across the genome, including pathways highly relevant to PAH pathogenesis, such as WNT signaling (8, 10, 11).

One of the findings in our study was that the positive effect of SRY on *BMPR2* expression had an upper limit, above which adding more SRY did not result in a corresponding increase in *BMPR2* expression. This is not a surprising finding, as most transcription factors have a limited range of function. Furthermore, *BMPR2* expression is likely controlled by a coordinated action of multiple different transcriptional regulators, and thus one transcription factor would not be expected to modify its expression to an unlimited extent. For example, previous studies have identified other factors that regulate *BMPR2* expression, such as estrogen receptor α (4, 5). Thus, the integration of multiple factors may explain why SRY has a limited, but important, capacity to increase *BMPR2* expression. Each factor may play a role in PAH susceptibility or resilience. It is important to acknowledge that in some assays, the effect sizes were modest; this may reflect the fact that multiple factors likely contribute to *BMPR2* expression, not simply SRY activity. Finally, much of this work was conducted using PAH fibroblasts because of the low expression of *SRY* in typical lung vascular cells. Although the amount of data suggesting that fibroblasts may contribute to PAH pathogenesis is growing, future work will determine whether SRY contributes to variations in lung vascular cell health and function.

In conclusion, SRY binds to and positively regulates *BMPR2* expression. This builds on recent novel work by Umar and colleagues, which demonstrated the relevance of the Y chromosome to pulmonary hypertension (7). Our findings advance the concept that protective factors on the Y chromosome contribute to pulmonary hypertension, with a focus on the reduced male incidence in PAH via sex-specific *BMPR2* regulation. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Ling Yan, Ph.D.
Joy D. Cogan, Ph.D.
Lora K. Hedges, B.S.
Bethany Nunley, B.S.
Rizwan Hamid, M.D., Ph.D.*
Eric D. Austin, M.D., M.Sc.*‡
Vanderbilt University Medical Center
Nashville, Tennessee

ORCID ID: 0000-0002-1709-9022 (E.D.A.).

*Co–senior authors.
‡Corresponding author (e-mail: eric.austin@vumc.org).

References

1. Atkinson C, Stewart S, Upton PD, Machado R, Thomson JR, Trembath RC, *et al*. Primary pulmonary hypertension is associated with reduced pulmonary vascular expression of type II bone morphogenetic protein receptor. *Circulation* 2002;105:1672–1678.
2. Soubrier F, Chung WK, Machado R, Grünig E, Aldred M, Geraci M, *et al*. Genetics and genomics of pulmonary arterial hypertension. *J Am Coll Cardiol* 2013;62(25, Suppl):D13–D21.
3. Larkin EK, Newman JH, Austin ED, Hemnes AR, Wheeler L, Robbins IM, *et al*. Longitudinal analysis casts doubt on the presence of genetic anticipation in heritable pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2012;186:892–896.
4. Austin ED, Hamid R, Hemnes AR, Loyd JE, Blackwell T, Yu C, *et al*. BMPR2 expression is suppressed by signaling through the estrogen receptor. *Biol Sex Differ* 2012;3:6.
5. Mair KM, Yang XD, Long L, White K, Wallace E, Ewart MA, *et al*. Sex affects bone morphogenetic protein type II receptor signaling in pulmonary artery smooth muscle cells. *Am J Respir Crit Care Med* 2015;191:693–703.
6. Lahm T, Frump AL, Albrecht ME, Fisher AJ, Cook TG, Jones TJ, *et al*. 17β-Estradiol mediates superior adaptation of right ventricular function to acute strenuous exercise in female rats with severe pulmonary hypertension. *Am J Physiol Lung Cell Mol Physiol* 2016;311:L375–L388.
7. Umar S, Cunningham CM, Itoh Y, Moazeni S, Vaillancourt M, Sarji S, *et al*. The Y chromosome plays a protective role in experimental hypoxic pulmonary hypertension. *Am J Respir Crit Care Med* 2018;197:952–955.
8. Lau YF, Li Y. The human and mouse sex-determining SRY genes repress the Rspol/beta-catenin signaling. *J Genet Genomics* 2009;36:193–202.
9. Schepers GE, Teasdale RD, Koopman P. Twenty pairs of sox: extent, homology, and nomenclature of the mouse and human sox transcription factor gene families. *Dev Cell* 2002;3:167–170.
10. Awad KS, West JD, de Jesus Perez V, MacLean M. Novel signaling pathways in pulmonary arterial hypertension (2015 Grover Conference Series). *Pulm Circ* 2016;6:285–294.
11. Wissmüller S, Kosian T, Wolf M, Finzsch M, Wegner M. The high-mobility-group domain of Sox proteins interacts with DNA-binding domains of many transcription factors. *Nucleic Acids Res* 2006;34:1735–1744.

Exposure to Humidifier Disinfectants Increases the Risk for Asthma in Children

To the Editor:

In South Korea, several types of chemical disinfectants that had been widely used in humidifiers since 1994 were found to be associated with lung injury and widespread lung fibrosis (1–4). After the humidifier disinfectants (HDs) were found to be the cause of the lung injury, they were withdrawn from the market in 2011, after which no new cases of lung injury have been reported (1). Although much research has examined the acute lung injury resulting from HD exposure in terms of outcomes such as mortality and HD-induced lung injury (HDLI), the long-term consequences of HD usage on health effects have not been reported. Patients with HDLI and people exposed to HDs have complained of asthma symptoms, but only one case of occupational asthma resulting from isothiazolinone exposure has been reported (5). A previous

This study was supported by the Korea Ministry of Environment as the Environmental Health Action Program (2016001360006), the Environmental Health Center for Hazardous Chemical Exposure funded by Ministry of Environment Republic of Korea (2018), and the research of Korea Centers for Disease Control and Prevention (2015-ER6601-00). This work was also supported by the Research Program funded by the Korea Centers for Disease Control and Prevention (2008-E33030-00, 2009-E33033-00, 2011-E33021-00, 2012-E33012-00, 2013-E51003-00, 2014-E51004-00, 2014-E51004-01, 2014-E51004-02, and 2017-E67002-00).

Author Contribution: J.Y. planned the project, acquired the data, helped interpret the data, and wrote the manuscript; S.-Y.L. contributed to the study conception, interpreted the results, and wrote the manuscript; S.-H.L. performed most of the animal experiments and data analysis and helped write the manuscript; E.M.K. was responsible for data transformation, database management, and statistical analysis; S.J., H.-J.C., E.L., and S.-IY. helped with the writing and review of the manuscript; S.-J.H. conceived and planned the project, acquired the data, analyzed the data, interpreted the results, and critically reviewed the manuscript.

Originally Published in Press as DOI: 10.1164/rccm.201805-0840LE on September 7, 2018

report has indicated that approximately 30% of young children in the general Korean population were exposed to HDs (6); however, little is known about the relationship between early-life HD exposure and asthma symptoms later in life. We therefore investigate this issue in two independent birth cohort studies.

A modified Korean version of the ISAAC (International Study of Asthma and Allergies in Childhood) questionnaire was previously validated as a tool for assessment and diagnosis of allergic diseases in Korean children (7, 8). The ISAAC questionnaires were completed by parents or guardians in two general population-based birth cohort studies: the PSKC (Panel Study of Korean Children) study (9) and the COCOA (Cohort for Childhood Origin of Asthma and Allergic Diseases) study (8). The PSKC study was conducted from 2013 to 2015, and the participating children were 5 to 7 years old (n = 1,577). The study participants were all born in 2008, and HDs were withdrawn from the Korean market in 2011; therefore, HD exposure was estimated to have occurred within 3 years of birth. We also included children born during 2007–2014 from the COCOA study (n = 1,829), and evaluated the occurrence of early-life wheezing between 0 and 3 years of age. We compared the occurrences of wheezing symptoms and asthma treatment before and after the discontinuation of HD sales and calculated the odds ratios (ORs) and 95% confidence intervals (CIs) for HD exposure by using logistic regression models. The Institutional Review Board of Asan Medical Center approved each study protocol (2015–0907, 2008–0616). The Wald statistic for trend in logistic regression was calculated by using SPSS version 23 (SPSS, Inc.).

In the PSKC study, children who developed acute bronchiolitis before 3 years of age and who had HD exposure showed a significantly increased risk for asthma treatment during the last 12 months (adjusted OR, 2.25; 95% CI, 1.01–5.00; data not shown). We divided the children into four groups according to bronchiolitis history and use of HD. The risk for wheezing symptoms during

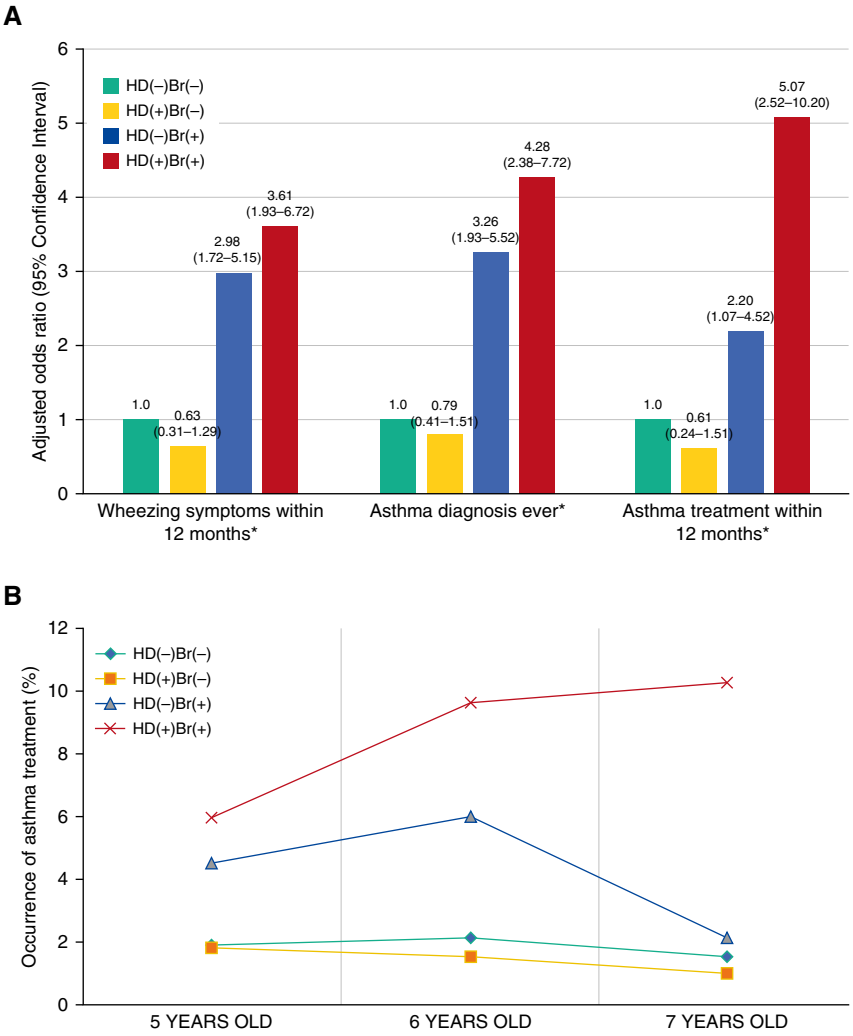

Figure 1. (*A*) Adjusted odds ratio (95% confidence interval) of asthma in the 5- to 7-year-old study participants with HD exposure and history of acute bronchiolitis. (*B*) Occurrence of asthma treatment according to HD exposure and history of acute bronchiolitis, adjusted by sex, socioeconomic status, environmental tobacco smoking, and family history of allergic disease. Br = history of bronchiolitis before 3 years of age; HD = humidifier disinfectant. *Trend P value (Wald statistic for trend in logistic regression) < 0.01.

the last 12 months (adjusted OR, 3.61; 95% CI, 1.93–6.72), asthma diagnosis ever (adjusted OR, 4.28; 95% CI, 2.38–7.72), and asthma treatment during the last 12 months (adjusted OR, 5.07; 95% CI, 2.52–10.20) were all significantly higher in children with bronchiolitis history than in those without bronchiolitis history (trend P value < 0.01; Figure 1A).

The occurrence of asthma treatment was consistently higher in children who were exposed to HD and had history of bronchiolitis, with 5.9% of 5-year-old children with both exposures having received asthma treatment in the last year, 9.6% of 6-year-olds, and 10.2% of 7-year-olds. Conversely, the children with history of bronchiolitis who were not exposed to HD were less likely to have received asthma treatment in the last year, with increasing age, with 4.5% of 5-year-olds having been treated, 5.9% of 6-year-olds, and 2.1% of 7-year-olds (Figure 1B). This finding suggested that HD exposure in the past may cause persistent asthma symptoms.

In the COCOA study, considering that HD sales were totally discontinued in 2011 (2), we divided children who were born from 2007 to 2010 (presumed to have been exposed to HD) and those born from 2012 to 2014 (not exposed to HD) and compared the occurrence of early-life wheezing during 3 years after birth. The occurrences of wheezing symptoms and asthma diagnosis between 0 and 3 years showed a significant decreasing trend (Figures 2A and 2B). The trend of the asthma treatment also tended to decrease, albeit not statistically significantly (Figure 2C).

Our current result from two independent general population-based cohort studies revealed the link between early-life HD exposure to asthma symptoms in childhood. In the PSKC cohort, only the group with history of bronchiolitis during the first 3 years of life showed correlation between HD exposure and childhood asthma in 5- to 7-year-olds. HD exposure showed a relationship with asthma development and persistency in 5- to 7-year-olds. Another independent birth cohort indirectly showed the difference in the occurrence of early-life wheezing before and after the cessation of HD sales in patients younger than 3 years. This was characterized by a significant decrease in the occurrences of wheezing symptoms, asthma diagnosis, and treatment for possible asthma development in childhood.

There were some notable limitations, including remote memory recall related to questionnaire responses and difficulty in discerning whether the wheezing started before or after HD exposure. We also could not determine the distinct effect of different HD component chemicals because of duplicate use of the components. Pandemic influenza infection in 2009 (10), and other respiratory viruses that cause acute bronchiolitis, need to be considered. Further evaluation to prove more concrete causal relationships and animal studies such as HD exposure in a mouse model of bronchiolitis to determine the pathophysiology or synergistic effect is needed. Despite these limitations, our study is meaningful, in that the relationship between HD use and asthma was identified through two independent general population-based birth cohorts.

In conclusion, our results are the first to link early-life HD exposure to the development and persistence of asthma in young children. It is an important issue because such chemical

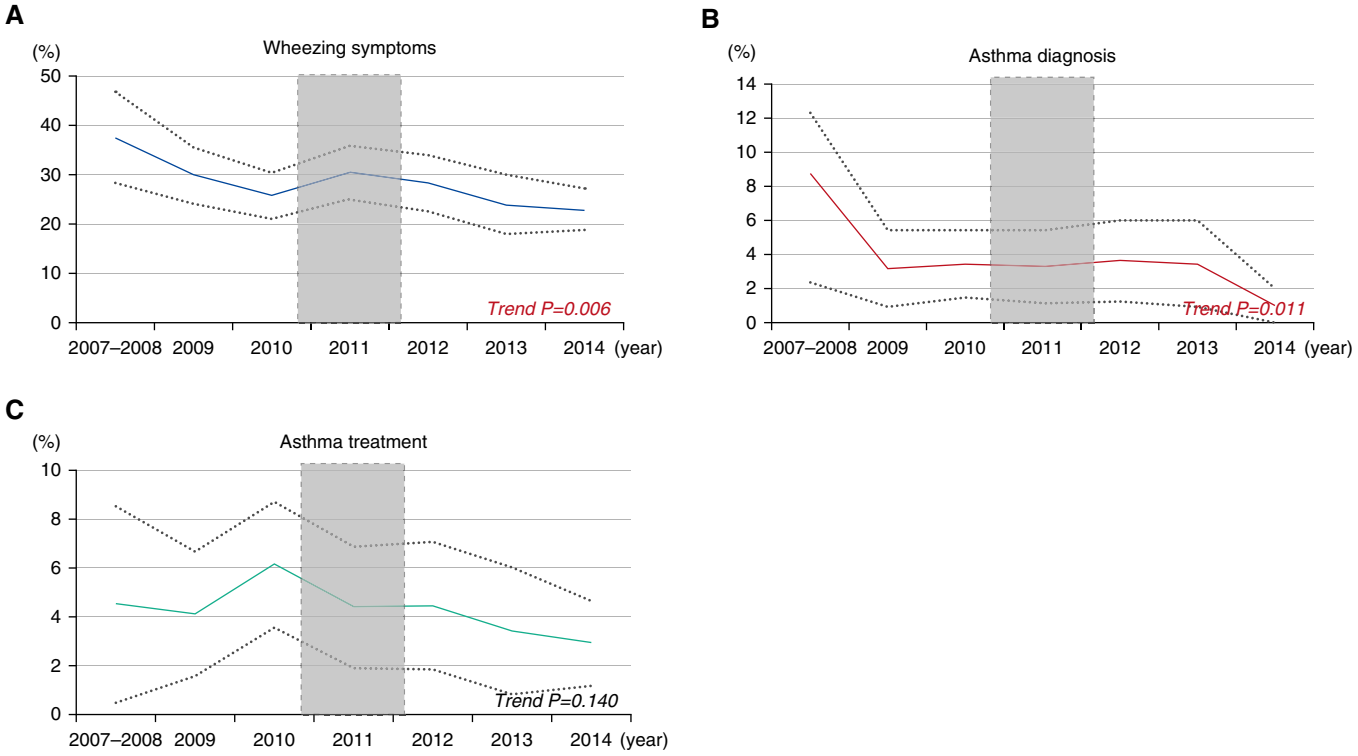

Figure 2. Occurrences of (*A*) wheezing symptoms, (*B*) asthma diagnosis, and (*C*) asthma treatment according to year of birth in the COCOA (Cohort for Childhood Origin of Asthma and Allergic Diseases) birth cohort. Children who were born in 2011 were excluded from the analysis.

inhalation can affect children's health not only in the acute phase such as HDLI but also years after the exposure. Thorough safety evaluation of household chemicals is needed to prevent future chemical-related fatalities and health crises in children. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Jisun Yoon, M.D.
Mediplex Sejong Hospital
Incheon, Korea

So-Yeon Lee, M.D., Ph.D.
Seung-Hwa Lee, M.S.
Eun Mi Kim, M.S.
Sungsu Jung, M.D.
University of Ulsan College of Medicine
Seoul, Korea

Hyun-Ju Cho, M.D.
Catholic Kwandong University
Incheon, Korea

Eun Lee, M.D., Ph.D
Chonnam National University College of Medicine
Gwangju, Korea

Song-I Yang, M.D., Ph.D.
Hallym University College of Medicine
Anyang, Korea

Soo-Jong Hong, M.D., Ph.D.*
University of Ulsan College of Medicine
Seoul, Korea

ORCID IDs: 0000-0002-4904-9118 (J.Y.); 0000-0002-2499-0702 (S.-Y.L.); 0000-0002-0559-4982 (S.J.); 0000-0003-4282-4000 (H.-J.C.); 0000-0002-7462-0144 (E.L.); 0000-0002-9648-4585 (S.-I.Y.); 0000-0003-1409-2113 (S.-J.H.).

*Corresponding author (e-mail: sjhong@amc.seoul.kr).

References

1. Kim KW, Ahn K, Yang HJ, Lee S, Park JD, Kim WK, *et al*. Humidifier disinfectant-associated children's interstitial lung disease. *Am J Respir Crit Care Med* 2014;189:48–56.
2. Park DU, Ryu SH, Roh HS, Lee E, Cho HJ, Yoon J, *et al*. Association of high-level humidifier disinfectant exposure with lung injury in preschool children. *Sci Total Environ* 2018;616-617:855–862.
3. Kim HJ, Lee MS, Hong SB, Huh JW, Do KH, Jang SJ, *et al*. A cluster of lung injury cases associated with home humidifier use: an epidemiological investigation. *Thorax* 2014;69:703–708.
4. Yang HJ, Kim HJ, Yu J, Lee E, Jung YH, Kim HY, *et al*. Inhalation toxicity of humidifier disinfectants as a risk factor of children's interstitial lung disease in Korea: a case-control study. *PLoS One* 2013;8: e64430.
5. Bourke SJ, Convery RP, Stenton SC, Malcolm RM, Hendrick DJ. Occupational asthma in an isothiazolinone manufacturing plant. *Thorax* 1997;52:746–748.
6. Yoon J, Cho HJ, Lee E, Choi YJ, Kim YH, Lee JL, *et al*. Rate of humidifier and humidifier disinfectant usage in Korean children: A nationwide epidemiologic study. *Environ Res* 2017;155:60–63.
7. Hong SJ, Lee MS, Sohn MH, Shim JY, Han YS, Park KS, *et al*. Self-reported prevalence and risk factors of asthma among Korean adolescents: 5-year follow-up study, 1995-2000. *Clin Exp Allergy* 2004;34:1556–1562.
8. Yang HJ, Lee SY, Suh DI, Shin YH, Kim BJ, Seo JH, *et al*. The Cohort for Childhood Origin of Asthma and allergic diseases (COCOA) study: design, rationale and methods. *BMC Pulm Med* 2014;14:109.
9. Nam S, Chun J. Influencing factors on mothers' parenting style of young children at risk for developmental delay in South Korea: the mediating effects of parenting stress. *Child Youth Serv Rev* 2014;36:81–89.
10. Lee E, Seo JH, Kim HY, Na S, Kim SH, Kwon JW, *et al*. Clinical characteristics and outcomes among pediatric patients hospitalized with pandemic influenza A/H1N1 2009 infection. *Korean J Pediatr* 2011;54:329–334.

The LIBERATE Trial: Options to Reduce the Risk of Post-procedural Pneumothorax and Length of Stay

To the Editor:

We read with great interest the recent article by Criner and colleagues of the LIBERATE (Lung Function Improvement after Bronchoscopic Lung Volume Reduction with Pulmonx Endobronchial Valves Used in Treatment of Emphysema) Study Group reporting their results from the first multicenter randomized controlled trial to evaluate the effectiveness and safety of Zephyr endobronchial valves (EBVs) in patients with little or no collateral ventilation out to 12 months (1). Chronic obstructive pulmonary disease represents a significant disease burden worldwide, and patients with advanced emphysema with hyperinflation have limited options apart from lung volume reduction surgery or transplantation (2). EBVs represent a minimally invasive option to achieve similar results in patients with little or no collateral ventilation; however, follow-up studies to date have been short term (limited to 3–6 mo) (3, 4). In this elegant study, Criner and colleagues concluded that Zephyr EBVs provided clinically meaningful benefits in lung function, exercise tolerance, dyspnea, and quality-of-life scores for at least 12 months after implantation.

However, as in previous studies, the authors reported that pneumothorax was the most common and significant serious adverse event during the treatment period, occurring in 44 of 128 patients with EBVs (34.4%) during the 12-month period. Seventy-six percent of these pneumothoraces occurred within 3 days of EBV placement, and 85% occurred within 5 days. This resulted in at least one valve removal in 12 patients, and 38 patients required placement of a chest drain. Eight patients were managed conservatively with observation only. No statistically significant risk factors for pneumothorax occurrence were identified. Of particular concern, three of the four mortalities reported during the treatment period resulted from a pneumothorax at Day 3 in two patients and Day 13 in one patient. Consequently, the authors advised a minimum hospital stay of 3 days after EBV placement, and the optimal post-procedural length of stay could justifiably extend to 5 days.

To address this issue, our group has begun placing a prophylactic chest drain on the side of the implanted EBV at the time of valve placement. We use a 16F chest drain (Thal-Quick Chest Tube Set; Cook Medical Inc.). The drain is placed on a Portex bag (Ambulatory Chest Drainage System; Smiths Medical International Ltd.) and the patient is discharged home with the drain

Originally Published in Press as DOI: 10.1164/rccm.201807-1396LE on September 19, 2018