Published in final edited form as:

J Allergy Clin Immunol. 2009 February ; 123(2): 385–390. doi:10.1016/j.jaci.2008.10.015.

Repeatability of Response to Asthma Medications

Ann Wu, MD, MPH^{1,2,3}, Kelan Tantisira, MD, MPH^{3,4,5}, Lingling Li, PhD¹, Brooke Schuemann, BS⁴, and Scott Weiss, MD, MS^{3,4,5} for the Childhood Asthma Management Program Research Group*

¹Department of Ambulatory Care and Prevention, Harvard Pilgrim Health Care and Harvard Medical School

²Department of Pediatrics, Children's Hospital, Boston

³Harvard Medical School, Boston, MA

⁴Channing Laboratory, Department of Medicine, Brigham and Women's Hospital

⁵Center for Genomic Medicine, Department of Medicine, Brigham and Women's Hospital, Boston MA

Abstract

Background—Pharmacogenetic studies of drug response in asthma assume that patients respond consistently to a treatment but that treatment response varies across patients, however, no formal studies have demonstrated this.

Objective—To determine the repeatability of commonly used outcomes for treatment response to asthma medications: bronchodilator response, forced expiratory volume in 1 second (FEV1), and provocative concentration of methacholine producing a 20% decline in FEV1 (PC20).

Methods—The Childhood Asthma Management Program (CAMP) was a multi-center clinical trial of children randomized to receiving budesonide, nedocromil, or placebo. We determined the intraclass correlation coefficient (ICC) for each outcome over repeated visits over four years in CAMP using mixed effects regression models. We adjusted for the covariates: age, race/ethnicity, height, family income, parental education, and symptom score. We incorporated each outcome for each child as repeated outcome measurements and stratified by treatment group.

Results—The ICC for bronchodilator response was 0.31 in the budesonide group, 0.35 in the nedocromil group, and 0.40 in the placebo group, after adjusting for covariates. The ICC for FEV1 was 0.71 in the budesonide group, 0.60 in the nedocromil group, and 0.69 in the placebo group, after adjusting for covariates. The ICC for PC20 was 0.67 in the budesonide and placebo groups and 0.73 in the nedocromil group, after adjusting for covariates.

©2010 American Academy of Allergy, Asthma and Immunology. Published by Mosby, Inc. All rights reserved.

Address correspondence to: Ann Wu, Department of Ambulatory Care and Prevention, 133 Brookline Avenue, 6th Floor, Boston, MA 02215-5301, Phone: 617-509-9823, Fax: 617-859-8112, ann.wu@childrens.harvard.edu.

*Members of the CAMP Research Group are detailed at the end of this manuscript.

Clinical Implications: Response to asthma medications appears to have a genetic basis. Thus, development of pharmacogenetic tests in asthma is possible.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conclusion—The within treatment group repeatability of FEV1 and PC20 are high; thus these phenotypes are heritable. FEV1 and PC20 may be better phenotypes than bronchodilator response for studies of treatment response in asthma.

Keywords

asthma; drug response; heritability; bronchodilator; pharmacogenetics

INTRODUCTION

The purpose of research in pharmacogenetics is to identify genetic predictors of individual response to medications.¹ This field assumes response to treatment is consistent for a given individual, however, this assumption has not been studied.¹

Asthma is a complex chronic condition and the response to medication for asthma is consequently variable. Multiple studies suggest familial aggregation of asthma, and twin studies suggest the heritability of asthma is between 36% - 70%.²⁻⁴ Asthma related phenotypes such as pulmonary function as measured by bronchodilator response, forced expiratory volume in 1 second (FEV₁), and provocative concentration of methacholine causing a 20% decrease in FEV₁ (PC20) also appear to be heritable.⁵⁻⁷ However, there is a dearth of evidence suggesting treatment response in asthma is heritable, yet this is assumed in pharmacogenetic studies. Asthma pharmacogenetics is a rapidly growing field that has the potential to have profound clinical implications.

For pharmacogenetic studies in asthma to have clinical implications, individuals must respond differently to medications. If variability in therapeutic response has a genetic basis, there must be evidence of both inter-individual variation and intra-individual repeatability in response.⁷ Many studies have demonstrated inter-individual variation in FEV₁ and PC20 responses to treatment for asthma.⁷⁻¹⁰ Variability in response to β_2 -agonists has been known for over five decades,¹¹ and variability in response to corticosteroids has been demonstrated relatively recently.^{9, 10, 12} To our knowledge, no studies demonstrate intra-individual repeatability in response to asthma medication, yet studies in asthma pharmacogenetics assume that individuals will have consistent response to medications. Longitudinal studies with repeated measures of treatment response may help clarify whether this assumption is true.

Twin studies are the ideal method for studying heritability because monozygotic twins who share 100 percent of genes have smaller intra-pair differences in pulmonary function than dizygotic twins who share an average of 50% of genes. Unfortunately conducting twin studies for studying heritability of most classes of drug response is logistically difficult. One way in which heritability may be inferred is by use of the intraclass correlation coefficient (ICC).¹³ Determining heritability through repeated measurements has been used extensively in genetic studies of animals,^{14, 15} and the principles apply to the study of heritability in humans. Therefore, repeatability studies involving drug-treatment response can also take advantage of the ICC. The ICC for medication response compares the variability of the responses within and between individuals over the course of repeated drug administration. ICC is given by $\sigma_b^2 / (\sigma_b^2 + \sigma_w^2)$ where σ_b^2 is the between subject variance and σ_w^2 is the within subject variance. Although this ICC for medication response does not utilize family data, by comparing the consistency of treatment response over time within an individual to the response between individuals the ICC does address the proportion of the response that is innate and, therefore, most likely heritable.

The objective of this report is to determine the ICC of bronchodilator response, FEV₁, and PC₂₀ over repeated visits while on specific asthma medications in a longitudinal cohort of children with asthma. We hypothesize that the ICC of these outcomes will be high.

METHODS

The Childhood Asthma Management Program is a multi-center trial that enrolled 1041 children between the ages of 5 and 12 years with mild to moderate persistent asthma between 1993-1995.¹⁶ Subjects were randomly assigned to receive budesonide, nedocromil, or placebo and were followed for four to six years every two to four months in order to study the long-term use of the medications. Details of this study have been previously published.¹⁶ The institutional review board at each of the eight participating institutions approved the study and parents or guardians of the subjects gave informed consent.¹⁶

Our main outcome measures were the following within treatment group responses: bronchodilator response, pre-bronchodilator FEV₁, and log PC₂₀ over repeated visits in the CAMP population.¹⁷ Research assistants obtained spirometry measurements on the subjects both before and after a bronchodilator twice yearly. Bronchodilator response was calculated at each visit as FEV₁ ([post-bronchodilator FEV₁ – pre-bronchodilator FEV₁]/pre-bronchodilator FEV₁). Each year, the subjects' airway responsiveness to methacholine was measured by calculating the concentration of methacholine that caused a 20 percent decrease in the FEV₁. The concentration that provoked a 20% decrease from post-diluent FEV₁ was obtained by linear interpolation of logarithmic dose-response curve expressed as PC₂₀. We used the outcome measures from randomization to month 48 post randomization for the outcome variables bronchodilator response, pre-bronchodilator FEV₁, and log PC₂₀.

With the help of parents or guardians, subjects completed diary cards daily to document recorded night awakenings due to asthma, morning and evening peak flow readings by a peak flow (Assess, HealthScan Products, Cedar Grove, N.J.), use of study medication, use of albuterol or prednisone, absences from school due to asthma, visits to their providers' offices or hospitals because of asthma and severity of symptoms. At each study visit, research assistants measured the subjects' height (using a Harpenden stadiometer) and weight. We divided the weight and height measurements at randomization into internal quartiles of weight and height based on the CAMP population.

We controlled for confounding by considering covariates that could influence the outcomes of bronchodilator response, pre-bronchodilator FEV₁, and log PC₂₀. Thus, we adjusted for the covariates: age at randomization, race/ethnicity, height, family income, parental education, and symptom score. For the outcome of bronchodilator response, we adjusted for pre-bronchodilator FEV₁. Race/ethnicity, family income, and parental education were determined by parental self-report. Symptom scores were developed based on daily diary measures of symptom control, including symptom frequency, number of asthma episode-free days per month, uses of albuterol for symptoms and to prevent exercise-induced bronchospasm per week, and number of night awakenings per month. Subjects were classified as having "mild symptoms" if they had less than 2 episodes a week of symptoms and "moderate symptoms" if they had 2 or more episodes per week of symptoms.

Statistical Analyses

We used mixed effects regression models to estimate the ICC for each outcome measure. We incorporated each outcome for each child as repeated outcome measurements and stratified by treatment group using SAS version 9.1 (SAS Institute, Cary, NC, 2007). For each outcome, to test the equivalence of ICCs across the three treatment groups, we constructed a chi-square test statistic using a bivariate vector and its covariance matrix. The entries of the bivariate vector

are the differences of ICCs between the groups of budesonide and nedocromil, and the groups of nedocromil and placebo. Then the p-values are obtained assuming the test statistic has an asymptotic chi-square distribution with 2 degrees of freedom under the null hypothesis.

RESULTS

The median bronchodilator response, pre-bronchodilator FEV1, and log PC20 values at randomization for each treatment group are presented in Table I. The median bronchodilator response for all subjects was 0.08 at randomization, and this value was similar in each treatment group. Bronchodilator response and log PC20 at randomization were not significantly different depending on treatment group, race/ethnicity, gender, mean internal quartiles of weight, mean internal quartiles of height, or parental education. Bronchodilator response was significantly different for household income. The pre-bronchodilator FEV1 was significantly different for race/ethnicity, mean internal quartile of weight, and mean internal quartiles of height. Bronchodilator response and log PC20 at randomization were significantly different for symptom score. The median bronchodilator response value was 0.09 for subjects with a symptom score indicating moderate symptoms compared to 0.07 for subjects with mild symptoms. This expected finding occurs because subjects with moderate symptoms start with pre-bronchodilator FEV1 values that are lower.

Mean responses for each outcome at visits between randomization and 48 months are depicted in the Figure. These graphs demonstrate the stability of the mean values with repeated measures over time. The slight increase in slope for the mean values for pre-bronchodilator FEV1 is expected because over the course of 48 months, subjects grow in height and weight, leading to increased values of FEV1. The increase in slope for both pre-bronchodilator FEV1 and log PC20 could reflect better asthma treatment over time because subjects were seen by their physicians who had the opportunity to make slight changes in medication regimens or due to treatment effect with the placebo group showing a placebo effect.

The ICC values for each outcome are shown in Table II. The ICC for bronchodilator response ranged from 0.31 to 0.40, after adjusting for age, race/ethnicity, height, family income, parental education, and symptom score. The ICC results were the same whether or not we adjusted for covariates. We chose to present the adjusted results in order to account for non-genetic factors. The ICC for pre-bronchodilator FEV1 ranged from 0.60 to 0.71, after adjusting for covariates. The ICC for log PC20 ranged from 0.67 to 0.73. According to Rosner, an ICC of less than 0.4 suggests poor reproducibility, an ICC between 0.4 and 0.75 indicates fair to good reproducibility, and an ICC over 0.75 suggests excellent reproducibility.¹⁸ Thus, the ICC for bronchodilator response has fair to poor reproducibility while the ICC for pre-bronchodilator FEV1 and log PC20 have good reproducibility. The ICCs for pre-bronchodilator FEV1 were significantly different ($p=0.006$) among the three treatment groups, suggesting that the repeatability of pre-bronchodilator FEV1 is high, only among subjects in the same treatment group. Similarly, the ICCs for bronchodilator response were also significantly different ($p=0.02$) among the treatment groups.

DISCUSSION

This report has three key findings. First, we found that FEV1 and log PC20 within each treatment group have high correlation within subjects over time which suggests that these phenotypes have high repeatability and heritability. Secondly, within subject repeatability is high for the phenotypes of pre-bronchodilator FEV1 and log PC20 regardless of age, gender, race/ethnicity, symptom score. Finally, the ICC is treatment specific.

The finding that pre-bronchodilator FEV1 and log PC20 within each treatment group have high repeatability is consistent with findings in previous studies. For example, FEV1 has been shown to help classify asthma severity,¹⁹ predict risk of asthma exacerbations,²⁰ and predict future FEV1,²¹ suggesting high intra-individual correlation. Similarly, PC20 has been demonstrated to predict future lung function.²¹ In addition, studies suggest high intra-individual response to inhaled steroids.^{9, 10, 12} The ICCs in this report can be interpreted in the context of other studies which find that the correlation coefficient of blood pressure between initial and subsequent measures is between 0.3-0.7²² and the ICC for height is 0.96 and for weight is 0.88.

Bronchodilator response appears to have fair to poor repeatability and heritability, yet many studies in asthma pharmacogenetics use bronchodilator response as an outcome. One reason for this low repeatability is that bronchodilator response is calculated through two FEV1 measurements, pre and post bronchodilator, thus there is a higher likelihood of variability. In addition, although trained research assistants conducted the spirometry measurements and administered the bronchodilator, technical factors in measurements could have decreased reproducibility of bronchodilator response. Furthermore, the group receiving budesonide had lower ICC (0.31) than the nedocromil (0.35) and placebo (0.40) groups, likely because budesonide has anti-inflammatory functions that had more of an influence on pre-bronchodilator FEV1 and less on the post-bronchodilator FEV1. Similarly, nedocromil has mild anti-inflammatory functions that may have contributed to the ICC that was lower than the placebo group yet higher than the budesonide group.

The ICC values did not change significantly after adjusting for age, gender, race/ethnicity and symptom score, further lending support to the hypothesis that bronchodilator response, FEV1, and PC20 are heritable. We adjusted for these covariates in order to account for other non-genetic factors, but they did not appear to play a role.

For each outcome, the ICC varied between treatment groups with the highest ICC for the bronchodilator response related to no active anti-inflammatory medications, and the highest ICC for FEV1 noted in the inhaled corticosteroid group. These treatment specific findings could be explained by effect modification or gene by environment interactions. For example, anti-inflammatory medications alone or interactions between anti-inflammatory medications and genetic factors could act as effect modifiers of bronchodilator response.

Strengths of this report include a well-characterized multi-center cohort, the ability to control for multiple confounders, and availability of repeated outcome measurements over several years. To our knowledge, this is the first report to examine the repeatability of response to asthma medications. The findings in this report suggest that studies of the genetics of response to asthma medications could use bronchodilator response as an outcome measure, but pre-bronchodilator FEV1 and PC20 may be even better outcome measures. Despite these strengths, these findings were in one cohort of children ages 5-12 years who were followed for four years, which may limit generalizability of our findings. In addition, our assessment of repeatability approximates heritability, but the gold standard method for assessing heritability is through studies of twins.

In conclusion, intra-individual response to asthma medications is high, suggesting response to asthma medications has a genetic basis. Our findings of high repeatability for FEV1 and PC20 suggest high heritability; thus, FEV1 and PC20 are good phenotypes for asthma pharmacogenetic studies.

* Members of the CAMP Research Group

Source of funding

The Childhood Asthma Management Program is supported by contracts NO1-HR-16044, 16045, 16046, 16047, 16048, 16049, 16050, 16051, and 16052 with the National Heart, Lung, and Blood Institute and General Clinical Research Center grants M01RR00051, M01RR0099718-24, M01RR02719-14, and RR00036 from the National Center for Research Resources.

Members of the CAMP Research Group

Clinical centers

ASTHMA, Inc, Seattle, WA: Gail G. Shapiro, MD (Director); Thomas R. DuHamel, PhD (Co-Director); Mary V. Lasley, MD (Co-Director); Tamara Chinn, MSN, ARNP (Coordinator). Michele Hinatsu, MSN, ARNP; Clifton T. Furukawa, MD; Leonard C. Altman, MD; Frank S. Virant, MD; Paul V. Williams, MD; Michael S. Kennedy, MD; Jonathan W. Becker, MD; Grace White. C. Warren Bierman, MD (1992-1997); Dan Crawford, RN (1996-2002); Heather Eliassen, BA (1996-1999); Babi Hammond (1996-1999); Dominick A. Minotti, MD (1992-2003); Chris Reagan (1992-2003); Marian Sharpe, RN (1992-1994); Timothy G. Wighton, PhD (1994-1998).

Brigham & Women's Hospital, Boston, MA: Scott Weiss, MD, MS (Director); Anne Fuhlbrigge, MD (Principal Investigator); Anne Plunkett, NP, MS (Coordinator). Nancy Madden, RN, BSN; Peter Barrant, MD; Christine Darcy; Kelly Thompson, MD. Walter Torda, MD (Co-Investigator Director, 1993-2003); Martha Tata, RN (1993-2002); Sally Babigian, RN (1997-1999); Linda Benson (1998-2004); Jose Caicedo (1998-1999); Tatum Calder (1998-2001); Anthony DeFilippo (1994-2000); Cindy Dorsainvil (1998-2001); Julie Erickson (1998-1999); Phoebe Fulton (1997); Mary Grace, RN (1994-1996); Jennifer Gilbert (1997-1998); Dirk Greineder, MD (1993-2000); Stephanie Haynes (1993-1998); Margaret Higham, MD (1996-1998); Deborah Jakubowski (1999); Susan Kelleher (1993-1997); Jay Koslof, PhD (1993-1995); Dana Mandel (1996-1998); Patricia Martin (2001-2003); Agnes Martinez (1994-1997); Jean McAuliffe (1994-1995); Erika Nakamoto (2002-2004); Paola Pacella (1993-1998); Paula Parks (1993-1995); Johanna Sagarin (1998-1999); Kay Seligsohn, PhD (1995-2004); Susan Swords (2003-2005); Meghan Syring (1998-2001); June Traylor, MSN, RN (1996-1998); Melissa Van Horn, PhD (1996-1999); Carolyn Wells, RN (1993-1995); Ann Whitman, RN (1994-1996).

The Hospital for Sick Children, Toronto, Ontario, Canada: Ian MacLusky, MD, FRCP(C) (Director); Joe Reisman, MD, FRCP(C), MBA (Director, 1996-1999); Henry Levison, MD, FRCP(C) (Director, 1992-1996); Anita Hall, RN (Coordinator). Jennifer Chay; Melody Miki, RN, BScN; Renée Sananes, PhD. Yola Benedet (1994-1999); Susan Carpenter, RN (1998-2001); Michelle Collinson, RN (1994-1998); Jane Finlayson-Kulchin, RN (1994-1998); Kenneth Gore, MA (1993-1999); Noreen Holmes, RRT (1998-1999); Sharon Klassen, MA (1999-2000); José Quenneville, MSc (1993-1995); Christine Wasson, PhD (1999).

Johns Hopkins Asthma & Allergy Center, Baltimore, MD: N. Franklin Adkinson, Jr, MD (Director); Peyton Eggleston, MD (Co-Director); Elizabeth H. Aylward, PhD; Karen Huss, DNSc (Co-Investigator); Leslie Plotnick, MD (Co-Investigator); Margaret Pulsifer, PhD (Co-Investigator); Cynthia Rand, PhD (Co-Investigator); Nancy Bollers, RN (Coordinator). Deborah Bull, LPN; Robert Hamilton, PhD; Kimberly Hyatt; Susan Limb, MD; Mildred Pessaro; Stephanie Philips, RN; Barbara Wheeler, RN, BSN.

National Jewish Medical and Research Center, Denver, CO: Stanley Szeffler, MD (Director); Harold S. Nelson, MD (Co-Director); Bruce Bender, PhD (Co-Investigator); Ronina Covar, MD (Co-Investigator); Andrew Liu, MD (Co-Investigator); Joseph Spahn, MD (Co-Investigator); D Sundström (Coordinator). Melanie Phillips; Michael P. White. Kristin Brelsford (1997-1999); Jessyca Bridges (1995-1997); Jody Ciacco (1993-1996); Michael Eltz (1994-1995); Jeryl Feeley, MA (Coordinator, 1992-1995); Michael Flynn (1995-1996); Melanie Gleason, PA-C (1992-1999); Tara Junk-Blanchard (1997-2000); Joseph Hassell (1992-1998); Marcia Hefner (1992-1994); Caroline Hendrickson, RN (1995-1998; Coordinator, 1995-1997); Daniel Hettleman, MA (1995-1996); Charles G. Irvin, PhD (1992-1998); Jeffrey Jacobs, MD (1996-1997); Alan Kamada, PharmD (1994-1997); Sai Nimmagadda, MD (1993-1996); Kendra Sandoval (1995-1997); Jessica Sheridan (1994-1995); Trella Washington (1993-1997); Eric Willcutt, MA (1996-1997). We also thank the pediatric allergy and immunology fellows for their participation (Kirstin Carel, MD; Neal Jain, MD; Harvey Leo, MD; Beth Macomber, MD; Chris Mjaanes, MD; Lora Stewart, MD; Ben Song, MD).

University of California, San Diego and Kaiser Permanente Southern California Region, San Diego, CA: Robert S. Zeiger, MD, PhD (Director); Noah Friedman, MD (Co-Investigator); Michael H. Mellon, MD (Co-Investigator); Michael Schatz, MD (Co-Investigator); Kathleen Harden, RN (Coordinator). Elaine M. Jenson; Serena Panzlau; Eva Rodriguez, RRT. James G. Easton, MD (Co-Director, 1993-1994); M. Feinberg (1997-1998); Linda L. Galbreath (1991-2002); Jennifer Gulczynski (1998-1999); Ellen Hansen (1995-1997); Al Jalowayski, PhD (Co-Investigator, 1991-2005); Alan Lincoln, PhD (Co-Investigator, 1991-2003); Jennie Kaufman (1994); Shirley King, MSW (1992-1999); Brian Lopez (1997-1998); Michaela Magiari-Ene, MA (1994-1998); Kathleen Mostafa, RN (1994-1995); Avraham Moscona (1994-1996); Catherine A. Nelle, RN (1991-2005); Jennifer Powers (2001-2003); Karen Sandoval (1995-1996); Nevin W. Wilson, MD (Co-Director, 1991-1993).

University of New Mexico, Albuquerque, NM: H. William Kelly, PharmD (Director); Aaron Jacobs (Co-Investigator); Mary Spicher, RN (Coordinator). Hengameh H. Raissy. Robert Annett, PhD (Co-Investigator, 1993-2004); Teresa Archibeque (1994-1999); Naim Bashir, MD (Co-Investigator, 1998-2005); H. Selda Bereket (1995-1998); Marisa Braun (1996-1999); Shannon Bush (2002-2006); Michael Clayton, MD (Co-Investigator, 1999-2001); Angel Colon-Semidey, MD (Co-Investigator, 1997-2000); Sara Devault (1993-1997); Roni Grad, MD (Co-Investigator, 1993-1995); David Hunt, RRT (1995-2004); Jeanne Larsson, RN (1995-1996); Sandra McClelland, RN (Coordinator, 1993-1995); Bennie McWilliams, MD (Co-Investigator, Director, 1992-1998); Elisha Montoya (1997-2000); Margaret Moreshead (1996-1999); Shirley Murphy, MD (Co-Investigator, 1992-1994); Barbara Ortega, RRT (1993-1999); David Weers (1997-1998); Jose Zayas (1995-1996).

Washington University, St. Louis, MO: Robert C. Strunk, MD (Director); Leonard Bacharier, MD (Co-Investigator); Gordon R. Bloomberg, MD (Co-Investigator); James M. Corry, MD (Co-Investigator); Denise Rodgers, RFPT (Coordinator). Lila Kertz, MSN, RN, CPNP; Valerie Morgan, RRT; Tina Oliver-Welker, CRTT; Deborah K. White, RPFT, RRT.

Resource centers

Chair's Office, National Jewish Medical and Research Center, Denver, CO: Reuben Cherniack, MD (Study Chair).

Coordinating Center, The Johns Hopkins University, Baltimore, MD: James Tonascia, PhD (Director); Curtis Meinert, PhD (Co-Director). Patricia Belt; Karen Collins; Betty Collison; Ryan Colvin, MPH; John Dodge; Michele Donithan, MHS; Judith Harle; Rosetta

Jackson; Hope Livingston; Jill Meinert; Kapreena Owens; Michael Smith; Alice Sternberg, ScM; Mark Van Natta, MHS; Margaret Wild; Laura Wilson, ScM; Robert Wise, MD; Katherine Yates, ScM.

Project Office, National Heart, Lung, and Blood Institute, Bethesda, MD: Virginia Taggart, MPH (Project Officer); Lois Eggers; James Kiley, PhD; Gang Zheng, PhD. Paul Albert, PhD (1991-1999); Suzanne Hurd, PhD (1991-1999); Sydney Parker, PhD (1991-1994); Pamela Randall (1992-2003); Margaret Wu, PhD (1991-2001).

Committees

Data and Safety Monitoring Board: Howard Eigen, MD (Chair); Michelle Cloutier, MD; John Connett, PhD; Leona Cuttler, MD; David Evans, PhD; Meyer Kattan, MD; Rogelio Menendez, MD; F. Estelle R. Simons, MD. Clarence E. Davis, PhD (1993-2003); Sanford Leikin, MD (1993-1999).

Executive Committee: Reuben Cherniack, MD (Chair); Robert Strunk, MD; Stanley Szeffler, MD; Virginia Taggart, MPH; James Tonascia, PhD. Curtis Meinert, PhD (1992-2003).

Steering Committee: Reuben Cherniack, MD (Chair); Robert Strunk, MD (Vice-Chair); N. Franklin Adkinson, MD; Robert Annett, PhD (1992-1995, 1997-1999); Bruce Bender, PhD (1992-1994, 1997-1999); Mary Caesar, MHS (1994-1996); Thomas R. DuHamel, PhD (1992-1994, 1996-1999); H. William Kelly, PharmD; Henry Levison, MD (1992-1996); Alan Lincoln, PhD (1994-1995); Ian MacLusky, MD; Bennie McWilliams, MD (1992-1998); Curtis L. Meinert, PhD; Sydney Parker, PhD (1991-1994); Joe Reisman, MD, FRCP(C), MBA (1991-1999); Denise Rodgers (2003-2005); Kay Seligsohn, PhD (1996-1997); Gail G. Shapiro, MD; Marian Sharpe (1993-1994); D Sundström (1998-1999); Stanley Szeffler, MD; Virginia Taggart, MPH; Martha Tata, RN (1996-1998); James Tonascia, PhD; Scott Weiss, MD, MS; Barbara Wheeler, RN, BSN (1993-1994); Robert Wise, MD; Robert Zeiger, MD, PhD.

Acknowledgments

Support: The Childhood Asthma Management Program is supported by contracts NO1-HR-16044, 16045, 16046, 16047, 16048, 16049, 16050, 16051, and 16052 with the National Heart, Lung, and Blood Institute and General Clinical Research Center grants M01RR00051, M01RR0099718-24, M01RR02719-14, and RR00036 from the National Center for Research Resources. This work was also supported by U01 HL65899.

References

1. Senn S. Individual response to treatment: is it a valid assumption? *BMJ* Oct 23;2004 329(7472):966–968. [PubMed: 15499115]
2. Duffy DL, Martin NG, Battistutta D, Hopper JL, Mathews JD. Genetics of asthma and hay fever in Australian twins. 1990;142(6 Pt 1)
3. Nieminen MM, Kaprio J, Koskenvuo M. A population-based study of bronchial asthma in adult twin pairs. 1991;100(1)
4. Sibbald B, Horn ME, Brain EA, Gregg I. Genetic factors in childhood asthma. 1980;35(9)
5. Ghio AJ, Crapo RO, Elliott CG, et al. Heritability estimates of pulmonary function. *Chest* 1989;96(4): 743–746. [PubMed: 2791667]
6. Hubert HB, Fabsitz RR, Feinleib M, Gwinn C. Genetic and environmental influences on pulmonary function in adult twins. *Am Rev Respir Dis* 1982;125(4):409–415. [PubMed: 7200340]
7. Drazen JM, Silverman EK, Lee TH. Heterogeneity of therapeutic responses in asthma. *Br Med Bull* 2000;56(4):1054–1070. [PubMed: 11359637]
8. Lemanske RF Jr, Allen DB. Choosing a long-term controller medication in childhood asthma. The proverbial two-edged sword. *Am J Respir Crit Care Med* 1997;156(3 Pt 1):685–687. [PubMed: 9309979]

9. Malmstrom K, Rodriguez-Gomez G, Guerra J, et al. Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma. A randomized, controlled trial. Montelukast/Beclomethasone Study Group. *Ann Intern Med* 1999;130(6):487–495. [PubMed: 10075616]
10. Szefer SJ, Martin RJ, King TS, et al. Significant variability in response to inhaled corticosteroids for persistent asthma. *J Allergy Clin Immunol* 2002;109(3):410–418. [PubMed: 11897984]
11. Osler's Principles and Practice of Medicine. London, UK: D Appleton-Century Company; 1942.
12. Szefer SJ, Phillips BR, Martinez FD, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J Allergy Clin Immunol* 2005;115(2):233–242. [PubMed: 15696076]
13. Clark DLHaAG. Principles of Population Genetics. Sunderland, MA: Sinauer Associates, Inc.; 1997.
14. Brown GP, Shine R. Repeatability and heritability of reproductive traits in free-ranging snakes. *J Evol Biol* 2007;20(2):588–596. [PubMed: 17305825]
15. Choy YH, Brinks JS, Bourdon RM. Repeated-measure animal models to estimate genetic components of mature weight, hip height, and body condition score. *J Anim Sci* 2002;80(8):2071–2077. [PubMed: 12211374]
16. Long-term effects of budesonide or nedocromil in children with asthma. The Childhood Asthma Management Program Research Group. *N Engl J Med* Dec;2000 343(15):1054–1063. [PubMed: 11027739]
17. The Childhood Asthma Management Program (CAMP) Design, Rationale, and Method. *Control Clin Trials* 1999;20(1):91–120. [PubMed: 10027502]
18. Rosner, B. Fundamentals of Biostatistics. 5. 2000.
19. Fuhlbrigge AL, Weiss ST, Kuntz KM, Paltiel AD. Forced expiratory volume in 1 second percentage improves the classification of severity among children with asthma. *Pediatrics* 2006;118(2):e347–355. [PubMed: 16864642]
20. Kitch BT, Paltiel AD, Kuntz KM, et al. A single measure of FEV1 is associated with risk of asthma attacks in long-term follow-up. *Chest* 2004;126(6):1875–1882. [PubMed: 15596687]
21. Tantisira KG, Fuhlbrigge AL, Tonascia J, et al. Bronchodilation and bronchoconstriction: predictors of future lung function in childhood asthma. *J Allergy Clin Immunol* 2006;117(6):1264–1271. [PubMed: 16750985]
22. Rosner B, Hennekens CH, Kass EH, Miall WE. Age-specific correlation analysis of longitudinal blood pressure data. *Am J Epidemiol* 1977;106(4):306–313. [PubMed: 910798]

Abbreviations

CAMP	Childhood Asthma Management Program
FEV1	Forced expiratory volume in 1 second
ICC	Intraclass correlation coefficient
PC20	Provocative concentration of methacholine producing a 20% decline in FEV1

Figure.

Mean responses for each outcome at visits between randomization and 48 months stratified by treatment group.

A. Bronchodilator Response

B. Pre-bronchodilator FEV1

C. log PC20

Table 1

Median values for bronchodilator response, Pre-bronchodilator FEV1, and log PC20 values at randomization stratified by covariates

	n	Bronchodilator Response		Pre-bronchodilator FEV1 (L)		log PC20 (mg/ml)	
		Median (25 th :75 th tile)	p-value	Median (25 th :75 th tile)	p-value	Median (25 th :75 th tile)	p-value
Treatment Group							
Budesonide	311	0.08 (0.04:0.15)	0.61	1.58 (1.32:1.92)	0.90	0.055 (-0.7:0.95)	0.59
Nedocromil	312	0.08 (0.04:0.15)		1.59 (1.28:1.93)		0.09 (-0.66:1.04)	
Placebo	417	0.08 (0.04:0.14)		1.58 (1.315:1.925)		0.09 (-0.71:0.95)	
Race/Ethnicity							
Hispanic	97	0.09 (0.05:0.16)	0.46	1.7 (-1.39:2.07)	0.0004	0.11 (-0.64:0.89)	0.71
Black	138	0.1 (0.05:0.16)		1.45 (1.16:1.76)		0.045 (-0.62:0.8)	
White	710	0.08 (0.04:0.15)		1.6 (1.33:1.93)		0.09 (-0.71:1.04)	
Other	94	0.085 (0.04:0.14)		1.56 (1.29:1.91)		-0.05 (-0.75:0.93)	
Gender							
Male	620	0.085 (0.04:0.15)	0.14	1.6 (1.33:1.93)	0.64	0.045 (-0.69:0.91)	0.42
Female	419	0.08 (0.04:0.14)		1.56 (1.28:1.92)		0.16 (-0.7:1.06)	
Weight							
<25 th percentile	247	0.08 (0.04:0.16)	0.80	1.19 (1:1.35)	<0.0001	0.07 (-0.82:0.91)	0.69
<50 th percentile	268	0.08 (0.04:0.14)		1.48 (1.32:1.67)		0.08 (-0.6:0.86)	
<75 th percentile	260	0.08 (0.05:0.15)		1.77 (1.545:1.96)		0.09 (-0.65:1.1)	
≥75 th percentile	260	0.08 (0.04:0.14)		2.12 (1.79:2.465)		0.14 (-0.72:1.13)	
Height							
<25 th percentile	254	0.08 (0.04:0.14)	0.85	1.17 (1:1.33)	<0.0001	0.12 (-0.7:0.86)	0.93
<50 th percentile	259	0.08 (0.04:0.15)		1.44 (1.32:1.62)		0.09 (-0.59:0.95)	
<75 th percentile	258	0.08 (0.04:0.15)		1.765 (1.59:1.91)		0.055 (-0.755:1.04)	
≥75 th percentile	258	0.09 (0.05:0.15)		2.185 (1.91:2.48)		0.085 (-0.76:1.13)	
Household Income							
<\$30,000	241	0.09 (0.04:0.16)	0.04	1.57 (1.27:1.91)	0.56	0.105 (-0.74:1.09)	0.53

	n	Bronchodilator Response		Pre-bronchodilator FEV1 (L)		log PC20 (mg/ml)	
		Median (25%tile:75%tile)	p-value	Median (25%tile:75%tile)	p-value	Median (25%tile:75%tile)	p-value
≥\$30,000	757	0.08 (0.04:0.14)		1.59 (1.32:1.93)		0.09 (-0.69:0.95)	
Parental Education	185						
High School or less	853	0.08 (0.04:0.13)	0.27	1.59 (1.31:1.93)	0.85	0.04 (-0.64:1.03)	0.87
Some College		0.08 (0.04:0.15)		1.58 (1.3:1.92)		0.09 (-0.71:0.97)	
Symptom Score			<0.001		0.38		<0.0001
Mild	496	0.07 (0.04:0.13)		1.56 (1.29:1.91)		0.26 (-0.525:1.205)	
Moderate	543	0.09 (0.05:0.17)		1.62 (1.33:1.94)		-0.09 (-0.88:0.68)	

ICC values for bronchodilator response, pre-bronchodilator FEV1, and log PC20 after adjusting for age, race/ethnicity, height, family income, parental education, and symptom score.

Table II

	Bronchodilator Response		Pre-bronchodilator FEV1		log PC20	
	ICC (95% confidence interval)	p-value	ICC (95% confidence interval)	p-value	ICC (95% confidence interval)	p-value
Budesonide	0.31 (0.26, 0.36)	0.02	0.71 (0.67, 0.75)	0.006	0.67 (0.63, 0.72)	0.11
Nedocromil	0.35 (0.31, 0.40)		0.60 (0.56, 0.65)		0.73 (0.68, 0.77)	
Placebo	0.40 (0.36, 0.44)		0.69 (0.66, 0.72)		0.67 (0.62, 0.71)	