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> Editor: Teresa Chipps, B.S. Copy-editor: Andrew Bender

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INSPIRE is Now Part of Something Bigger

by Tina Hartert, M.D., M.P.H.

At this time of the year, we like to connect with our study families to express our gratitude for your continued participation and commitment to the INSPIRE study.

Your participation has been instrumental in the success of this program. Thanks to you, INSPIRE is now part of the National Institutes of Health's National Children's Study called ECHO (Environmental Influences on Child Health Outcomes). The overarching goals of the program are to improve the health of children for generations to come.¹ We look forward to continuing to work with you as we move forward with INSPIRE!

INSPIRE is 1 of 12 studies at ten locations across the United States (see Figure 1) that will conduct research in childhood respiratory health as part of the ECHO consortium. This research includes more than 10,000 children across the U.S.

For our families participating in INSPIRE, not much will change. We will now follow your children through 10 years of age. This will not only allow us to track and follow parents' and children's health over a longer time period, but it will also allow us to collect additional data that we will share with our families. Ultimately, improving our understanding respiratory illnesses (such as colds), allergies, and asthma will lead to new treatments and disease prevention.

As we continue our annual phone surveys with our INSPIRE parents, you will begin hearing about this exciting opportunity to partner with us as INSPIRE teams up with ECHO. We encourage you to reach out to us if you have questions or would like further information on the INSPIRE – ECHO research program.

¹National Institutes of Health (NIH) Environmental Influences on Child Health Outcomes (ECHO), Rockville, MD available online at: www.echochildrens.org





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What does being part of ECHO mean for our study families?

- INSPIRE will not change!
- You will have an option to participate in new study-related visits and surveys that are part of the ECHO research program.
- You will be compensated for your time.
- You will receive results of any clinical studies.



INSPIRE Study/ECHO Study Timeline



The INSPIRE Study Information Flow

Our study team collects information and samples from you and your child throughout the course of INSPIRE: when your family first joined the study, during your child's first "cold season," around the time your child turned 1 year old, and when your child was about 2, 3, and 4 years of age. We want to share with you why we collect this information and samples, what we do with them, and how they contribute to INSPIRE.



Hello from the INSPIRE laboratory crew!

The yearly surveys you complete give us valuable information to track changes in health among the INSPIRE children. The samples you provide allow us to run experiments and tests to help answer INSPIRE's big question: how do respiratory infections (colds) in early life impact a child's future health? We have performed many scientific tests with these samples as we discover why each

When samples are collected, they are immediately taken to the INSPIRE laboratory where they are processed and stored by our lab director, Kaitlin, and her assistant, Marian. Our laboratory, as well as our many partner laboratories, then runs various experiments using these biospecimen samples. For example, a few of our past projects have included testing urine for cortisol (a stress hormone) and cytokines (substances that are part of our body's inflammatory response), testing blood for the presence of antibodies (proteins the body makes to fight off an illness), and testing nasal washes for the presence of respiratory viruses. We collect lots of information from these tests, and we use this information to discover why children are healthy or why they may develop

When samples are not being used, they are stored in large freezers. Most of the freezers keep our samples at a chilly -80° C (-176° F), but some special samples are kept at even colder temperatures (-384° F) in liquid nitrogen! In addition to freezers, our laboratory is filled with equipment and materials that we use to store, test, and ship samples. There is never a boring day in the laboratory!

> The success of INSPIRE would not be possible without these samples and the time you provide us. Thank you for your continued support of science, INSPIRE, and the goal of learning how to keep all children healthy!

Kaitlin & Marian





Kaitlin (L) and Marian (R) working in the INSPIRE laboratory

Different Kinds of Vitamin E During Pregnancy May Have Different Effects on Childhood Wheezing



by Cosby Stone, Jr., M.D., M.P.H

Vitamin E (also called tocopherol) is an essential micronutrient we only get from what we eat and drink. Our bodies do not make it on their own. Recent research suggests that during pregnancy, vitamin E is important for the health of the growing baby's lungs and immune system. It may also influence the immune system's development and response to early life challenges, like viruses and allergens. There are eight kinds of vitamin E, and the individual effects of these kinds of vitamin E have not been well studied. The two most common kinds of vitamin E in the human diet are alpha- and gamma-tocopherol.

A group of INSPIRE mothers gave fingerstick samples of blood when they enrolled in the study. These samples were tested to determine plasma concentrations of alpha- and gamma-tocopherol. As fat-soluble vitamins, concentrations of tocopherols in the body do not change rapidly and can be measured to give us a sense of what levels were like during

pregnancy. During the surveys that we asked every year since enrollment, parents have given us information about whether or not their children wheezed, either a few times or over and over again.

At age 2, the most current data that is available, children who wheezed had mothers with significantly lower plasma concentrations of alpha-tocopherol during pregnancy. Higher concentrations of alpha-tocopherol decreased the odds of child-hood wheezing by 31%.

We believe from these findings that it is important for our team to continue to study the effects of vitamin E on childhood health and to raise awareness of the fact that not every kind of vitamin E may have the same effects. Vitamin E is mostly found in oils, in fatty vegetables, nuts, seeds, and fish. Sunflower and safflower oils are highest in the vitamin E isoform alphatocopherol, while corn, soy and canola oil are higher in the vitamin E isoform gamma-tocopherol (Figure 2). Current supplement and food labels do not provide accurate information on which isoform of vitamin E is present.

While dietary changes favoring oils containing alpha-tocopherol may seem reasonable, our current observed effect is only an association. Further studies, including observation to older ages and randomized controlled trials, are needed to determine if vitamin E isoforms are the true cause of the changes in wheezing we observed. We hope that this discovery, made possible by the INSPIRE families, may one day lead to a new tool for the prevention of childhood wheezing, allergies, or asthma and the promotion of maternal and child health.



Figure 2

RELEVANT CENTER PUBLICATIONS

- 1. A review of metabolomics approaches and their application in identifying causal pathways of childhood asthma. Turi KN, Romick-Rosendale L, Ryckmann KK, Hartert TV. J Allergy Clin Immunol. 2017 May 4 [Epub ahead of print. PMID: 28479327.
- 2. Preventing Respiratory Syncytial Virus Infection to Prevent Asthma: The Missing Link. Gebretsadik T, Wu P, Carroll K, Dupont W, Hartert T. *Am J Respir Crit Care Med*. 2017 Jul 1;196(1):116-117. PMID: 28379714.
- Interference Between Respiratory Syncytial Virus and Human Rhinovirus Infection in Infancy. Achten NB, Wu P, Bont L, Blanken MO, Gebretsadik T, Chappell JD, Wang L, Yu C, Larkin EK, Carroll KN, Anderson LJ, Moore ML, Sloan CD, Hartert TV. J Infect Dis. 2017 Apr 1;215(7):1102-1106. PMID: 28368456.
- 4. The impact of temperature and relative humidity on spatiotemporal patterns of infant bronchiolitis epidemics in the contiguous United States. Sloan C, Heaton M, Kang S, Berrett C, Wu P, Gebretsadik T, Sicignano N, Evans A, Lee R, Hartert T. *Health Place*. 2017 May;45:46-54. Epub 2017 Mar 10. PMID: 28285184.
- 5. Prenatal exposures and the development of childhood wheezing illnesses. Rosas-Salazar C, Hartert TV. Curr Opin Allergy Clin Immunol. 2017 Apr;17(2):110-115. PMID: 28079560.
- 6. Differences in the Nasopharyngeal Microbiome During Acute Respiratory Tract Infection With Human Rhinovirus and Respiratory Syncytial Virus in Infancy. Rosas-Salazar C, Shilts MH, Tovchigrechko A, Schobel S, Chappell JD, *Larkin EK, Shankar J, Yooseph S, Nelson KE, Halpin RA, Moore ML, Anderson LJ, Peebles RS Jr, Das SR, Hartert TV. J Infect Dis. 2016 Dec 15;214(12):1924-1928. PMID: 27923952. PMCID: PMC5142087 [Available on 2017-12-15].
- Predictors of asthma following severe respiratory syncytial virus (RSV) bronchiolitis in early childhood. Lu S, Hartert TV, Everard ML, Giezek H, Nelsen L, Mehta A, Patel H, Knorr B, Reiss TF. *Pediatr Pulmonol.* 2016 Dec;51(12):1382-1392. Epub 2016 May 6. PMID:27152482.
- Interaction of vitamin E isoforms on asthma and allergic airway disease. Cook-Mills J, Gebretsadik T, Abdala-Valencia H, Green J, Larkin EK, Dupont WD, Shu XO, Gross M, Bai C, Gao YT, Hartman TJ, Rosas-Salazar C, Hartert T. *Thorax.* 2016 Oct;71(10):954-6. PMID: 27257004.
- 9. Respiratory syncytial virus infection activates IL-13-producing group 2 innate lymphoid cells through thymic stromal lymphopoietin. Stier MT, Bloodworth MH, Toki S, Newcomb DC, Goleniewska K, Boyd KL, Quitalig M, Hotard AL, Moore ML, Hartert TV, Zhou B, McKenzie AN, Peebles RS Jr. *J Gen Virol*. 2015 Sep;96(9):2543-56. PMID:27156176. PMCID: PMC4635495 [Available on 2017-09-01].

RELEVANT NATIONAL MEETING PRESENTATIONS

- Identification of Infant Acute Respiratory Illness Cytokine-Response Subgroups Associated with Recurrent Wheezing Phenotype." Keystone Symposia on Molecular and Cellular Biology, Keystone, CO, February 13, 2017. Invited Speaker, Kedir Turi, Ph.D.
- "Maternal Vitamin E Plasma Isoform Concentrations and Association with Child Wheezing and Asthma Outcomes." American Academy of Allergy Asthma & Immunology (AAAAI) Annual Meeting, Atlanta, GA, March 4, 2017. Press Conference and Invited Speaker, Cosby Stone, Jr., M.D., M.P.H.
- "Barbarians at the gate: viruses and the airway epithelium in asthma." ATS Symposium A006, 2017 American Thoracic Society (ATS) International Conference, Washington, DC, May 21, 2017. Invited Speaker, Tina Hartert, M.D., M.P.H.
- 4. "Early-Life Naso-pharyngeal Colonization with Lactobacillus Reduces Risk of Childhood Wheezing Illnesses Following Respiratory Syncytial Virus Infection in Infancy." Mini Symposium, 2017 American Thoracic Society (ATS) International Conference, Washington, DC, May 21, 2017. Invited Speaker, Christian Rosas-Salazar, M.D., M.P.H.
- "Identification of Two Novel Acute Respiratory Illness Cytokine-Response Subgroups Associated with Wheezing Phenotype." Mini Symposium, 2017 American Thoracic Society (ATS) International Conference, Washington, DC, May 21, 2017. Invited Speaker, Kedir Turi, Ph.D.
- "The Role of Oxidative Stress in the Pathogenesis of Recurrent Wheeze in Children Following Infant Viral Respiratory." Mini Symposium, 2017 American Thoracic Society (ATS) International Conference, Washington, DC, May 22, 2017. Invited Speaker, Christian Rosas-Salazar, M.D., M.P.H.
- "Evolution and Impact of the Microbiome in Pediatric Inflammatory Airway Diseases." Symposium, 2017 American Thoracic Society (ATS) International Conference, Washington, DC, May 23, 2017. Invited Speaker, Christian Rosas-Salazar, M.D., M.P.H.
- 8. "Derivation of a Clinical Prediction Model for Severe Bronchiolitis Outcome." Poster, 2017 American Thoracic Society (ATS) International Conference, Washington, DC, May 23, 2017. Niek Achten, M.D.
- 9. "Primary Prevention of Asthma: The Role of RSV in the Early Life Origins of Disease." RSV Vaccines for the World Conference 2017. Malaga Spain, December 1, 2017. Invited Speaker, Tina Hartert, M.D., M.P.H.







We send our thanks to each one of our study families for your to work with us on the INSPIRE Study. We look forward to our collaboration and will continue to provide results from this research that will impact your child's health.

INSPIRE Study Team

Understan ding Children's Health Through Research

willingness continued

Principal Investigator Tina V. Hartert, MD, MPH

Investigators Steve Brunwasser, PhD Christian Rosas-Salazar, MD, MPH Cosby Stone, Jr. MD, MPH Kedir Turi, PhD Larry Anderson, MD, Emory/CDC Marty Moore, PhD, Emory

Administration Teresa Chipps, BS Christian Lynch, MPH

Research Study Nurses

Kelsie McMurtry, RN, BSN Pat Russell, RN, BSN Kim Woodward, RN, MSN

Research Study Staff

Alexandra Connolly, BS Rebecca Gammell, BA Kayla Goodman Alyssa Bednarek Andrew Bender Karin Han

Laboratory

Sandy Alvarez Calvillo, BS James Chappell, PhD Kaitlin Costello, BA Marian Dorst, BA

Biostatistics

William Dupont, PhD Tebeb Gebretsadik, MPH Zhouwen Liu, MS

Medical Monitor Barron Patterson, MD



INSPIRE Study 6100 Medical Center East, North Tower 1215 21st Avenue, South Nashville, TN 37232-8300

Phone: 615-875-BABY (2229) Toll-free: 1-888-664-0505 Email: INSPIRE@vanderbilt.edu Website: my.vanderbilt.edu/inspire



VANDERBILT WUNIVERSITY MEDICAL CENTER



Infant Susceptibility to Pulmonary Infections and Asthma Following RSV Exposure (INSPIRE) IRB #111299 • Funded by NIAID/AADCRC

> Environmental Influences on Child Health Outcomes (ECHO) Funded by NIH

> > Kids Graphics from https://www.tes.com/member/zingbadabling96



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