Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Jackson DJ, Bacharier LB, Mauger DT, et al. Quintupling inhaled glucocorticoids to prevent childhood asthma exacerbations. N Engl J Med 2018;378:891-901. DOI: 10.1056/NEJMoa1710988

Quintupling Inhaled Glucocorticoids to Prevent Childhood Asthma Exacerbations

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AsthmaNet STICS
Grant Support / Acknowledgement Roster

Site I	Grant Support	Author	Investigator	Coordinator	Site Affiliation
	Boston				
111	**HL098102**	*Elliot Israel*	*Juan Carlos Cardet*		*Brigham & Women's Hospital* *75 Francis St.* *Boston, MA 02115*
112	**HL098102**	*Jonathan Gaffin* *Wanda Phipatanakul* *William Sheehan* *Sachin Baxi*	*Elizabeth Burke-Roberts* *Marissa Hauptman* *Bridget Hron* *Lianne Kopel* *Stavroula Osganian* *Perdita Permaul* *Lakiea Wright*	*Christopher Burke* *Matthew Cavanaugh* *Amparito Cunningham* *Amanda Dimas* *Alana Gerald* *Latasha Nisbett* *Benjamin Peterson* *Daila Regos* *Timothy Ryan* *Doris Schierembergg* *Brian Volonte*	*Children's Hospital, Boston* *333 Longwood Ave, Suite 403* *Boston, MA 02115*
	Chicago				
122	**HL098096** **UL1TR001422**	*Jacqueline Pongracic* *Rachel Robison*	*Rajesh Kumar* *Melanie Makhija* *Christine Szychlinski*	*Iliana Flexas* *Kristen Koridek-Phillips* *James Lane*	*Ann & Robert H. Lurie Children's Hospital* *Division of Allergy & Immunology* *225 East Chicago Avenue #60* *Chicago, IL 60611*
125	**HL098096**	*James Moy*	*Christopher Codispoti* *Byung Yu*	*AnnaMaria Kayaloglou* *Grace Li* *Shannon Stevens* *Samantha Zitzer*	*Rush University Medical Center* *1725 W. Harrison St, Ste 117* *Chicago, IL 60612*
126	**HL098096**	*Jerry Krishnan* *Harsha Kumar*	*Sharmilee Nyenhuis*	*Vanessa Gonzalez* *Melissa Morales-Perez* *Victoria Morken*	*University of Illinois – Chicago* *1220 S Wood Street* *Chicago, IL 60608*

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	Denver				
132	***HL098075*** ***UL1 TR001082***	*Ronina Covar* *Tod Olin*	*Gayle Spears* *Stanley Szefler* *Michael E. Wechsler* *Lea Davies*	*Stephanie Jump* *Joseph Ruybal* *D Sundstrom* *Michael White*	*National Jewish Health* *Room A303* *1400 Jackson St.* *Denver, CO 80206-2761*
133	***HL098075*** ***UL1TR001449***	*Hengameh Raissy*	*Laura Caffey*	*Christina Batson* *Franceska Kelly* *Abby Redway*	*University of New Mexico* *Health Sciences Center* *MSC 10-5590* *1 University of New Mexico* *Albuquerque, NM 87131-0001*
	Madison				
141	***HL098090***	*Daniel Jackson* *Robert Lemanske*	*Sima Ramratnam*	*Megan Knutson* *Shelly Olson* *Valerie Schend* *Tanya Watson*	*University of Wisconsin-Madison,* *K4/968 CSC, MC 9988* *600 Highland Avenue* *Madison, WI 53792*
142	***HL098090***	*Christine Sorkness*	*Loren Denlinger*	*Julia Bach*	*University of Wisconsin-Madison,* *4238 HSLC* *750 Highland Avenue* *Madison, WI 53705*

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	Pittsburgh				
152	***HL098177*** ***ULITR000439***	*Fernando Holguin*	*Juan Celedon* *Hey Chong* *Erick Forno* *Todd Green* *Geoggrey Kurland* *Allyson Larkin* *Jonathan Spahr* *Daniel Weiner*	*Cindy Granny* *Erinn Kasubinski* *Adam Kufen* *Rose Lanzo* *Susan Richey*	*Clinical Research Coordinator* *Department of Pulmonary Medicine, Allergy and Immunology* *Children's Hospital of Pittsburgh of UPMC* *One Children's Hospital Drive* *4401 Penn Avenue, AOB 3rd Fl., Ste. 3300*
153	***HL098177***	*James Chmiel* *Ross Myers* *Kristie Ross*	*Megan Hart*	*Adam Gluvna* *Laurie Logan* *Laura Veri*	*Rainbow Babies and Children's Hospital* *11100 Euclid Ave., Ste 3001, MS 6006* *Cleveland, OH 44106*
154	***HL098177***	*Deborah Gentile*	*David Skoner*	*Erica Butler* *Sara Misplay* *Nicole Sossong*	*ASRI/AGH* *Department of Allergy, Asthma and Immunology* *490 East North Ave, Suite 207* *Pittsburgh, PA 15212*
	St. Louis				
162	***HL098098*** ***UL1 TR000448***	*Leonard Bacharier* *Avraham Beigelman*	*Andrea Coverstone* *Alysa Ellis* *Caroline Horner* *Lila Kertz* *Katherine Rivera-Spoljaric* *Robert Strunk*	*Melissa Navin* *Tina Norris* *Molly Siegel* *Wanda Caldwell*	*Washington University School of Medicine* *Campus Box 8116* *660 S. Euclid Avenue,* *St. Louis, MO 63110*

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	San Francisco				
171	***HL098107***	*Stephen Lazarus*			*University of California – San Francisco, Airway Clinical Research Center* *505 Parnassus Avenue* *M-1083* *San Francisco, CA 94143-0130*
172	***HL098107*** ***UL1TR991872***	*Michael Cabana* *Ngoc Ly*		*Michael Bentz* *Nancy Carmona* *Judy Gonzalez-Vargas* *Ariel Herm* *Alyssa Sparatta*	*University of California – San Francisco* *550 16th Street, 5th Floor* *San Francisco, CA 94143* *University of California – San Francisco* *Clinical Translational Science Institute* *550 16th Street, 6th Floor* *San Francisco, CA 94143*
173	***HL098107***	*Mindy Benson* *Dayna Long* *Jyothi Marbin*	*Javay Ross*	*Rigoberto DelToro* *Cherri Harris* *Robert Mok* *Cindy Nelson-Purdy* *Hollie Stessel*	*Benioff Children's Hospital - Oakland* *5220 Claremont Ave* *Oakland, CA 94618*

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	Tucson				
181	***HL098112***	*Wayne Morgan* *Fernando Martinez*	*Perla Aguilar* *Tara Carr* *Cori Daines* *Michael Daines* *Lynn Gerald* *Mark Goforth* *Jamie Goodwin* *Roni Grad* *Anunya Hiranratta* *Ashish Mathur*	*Argelia Benavides* *Valeria Bloss* *Samantha Castro* *Czarina Cooper* *Sarah David* *Silvia Lopez* *Patricia Oremelendez* *Marisol Posada* *Martha Preciado* *Janette Priefert* *Natalie Provencio* *Elizabeth Ryan* *Ron Schunk* *Faryal Shareef* *Ian Thomas* *Monica Vasquez* *Jesus Wences*	*Asthma & Airway Disease Research Center* *University of Arizona* *1501 N. Campbell Avenue, Room 23449* *PO Box 245030* *Tucson, AZ 85724-5030*

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Grant Support / Acknowledgement Roster

	WS/Emory				
191	**HL098103**	*Stephen Peters*	*William Gower* *Victor Ortega*	*Cheryl Wilmoth*	*Wake Forest University School of Medicine* *Section on Pulmonary, Critical Care, Allergy & Immunological Diseases* *2132 Cloverdale Avenue* *Winston-Salem, NC 27103*
194	**HL098103** **UL1 TR000454**	*Anne Fitzpatrick*		*Alice Bruce* *Jennifer Dodds*	*Emory University* *Department of Pediatrics* *2015 Uppergate Drive, Rm 326* *Atlanta, GA 30322*
195	**HL098103**	*Kathryn Blake* *John Lima*	*David Schaeffer*	*Jenny Batalla* *Kathleen Joyce* *Greta LaFave* *Michelle Littlefield* *Kimberly Ponthieux* *Brooke Riber* *Sally Rutledge*	*Nemours Children's Specialty Care* *807 Children's Way* *Jacksonville, FL 32207*
196	**HL098103**	*Jason Lang*	*Tarig Ali-Dinar* *Floyd Livingston*	*Shanae Brown* *Omar Oquendo* *Mariela Pena-Rufino* *Karen Walker*	*Nemours Children's Hospital* *13535 Nemours Parkway* *Orlando FL 32827*

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	Pennsylvania State University, Hershey				
DCC	***HL098115***	*David Mauger* *Sue Boehmer*	*Vernon Chinchilli* *Timothy Craig* *Tonya King* *Ian Paul* *Ann-Marie Dyer* *Susan Kunselman*	*Aimee Merchlinski* *Angela Updegrave* *Jonathan Nelson* *Kelly Nye* *Kendall Baab* *Ronald Zimmerman* *Linda Ferrari* *Lindsay Texter*	*Pennsylvania State University* *College of Medicine* *Department of Public Health Sciences* *90 Hope Drive* *Hershey, PA 17033*

Quintupling Inhaled Glucocorticoids to Prevent Childhood Asthma Exacerbations

Supplementary Materials

Daniel J. Jackson, MD, Leonard B. Bacharier, MD, David T. Mauger, PhD, Susan Boehmer, MA, Avraham Beigelman, MD, James F. Chmiel, MD, Anne M. Fitzpatrick, PhD, Jonathan M. Gaffin, MD, Wayne J. Morgan, MD, Stephen P. Peters, MD, PhD, Wanda Phipatanakul, MD, MS, William J. Sheehan, MD, Michael D. Cabana, MD, MPH, Fernando Holguin, MD, Fernando D. Martinez, MD, Jacqueline A. Pongracic, MD, Sachin N. Baxi, MD, Mindy Benson, MSN, PNP, Kathryn Blake, PharmD, Ronina Covar, MD, Deborah Ann Gentile, MD, Elliot Israel, MD, Jerry A. Krishnan, MD, PhD, Harsha Vardhan Kumar, MD, Jason E. Lang, MD, MPH, Stephen C. Lazarus, MD, John J. Lima, PharmD, Dayna Long, MD, Ngoc Ly, MD, Jyothi Marbin, MD, James N. Moy, MD, Ross E. Myers, MD, J. Tod Olin, MD, Hengameh H. Raissy, PharmD, Rachel G. Robison, MD, Kristie Ross, MD, Christine A. Sorkness, PharmD, and Robert F. Lemanske, Jr., MD on behalf of the National Heart Lung and Blood Institute's AsthmaNet

Affiliations:

Jackson, Daniel; University of Wisconsin School of Medicine and Public Health, Department of Pediatrics, Madison, WI

Bacharier, Leonard; Washington University in St. Louis School of Medicine and St. Louis Children's Hospital, Department of Pediatrics. St Louis, MO

Mauger, David; Penn State University, Department of Public Health Sciences, Hershey, PA

Boehmer, Sue; Penn State University, Department of Public Health Sciences, Hershey, PA

Beigelman, Avraham; Washington University School of Medicine and St. Louis Children's Hospital, Department of Pediatrics. St Louis, MO

Chmiel, James; Department of Pediatrics, Case Western Reserve University School of Medicine, Rainbow Babies and Children's Hospital, Cleveland, OH

Fitzpatrick, Anne; Emory University, Department of Pediatrics, Atlanta, GA

Gaffin, Jonathan; Boston Children's Hospital, Division of Respiratory Diseases, Harvard Medical School, Boston, MA

Morgan, Wayne; University of Arizona, Arizona Respiratory Center, Tucson, AZ

Peters, Stephen; Wake Forest University School of Medicine, Winston-Salem, NC

Phipatanakul, Wanda; Boston Children's Hospital, Division of Allergy/Immunology, Harvard Medical School, Boston, MA

Sheehan, William; Boston Children's Hospital, Division of Allergy/Immunology, Harvard Medical School, Boston, MA

Cabana, Michael; University of California - San Francisco, Departments of Pediatrics, Epidemiology and Biostatistics, UCSF Benioff Children's Hospital, San Francisco, CA

Holguin, Fernando; The University of Pittsburgh Asthma Institute at UPMC/UPSOM, Pittsburgh, PA

Martinez, Fernando; University of Arizona, Arizona Respiratory Center, Tucson, AZ

Pongracic, Jacqueline; Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL

Baxi, Sachin; Boston Children's Hospital, Division of Allergy/Immunology, Harvard Medical

School, Boston, MA
Benson, Mindy; University of California San Francisco Benioff Children's Hospital Oakland, Oakland, CA
Blake, Kathryn; Nemours Children's Health System, Jacksonville, FL
Covar, Ronina; National Jewish Health, Pediatrics, Denver, CO
Gentile, Deborah; Allegheny General Hospital, Department of Pediatrics, Pittsburgh, PA
Israel, Elliot; Brigham & Women's Hospital, Harvard Medical School, Boston, MA
Krishnan, Jerry; University of Illinois at Chicago, Chicago, IL
Kumar, Harsha Vardhan; University of Illinois at Chicago, Chicago, IL
Lang, Jason; Nemours Children's Hospital, University of Central Florida College of Medicine, Orlando, FL
Lazarus, Stephen; University of California, San Francisco, Medicine, San Francisco, CA
Lima, John; Nemours Children's Health System, Jacksonville, FL
Long, Dayna; University of California San Francisco Benioff Children's Hospital Oakland, Oakland CA
Ly, Ngoc; University of California - San Francisco, Department of Pediatrics, UCSF Benioff Children's Hospital, San Francisco, CA
Marbin, Jyothi; University of California San Francisco Benioff Children's Hospital Oakland, Oakland CA
Moy, James; Stroger Hospital of Cook County, Department of Pediatrics, Rush University Medical Center, Chicago, IL
Myers, Ross; Department of Pediatrics, Case Western Reserve University School of Medicine, Rainbow Babies and Children's Hospital, Cleveland, OH
Olin, Tod; National Jewish Health, Department of Pediatrics, Denver, CO
Raissy, Hengameh; University of New Mexico, Pediatrics / Pulmonary, Albuquerque, NM
Robison, Rachel; Ann & Robert H Lurie Children's Hospital of Chicago, Chicago, IL
Ross, Kristie; Department of Pediatrics, Case Western Reserve University School of Medicine, Rainbow Babies and Children's Hospital, Cleveland, OH
Sorkness, Christine; University of Wisconsin-Madison, Madison, WI
Lemanske, Jr., Robert F.; University of Wisconsin School of Medicine and Public Health, Pediatrics, Madison, WI

Corresponding Author:
Daniel J. Jackson, MD
Department of Pediatrics
University of Wisconsin School of Medicine and Public Health
600 Highland Avenue K4/936 CSC
Madison, WI 53792-9988
Phone: 608-263-7686
Email: djj@medicine.wisc.edu

Methods

Participant Characterization:

Specific IgE (ImmunoCAP®) was performed centrally at National Jewish Health (Denver, CO) for the following allergens: 1) cat dander, 2) dog dander, 3) mouse urine proteins, 4) mold mix (*Penicillium chrysogenum, Cladosporidium herbarum, Aspergillus fumigatus, Alternaria alternata*), 5) German cockroach (*Blatella germanica*), 6) grass mix (bermuda, rye, Timothy, Kentucky bluegrass, Johnson, Bahia), 7) tree mix (oak, elm, sycamore, cottonwood, willow), 8) tree mix (box-elder, birch, beech, oak, walnut), 9) weed mix (common ragweed, mugwort, plantain, lamb's quarter, Russian thistle), 10) giant ragweed, 11) mite (*Dermatophagoides farinae*), 12) mite (*Dermatophagoides pteronyssinus*), and 13) rat urine proteins.

Statistical Analyses:

Primary analysis:
The primary outcome is the number of asthma exacerbations occurring during study follow-up. The primary efficacy analysis utilized maximum likelihood estimation based on the log-linear model for outcomes following the negative binomial distribution. Covariates included study site and treatment assignment. Since not all participants complete 48 weeks of follow-up, the logarithm of the observed follow-up time (in years) was incorporate as an offset in the model. Since the follow-up time is expressed as years, the parameter estimates from the model represent annualized rates. The actual study follow-up time is 48 weeks so annualized rates represent a 9% extrapolation.

Analyses of secondary outcomes:
For outcomes measured as counts over the entire follow-up period, such as number of unscheduled visits for acute wheezing episodes, the same negative binomial log-linear model as in the primary analysis was applied. For sparse outcomes such as hospitalizations, Fisher's exact test was used. For outcomes measured on a roughly continuous scale over the entire follow-up period, such as total steroid exposure, ANOVA was applied. For continuous outcomes that did not exhibit an approximately normal distribution, appropriate transformations were applied prior to ANOVA.

For outcomes captured at multiple times during follow-up, such as symptoms during yellow zones, linear mixed effects models were applied with treatment assignment serving as a fixed effect and participant as a random effect. Outcomes measured as counts, such as albuterol puffs and number of symptoms, were modeled under the negative binomial likelihood, binary outcomes were modeled under the binomial likelihood, outcomes measured as proportions, such as the proportion of ACD, were modeled under the beta likelihood, and outcomes measured on a roughly continuous scale were modeled under the normal likelihood with appropriate transformation if necessary.

For outcomes measured as time-to-event, such as time to treatment failure, Kaplan-Meier curves were constructed and treatments compared by log-rank test.

P-values:

P-values associated with analyses of the primary outcome and pre-specified exploratory outcomes are reported without adjustment. P-values associated with analyses of exploratory outcomes including ACD and PEF during yellow zones, and analyses of treated and untreated yellow zones were adjusted for multiple testing using the Šidák method for 10 tests (ACD and PEF during yellow zones, and Symptoms, Albuterol use, ACD, and PEF during treated and untreated yellow zones).

Missing data:

Missing visit and diary data were assumed to be missing completely at random and imputation methods were not applied. We examined the patterns of early dropout and likelihood of missing data. Neither was significantly associated with, treatment, sex, age, race, or the primary outcome.

Identification of Yellow Zones:

Yellow zones were identified using data from the E-diary. As described in the Methods, an alert was provided to the participant by the E-diary when any of the following occurred: 2 doses (4 inhalations) of rescue albuterol in 6 hours, 3 doses (6 inhalations) of rescue albuterol in 24 hours, or 1 night-awakening due to asthma treated with albuterol. The E-diary algorithm for providing the alert did not use information from prior days. Because a yellow zone comprised 7 days of treatment of blinded therapy, it was possible for the E-diary to provide multiple alerts within the same 7-day yellow zone if the criteria above were met on multiple days. Thus, it was necessary to process the diary data in order identify distinct yellow zones for the purpose of analysis. E-diary data was processed sequentially for each subject beginning with the day the subject was randomized and the first yellow zone was identified by the first E-diary alert following randomization. The following algorithm was used to identify subsequent yellow zones:

1. The start date for the first yellow zone was the date of the first E-diary alert following randomization
2. Subsequent alerts occurring within 10 days of the yellow zone start date were attributed to that yellow zone and did not constitute the start of a new yellow zone
3. Subsequent alerts occurring more than 13 days after the yellow zone start date constituted the start of a new yellow zone
4. Subsequent alerts occurring 10-12 days after the yellow zone start date constituted the start of a new yellow zone only if the subject had been symptom free for at least 6 days.

Calculation of annualized hydrocortisone equivalents exposure:

In order to estimate total hydrocortisone exposure from the combined use of daily open-label maintenance ICS (fluticasone 44mcg/inhalation), blinded yellow zone ICS (fluticasone 44mcg/inhalation or 220mcg/inhalation), and prednisone given for exacerbations (total 6

mg/kg over four days up to a maximum 180mg), we first converted both fluticasone and prednisone to dexamethasone units. The following calculations were used:

- total fluticasone delivered in mcg (based on diary reported use of study inhalers) was multiplied by 0.40 to estimate total systemic fluticasone exposure in mcg, which was then multiplied by 14 to estimate total systemic dexamethasone exposure in mcg and divided by 1000 to convert to dexamethasone exposure in mg.
- total prednisone delivered in mg was divided by 6 to estimate total systemic dexamethasone exposure in mg

In order to calculate annualized hydrocortisone equivalents exposure, the total dexamethasone exposure was divided by the number of days on study (from randomization until termination) to estimate the average daily dexamethasone exposure and then multiplied by 365 to estimate the annualized dexamethasone exposure. That result was multiplied by 30 to estimate annualized hydrocortisone equivalents exposure.

Growth analyses:

As described in the Methods, linear mixed effects models were applied to estimate the effects of blinded therapy on growth. Specifically, height measured at study visits (every 8 weeks post-randomization) was the model outcome and main effect covariates included Age (at baseline), Sex, Time, and Treatment as fixed effects and Subject as a random effect. Interaction effects between Time and the other main effects were also included. Since the Time effect represented the time between study visits (in years), the regression coefficients corresponding to the interactions represented the effects of the covariates on the estimated annual growth rate. The Treatment Effect reported in Table 2 corresponds to the interaction between Time and Treatment. To explore a possible dose-response effect of 5xICS, we added an ICS exposure covariate to the model above. In order to capture actual ICS exposure, the exposure covariate was based on the number of doses of blinded therapy recoded as taken in the E-diary. Thus, doses of blinded therapy taken outside of identified yellow zones (i.e., off-protocol) were counted in the exposure covariate. In order to examine the possibility of differential dose response in smaller/younger children who have significantly more rapid growth, we also stratified by age at enrollment (5-7 years and 8-11 years). Data points shown in Figure S1 represent empirical best linear unbiased predictors for the Time effect in a random effects model which did not include treatment.

Figure S1. Linear Growth

This figure examines the impact of treatment group (1x vs. 5x) on linear growth and demonstrates that there was a significant dose response relationship where each yellow zone in children 5-7 years of age was associated with a 0.12 cm/yr reduction in linear growth. No impact of this strategy was observed in children 8-11 years of age (see supplement for modeling details).

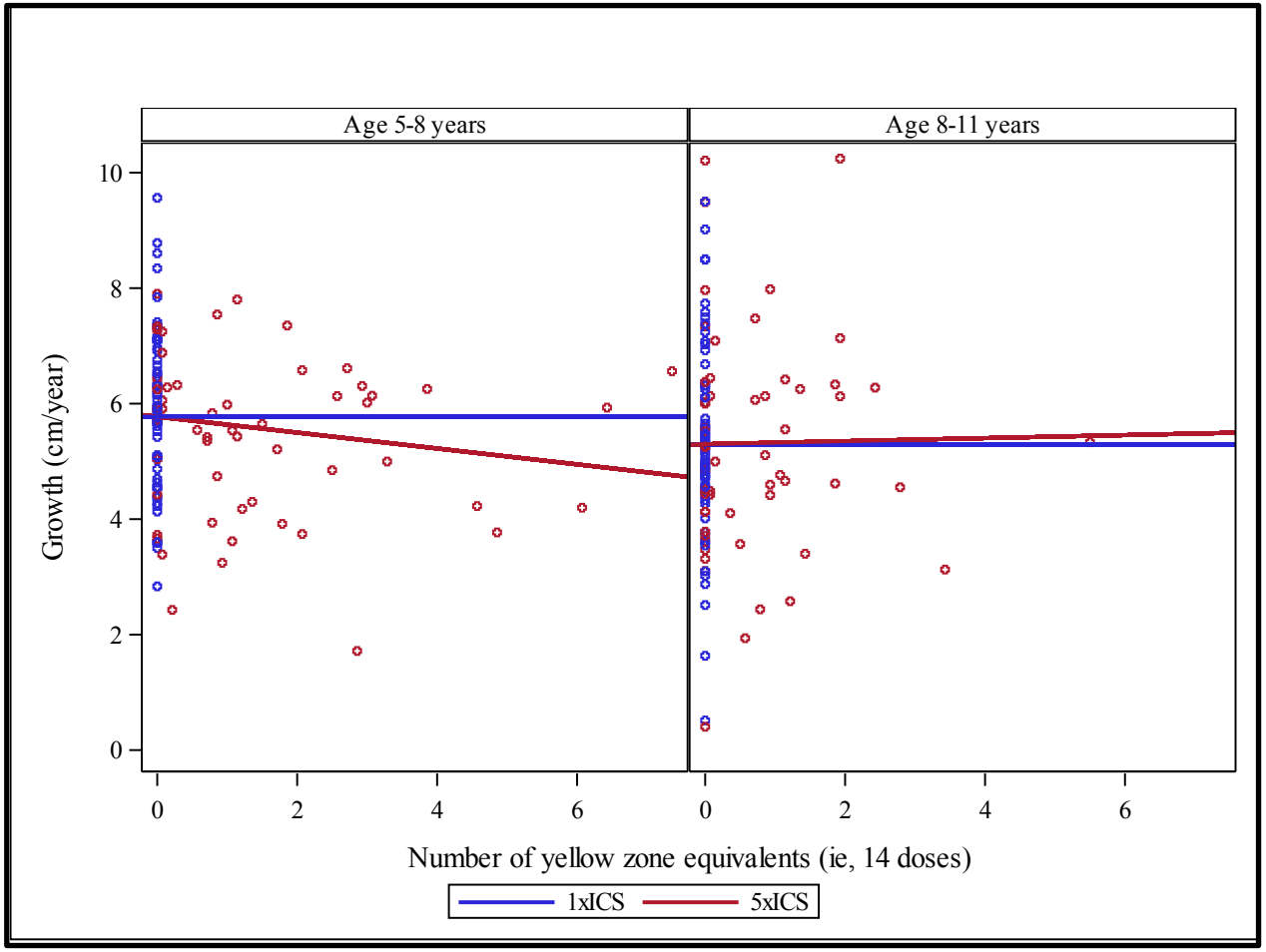

Figure S2. Outcomes in Treated Yellow Zones

The percentage of non-asthma control days the 7 days prior to and 14 days after the onset of yellow zone alerts is depicted in panel A. Panel B shows the percentage of days with peak flows <80% of their reference value during the yellow zone time period. P-values shown were adjusted for multiple testing using the Šidák method.

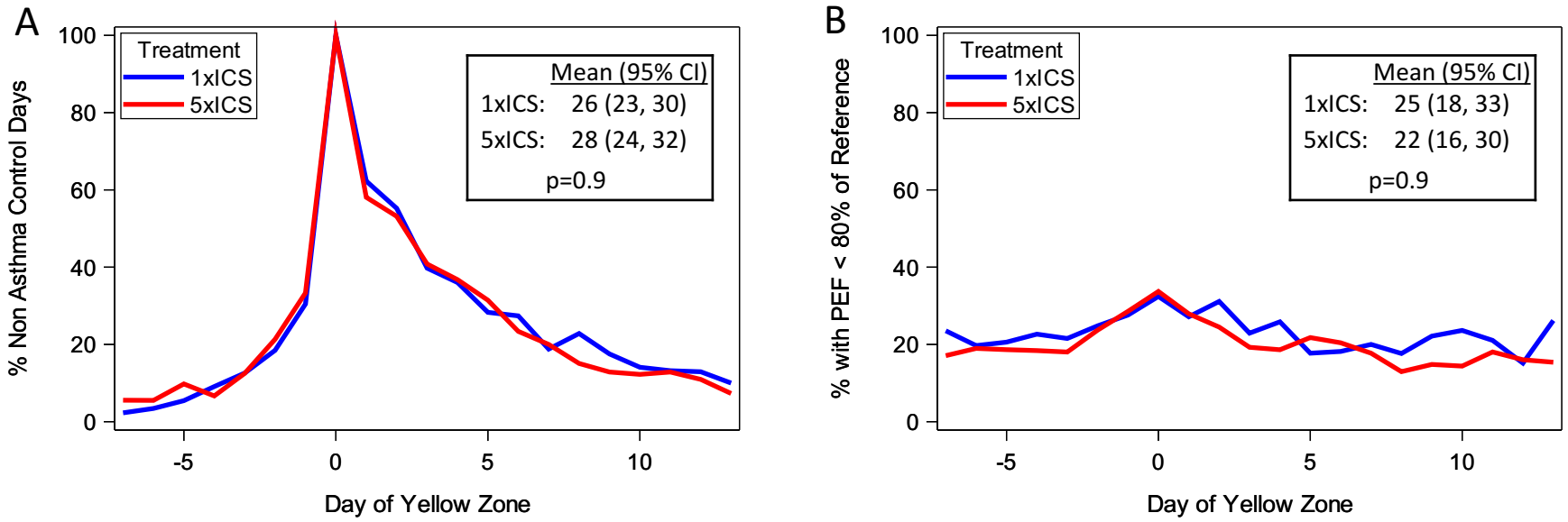

Figure S3. Outcomes in Treated vs. Untreated Yellow Zones

This exploratory analysis compares outcomes in treated and untreated yellow zones. Panel A shows mean total symptom scores. Panel B shows albuterol use (inhalations per day). Panel C shows asthma control days. Finally, Panel D shows the percentage of participants who had peak flows <80% of their reference value. P-values shown were adjusted for multiple testing using the Šidák method.

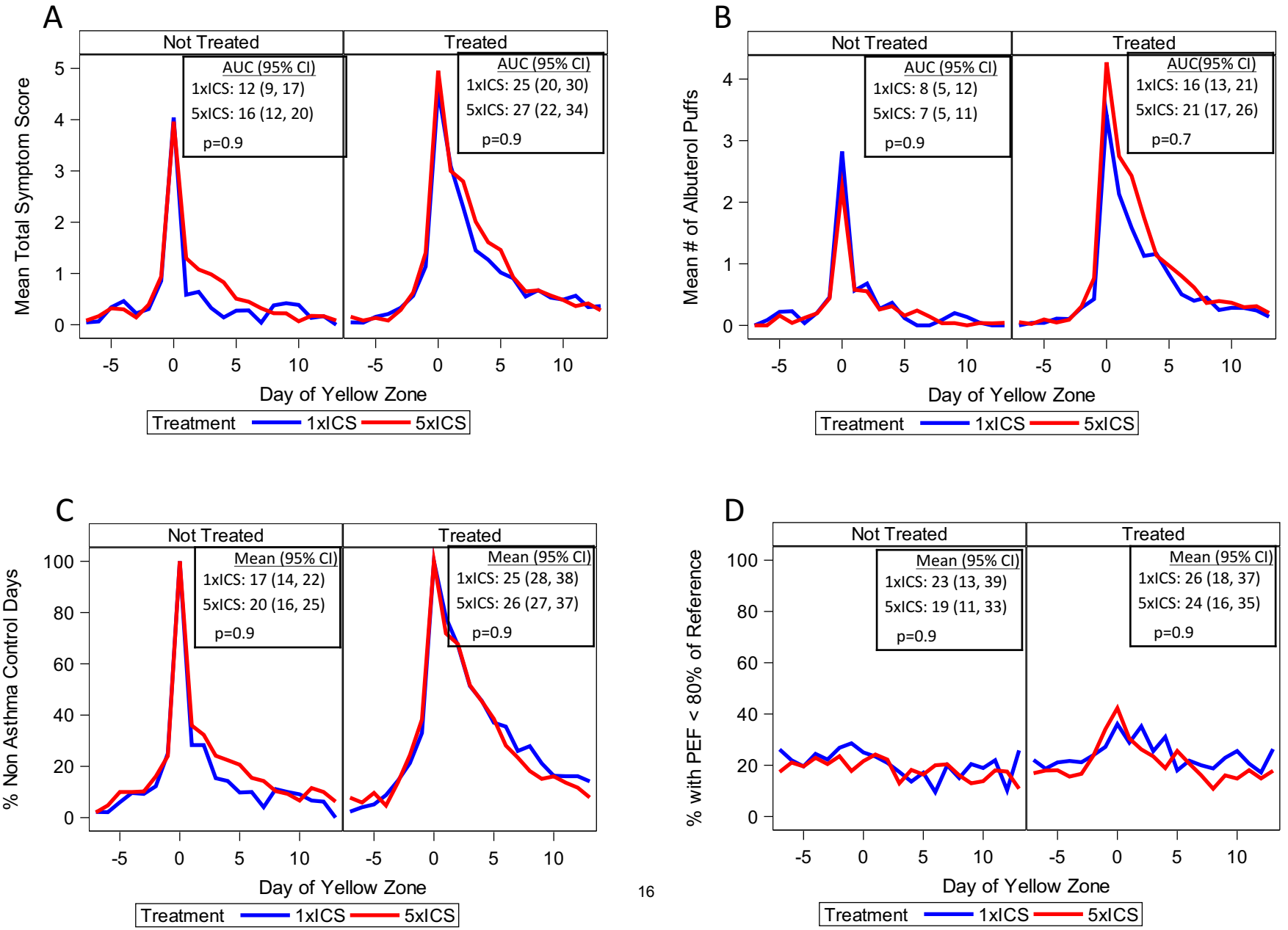

TABLE S1	Combined	1xICS	5xICS
N	254	127	127
Age at enrollment	8.0 +/- 1.9	7.9 +/- 1.9	8.1 +/- 1.8
5-7 years	126 (49.6%)	63 (49.6%)	63 (49.6%)
8-11 years	128 (50.4%)	64 (50.4%)	64 (50.4%)
Age at symptom onset	2.2 +/- 1.9	2.3 +/- 1.8	2.1 +/- 1.9
Age at asthma diagnosis	3.3 +/- 2.1	3.2 +/- 2.0	3.3 +/- 2.2
BMI Percentile	66.8 +/- 28.0	67.9 +/- 27.3	65.8 +/- 28.8
Male Sex	163 (64.2%)	80 (63%)	83 (65.4%)
Race White	140 (55.1%)	64 (50.4%)	76 (59.8%)
Black or African American	56 (22%)	29 (22.8%)	27 (21.3%)
American Indian or Alaskan Native	6 (2.4%)	1 (0.8%)	5 (3.9%)
Asian	8 (3.1%)	6 (4.7%)	2 (1.6%)
More than 1 race specified	44 (17.3%)	27 (21.3%)	17 (13.4%)
Hispanic or Latino	75 (29.5%)	36 (28.3%)	39 (30.7%)
Parental asthma	143 (56.3%)	70 (55.1%)	73 (57.5%)
Tobacco smoke exposure	97 (38.2%)	46 (36.2%)	51 (40.2%)
Eczema	152 (59.8%)	75 (59.1%)	77 (60.6%)
Controller Therapy at Enrollment Step 2	181 (71.3%)	96 (75.6%)	85 (66.9%)
Step 3	43 (16.9%)	18 (14.2%)	25 (19.7%)
Naive to Controller Therapy	30 (11.8%)	13 (10.2%)	17 (13.4%)
Pets in Home	140 (55.1%)	68 (53.5%)	72 (56.7%)
Number of Positive Allergen Specific IgE Tests (out of 16)	5.0 +/- 4.4	4.8 +/- 4.2	5.2 +/- 4.5
At Least One Positive Allergen	196 (80.7%)	91 (77.1%)	105 (84%)
At Least One Positive Aeroallergen	187 (77%)	88 (74.6%)	99 (79.2%)
At Least One Positive Food Allergen	121 (49.8%)	55 (46.6%)	66 (52.8%)
At Least One Positive Perennial Aeroallergen	170 (70%)	79 (66.9%)	91 (72.8%)
Blood Eosinophils %	4.9 +/- 3.6	4.9 +/- 3.5	4.8 +/- 3.6
Blood Eosinophils count	346.4 +/- 268.2	367.4 +/- 299.8	326.6 +/- 234.3
IgE (kU/L)	401.3 +/- 586.4	418.3 +/- 655.9	385.4 +/- 515.1
Oral steroid courses taken in past year	1.7 +/- 0.9	1.8 +/- 0.9	1.7 +/- 0.9
Urgent/ED visits in the past year	2.0 +/- 1.7	2.0 +/- 1.7	2.0 +/- 1.7
Hospitalized in the past year	31 (12%)	16 (13%)	15 (12%)