)
Yes		46 (43 %)		42 (38 %)
MUA[c]	107		111	
No		81 (76 %)		78 (70 %)
Yes		26 (24 %)		33 (30 %)

[a] n (%).
[b] Geographic Health Provider Shortage Area.
[c] Medically Underserved Areas.

Table 2
Analytic Sample Characteristics at baseline of full STICS population (n = 254) and ancillary analyses (n = 219).

Characteristic	Full STICS		Ancillary STICS	
	1xICS	5xICS	1xICS	5xICS
	N = 127	N = 127	N = 107	N = 111
Age Group				
5–8 yrs	63 (50 %)	63 (50 %)	53 (50 %)	57 (51 %)
8–11 yrs	64 (50 %)	64 (50 %)	54 (50 %)	54 (49 %)
Body Mass Index	17.1 (15.6, 19.4)	17.1 (15.6, 20.1)	17.0 (15.6, 19.2)	16.8 (15.6, 20.0)
Sex				
Male	80 (63 %)	83 (65 %)	66 (62 %)	74 (67 %)
Female	47 (37 %)	44 (35 %)	41 (38 %)	37 (33 %)
Race				
White	37 (29 %)	49 (39 %)	31 (29 %)	46 (41 %)
Black	27 (21 %)	26 (20 %)	23 (21 %)	22 (20 %)
Hispanic	36 (28 %)	39 (31 %)	32 (30 %)	32 (29 %)
Other	27 (21 %)	13 (10 %)	21 (20 %)	11 (9.9 %)

and 0.25, respectively) (Fig. 1). However, HPSA, age, and MUA modified the rate of exacerbation (P for interaction = 0.003, 0.04 and 0.03, respectively) (Fig. 2). We found the difference in asthma rates in children treated with 5xICS versus treated 1xICS for those living in non-HPSAs is 2.28/year (95 % CI: 1.17, 4.45, [P = 0.02]); in contrast, the difference in asthma rates in children treated with 5xICS versus 1xICS for those living in HPSAs was 0.39/year (95 % CI: 0.14, 1.04, [P = 0.06]). Additionally, our results show a significant interaction between treatment and MUAs. While the rate of asthma exacerbation for children treated with 5xICS versus 1xICS among MUAs was 1.82 exacerbations/follow up period (95 % CI: 0.99, 3.34, [P = 0.05]), the difference between treatment with 5xICS versus 1xICS in non-MUAs was 0.48 exacerbations/follow up period (95 % CI: 0.17, 1.37, P = 0.17) (Fig. 2).

3.3. Time to prednisone and time to treatment failure

Our analyses reveal that the effect of receiving 5xICS, as compared with 1xICS on the time to prednisone was stronger for children living in areas with a shortage of health professionals (HR: 2.09; 95 % CI: 0.74, 5.95) than for children living in non-shortage areas (HR: 0.40; 95 % CI: 0.21, 0.77). This difference was statistically significant (P = 0.01). Within strata of HPSA, we saw a shorter time to prednisone use among children taking the 5xICS, compared to children taking the 1xICS (Fig. 3); however, this was only among the non-HPSAs. The effect of receiving 5xICS, as compared with 1xICS, on the time to treatment failure was stronger for children living in HPSA (HR: 4.25; 95 % CI: 0.49, 36.5; p-value = 0.04) than for children living in no shortage areas (HR: 0.27; 95 % CI: 0.05, 1.28). This difference was statistically significant (P = 0.04). There were no observable differences in the time to treatment failure within strata. Sensitivity analyses performed did not yield different results, as described in Supplementary Materials.

4. Discussion

In this study, we aimed to evaluate whether socio-environmental factors, specifically $PM_{2.5}$ exposure and neighborhood-level indicators of healthcare access, modify the therapeutic effect of Step-Up Inhaled Corticosteroids. To our knowledge, this is the first *post hoc* analysis to simultaneously investigate the influence of social and environmental factors on ICS treatment efficacy for asthma and to examine variations in efficacy within groups identified by well-known determinants of asthma.

In the present study we showed a statistically significant difference in the effect of treatment with a "stepped up" dose (5xICS) versus 1xICS on the yearly rates of asthma exacerbation. There was a stronger effect of receiving 5xICS, as compared to the 1xICS for children living in HPSAs than for children in non-HPSAs for all three outcomes of interest. Further, participants who received 5xICS compared to 1xICS and lived in a non-MUA census block groups had a lower rate of asthma exacerbation than children living in MUA census blocks. These findings corroborate our hypothesis that social stressors influence treatment efficacy, and that said efficacy can be differentially generalizable to specific subpopulations. Previous research has consistently highlighted HPSAs as regions with not only limited access to healthcare professionals but also as areas potentially characterized by higher environmental risks, which may exacerbate asthma symptoms [27].

Likewise, for individuals living in non-MUAs and receiving a 5xICS dose (compared to 1xICS), there is an observed increase in the rate of asthma. This finding suggests that the benefits of increasing ICS dosages may not uniformly extend across different populations, particularly those outside of traditionally underserved regions and challenges the assumption that higher doses of ICS are universally beneficial for asthma control [28]. These results add to the growing literature that demonstrate that, among children with asthma, stepping up the ICS dose is not only insufficient to mitigate the respiratory health impact associated with air pollution, but this treatment could also worsen it.

In a systematic review for the Cochrane Database of Systematic Reviews, results indicated that while stepping up ICS doses can improve lung function and reduce exacerbations in the short term, the benefits

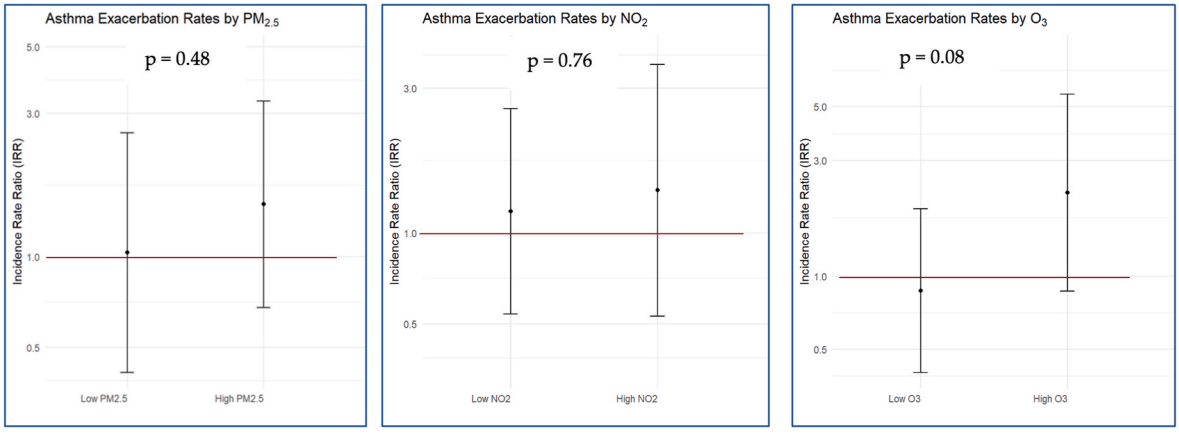

Fig. 1. Associations between treatment with 5xICS (versus 1xICS) and severe asthma exacerbations treated with systemic glucocorticoids by A) Median dichotomized NO_2 exposure among children in STICS trial, B) Median dichotomized O_3 exposure among children in STICS trial C) Median dichotomized $PM_{2.5}$ exposure among children in STICS trial. Incidence Rate Ratios (IRR) and 95 % confidence intervals are presented, and P-values shown are for the interaction term between treatment and each modifier.

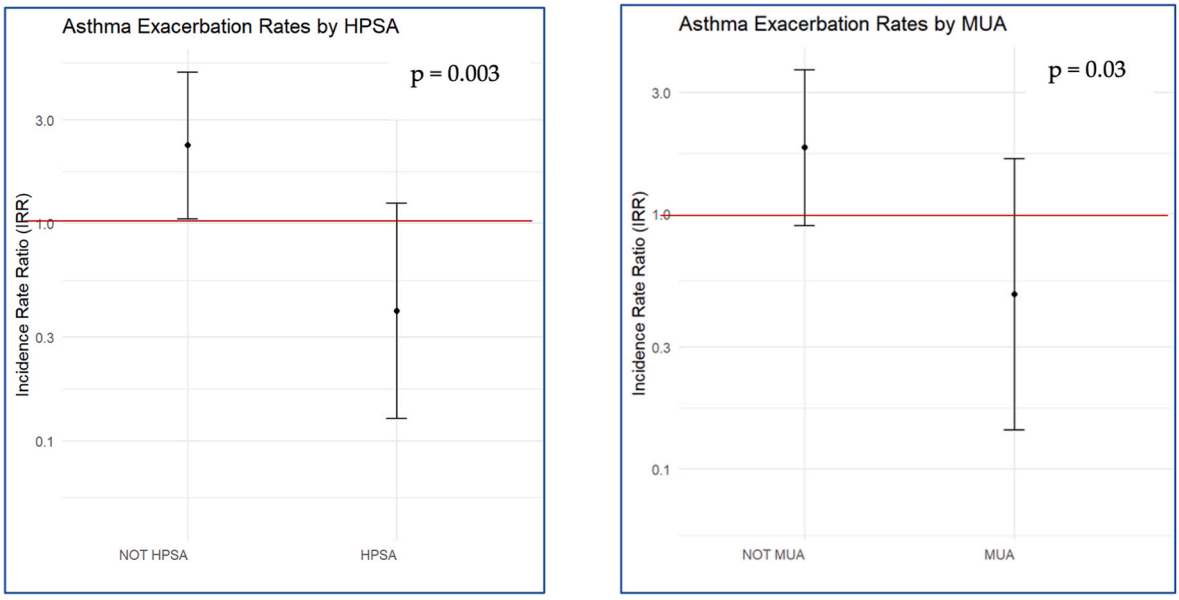

Fig. 2. Associations between treatment with 5xICS (versus 1xICS) and severe asthma exacerbations treated with systemic glucocorticoids by 1) Health provider shortage areas (left) 2) Medically Underserved Areas (right). Incidence Rate Ratios (IRR) and 95 % confidence intervals are presented, and P-values shown are for the interaction term between treatment and each modifier.

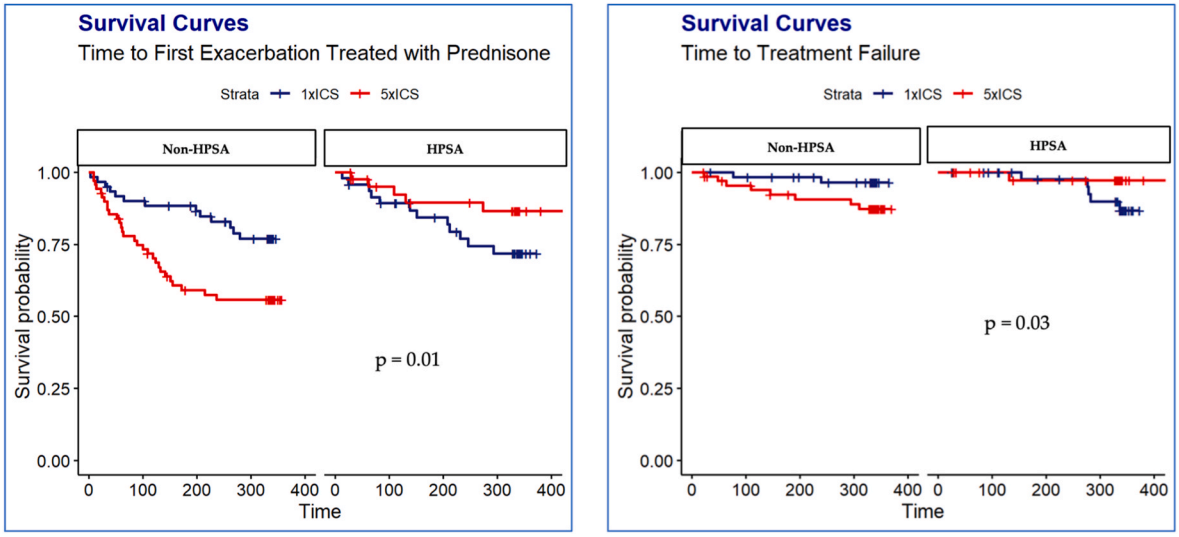

Fig. 3. Time to prednisone use in non-HPSA and HPSA (left) areas (p for interaction = 0.01). Time to treatment failure in non-HPSA and HPSA (right) areas (p for interaction 0.03). Blue line = low dose group (1xICS); red line = high dose group (5xICS). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

plateau at moderate doses, with minimal additional gains in control but increased risks of side effects at higher doses [29]. Jackson et al., found similar results in the main analysis of the STICS trial, there were no benefits of the stepped up dose on the time to first asthma exacerbation or time to treatment failure, nor did the 5xICS reduce the symptom scores or albuterol use [1]. This is corroborated by the Global INitiative for Asthma (GINA) guidelines, which advocate for the lowest effective ICS dose to manage asthma [30].

Although, understanding of the complex interactions between social stressors and asthma treatment outcomes continues to advance, the current body of literature exploring how the efficacy of ICS on asthma morbidity may be influenced by social stressors remains limited. The potential mechanisms through which social stressors interact with asthma treatment are multifaceted. For one, chronic stress may alter immune system responses, potentially affecting the inflammatory pathways that ICS aim to control [31]. Moreover, access healthcare constitutes a social determinant of health, and lack of accessible and readily available care can negatively influence asthma disease progression and control [32].

While RCTs increase the internal validity of study findings by employing rigorous screening during recruitment, social and environmental co-exposures that may modify treatment efficacy are often overlooked during this process. The results of this study show that social and environmental co-exposures can modify treatment effects, especially in smaller trials where randomization may not balance unmeasured covariates. Further consideration of variation in treatment efficacy among sub-populations differing in such co-exposures is essential to better understand the results of clinical trials and make them more generalizable to the asthma population.

4.1. Strengths and limitations

Strengths of this study include some of the strengths of the trial overall, as well as the strengths of our approach to this secondary analysis. The trial included rigorous screening protocols which were identical across multiple cities across the United States. This study incorporated GIS-based methods to locate each participant and characterize their neighborhood environment precisely. Additionally, mean $PM_{2.5}$, NO_2 and O_3 exposures over each participant follow-up period were estimated using a validated national spatiotemporal model and assigned at a fine spatio-temporal scale. However, our work is not without limitations. First, in this study, the two treatment groups had different income and racial/ethnic backgrounds at baseline; those in the higher treatment dose were more likely to be white and to live in wealthier census tracts than those in the lower-dose arm. These differences in the groups at baseline may help explain the lack of observed differences between treatment arms [1]. Nonetheless, we attempted to address these differences through adjustment for pre-randomization factors; however, it is possible that unmeasured confounders remained. Second, in this analysis we retained 86 % of the original trial population (219/254) with drop off primarily due to lack of consent-related to ancillary analyses. After excluding participants who did not consent to geocode their addresses, the remaining cohort had a lower reported prevalence of secondhand smoke exposure. This finding suggests that the process of obtaining consent for secondary analyses could inadvertently result in the loss of participants with certain risk factors or exposures. Nonetheless, after ancillary selection, the distribution of tobacco exposure remained balanced between treatment arms (Table 1). Lastly, a significant limitation lies in post hoc analyses of clinical trial data. While useful for generating hypotheses and uncovering trends not initially targeted, there is an inherent increased risk of Type I errors. But despite their limitations, post hoc analyses offer a valuable advantage in that they can maximize the utility of existing data, can help guide future research directions and identify potential associations and trends within the data.

5. Conclusions

Our post-hoc analysis does not change the primary conclusions of the original STICS trial, which found that quintupling the ICS dose at the early signs of loss of asthma control did not provide a significant overall benefit compared to maintaining the regular dose. But rather we found quintupling ICS may lead to worse outcomes in some higher-SES settings. While RCTs increase the internal validity of study findings by employing rigorous screening during recruitment, social and environmental co-exposures that may modify treatment efficacy are often overlooked during this process. The results of this study show that social and environmental co-exposures can modify treatment effects, especially in smaller trials where randomization may not balance unmeasured covariates. Further consideration of variation in treatment efficacy among sub-populations differing in such co-exposures is essential to better understand the results of clinical trials and make them more generalizable to the broader asthma population.

We observed weaker effects of treatment with high doses of inhaled corticosteroids (ICS) in children living in non-HPSA and non-MUAs, compared to HPSAs and MUAs. These findings suggest that participants' social and environmental co-exposures play a role in observed treatment efficacies, and that access to healthcare contributed to the lack of benefit of step-up therapy in the STICS ancillary analyses. Our study highlights the need for future research to consider the potential role of social and environmental factors when designing and analyzing clinical trials for asthma treatment and underscores the importance of individual's unique social and environmental context with respect to their treatment guidelines.

CRediT authorship contribution statement

Lizbeth F. Gómez: Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis, Conceptualization. **Ellen Kinnee:** Writing – review & editing, Supervision, Software, Data curation, Conceptualization. **Joel D. Kaufman:** Writing – review & editing, Data curation. **Michael T. Young:** Writing – review & editing, Resources, Data curation. **Anne M. Fitzpatrick:** Writing – review & editing. **Wanda Phipatanakul:** Writing – review & editing. **David T. Mauger:** Writing – review & editing, Supervision, Data curation, Conceptualization. **Leslie A. McClure:** Writing – review & editing, Supervision. **Usama Bilal:** Writing – review & editing, Supervision. **Fernando Holguin:** Writing – review & editing, Supervision, Conceptualization. **Jane E. Clougherty:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Data sharing

Data collected for this study, including individual participant data and a data dictionary defining each field in the set, will not be made available to others. Deidentified participant data, data dictionary, study protocol, statistical analysis plan, and informed consent form can be made available upon request. Access to the data will be granted after approval of a proposal and the signing of a data access agreement. Additional restrictions may apply depending on the proposed analysis and intended use of the data.

Contributions

The first draft of the manuscript was written by Lizbeth Gómez. GIS methods were written by Ellen Kinnee, and clinical relevance discussion was written by Fernando Holguin, Jane E. Clougherty, Usama Bilal and Leslie McClure completed all copy editing for this manuscript. All other authors contributed to the writing and editing of the final version of the manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2024.107853.

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