and may provide a explanation for the reductions in lung function observed with reduced serum 25(OH)D, both in asthma and in populations without asthma (15). Until the various hypotheses raised by this work are refined and tested further, we are left concluding that vitamin D status is an easily measurable and correctable clinical state that might have direct bearing on important clinical parameters such as lung function, bronchodilator responsiveness, and airway hyperresponsiveness, in part via effects on ASM. The inclusion of appropriate surrogate clinical outcomes and translational mechanistic aims into ongoing and future clinical vitamin D supplementation trials in asthma is an opportunity to determine if this is the case.

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References

1. Gupta A, Sjoukes A, Richards D, Banya W, Hawrylowicz C, Bush A, Saglani S. Relationship between serum vitamin D, disease severity, and airway remodeling in children with asthma. *Am J Respir Crit Care Med* 2011;184:1342–1349.
2. Brehm JM, Celedon JC, Soto-Quiros ME, Avila L, Hunninghake GM, Forno E, Laskey D, Sylvia JS, Hollis BW, Weiss ST, *et al.* Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. *Am J Respir Crit Care Med* 2009;179:765–771.
3. Brehm JM, Schuemann B, Fuhlbrigge AL, Hollis BW, Strunk RC, Zeiger RS, Weiss ST, Litonjua AA. Serum vitamin D levels and severe asthma exacerbations in the childhood asthma management program study. *J Allergy Clin Immunol* 2010;126:52–58.
4. Searing DA, Zhang Y, Murphy JR, Hauk PJ, Goleva E, Leung DY. Decreased serum vitamin D levels in children with asthma are associated with increased corticosteroid use. *J Allergy Clin Immunol* 2010; 125:995–1000.
5. Majak P, Olszowiec-Chlebna M, Smejda K, Stelmach I. Vitamin D supplementation in children may prevent asthma exacerbation triggered by acute respiratory infection. *J Allergy Clin Immunol* 2011;127: 1294–1296.
6. Panettieri RA Jr. Asthma persistence versus progression: does airway smooth muscle function predict irreversible airflow obstruction? *Allergy Asthma Proc* 2009;30:103–108.
7. Damera G, Fogle HW, Lim P, Goncharova EA, Zhao H, Banerjee A, Tliba O, Krymskaya VP, Panettieri RA, Jr. Vitamin D inhibits growth of human airway smooth muscle cells through growth factor-induced phosphorylation of retinoblastoma protein and checkpoint kinase 1. *Br J Pharmacol* 2009;158:1429–1441.
8. Banerjee A, Damera G, Bhandare R, Gu S, Lopez-Boado Y, Panettieri R, Jr., Tliba O. Vitamin D and glucocorticoids differentially modulate chemokine expression in human airway smooth muscle cells. *Br J Pharmacol* 2008;155:84–92.
9. Zosky GR, Berry LJ, Elliot JG, James AL, Gorman S, Hart PH. Vitamin D deficiency causes deficits in lung function and alters lung structure. *Am J Respir Crit Care Med* 2011;183:1336–1343.
10. Li Y, Spataro BC, Yang J, Dai C, Liu Y. 1,25-dihydroxyvitamin D inhibits renal interstitial myofibroblast activation by inducing hepatocyte growth factor expression. *Kidney Int* 2005;68:1500–1510.
11. Vega RB, Rothermel BA, Weinheimer CJ, Kovacs A, Naseem RH, Bassel-Duby R, Williams RS, Olson EN. Dual roles of modulatory calcineurin-interacting protein 1 in cardiac hypertrophy. *Proc Natl Acad Sci USA* 2003;100:669–674.
12. Bosse Y, Maghni K, Hudson TJ. 1alpha,25-dihydroxy-vitamin D3 stimulation of bronchial smooth muscle cells induces autocrine, contractility, and remodeling processes. *Physiol Genomics* 2007; 29:161–168.
13. Sutherland ER, Goleva E, Jackson LP, Stevens AD, Leung DY. Vitamin D levels, lung function, and steroid response in adult asthma. *Am J Respir Crit Care Med* 2010;181:699–704.
14. Hidalgo AA, Deeb KK, Pike JW, Johnson CS, Trump DL. Dexamethasone enhances 1{alpha},25-dihydroxyvitamin D3 effects by increasing vitamin d receptor transcription. *J Biol Chem* 2011;286: 36228–37.
15. Black PN, Scragg R. Relationship between serum 25-hydroxyvitamin D and pulmonary function in the third national health and nutrition examination survey. *Chest* 2005;128:3792–3798.

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Ambient Particulate Air Pollution, Environmental Tobacco Smoking, and Childhood Asthma: Interactions and Biological Mechanisms

The World Health Organization (WHO) estimates that 24% of the global burden of disease is caused by environmental factors that can be averted (1). Understanding the role of the environment in asthma is a natural ambition in the overall search to understand environmental burdens: In an individual expressing the asthmatic phenotype, worsening of asthma control is logically related to environmental agents, and the airways are directly exposed to environmental challenges. As much as 44% of the asthma disease burden has been attributed to mitigable environmental risk factors, as opposed to genetic/familial factors or risk factors such as outdoor exposure to pollens (deemed not modifiable) (1).

Childhood asthma is exacerbated by environmental agents, many of which are modifiable, including allergens from dust mites, cockroaches, and other animal and fungal sources; indoor exposure to dampness; indoor smoke from solid fuels; secondhand smoke (SHS); and ambient air pollution (1–4). On a typical day children may be exposed to a number of different environmental agents at home, in daycare centers and schools, and outdoors. Most research conducted thus far has focused on the investigation of isolated risk factors. Little is known about the effects on children of concurrent exposures to multiple risk factors, and whether they interact with each other to potentiate adverse effects on asthma or whether one factor might produce an effect that reduces the effect of another.

In this issue of the *Journal*, Rabinovitch and colleagues (pp. 1350–1357) report novel results from a repeated-measures study of children aged 6 to 15 years that begins to address this gap (5). Rather than focusing on individual asthma triggers in isolation, these investigators used an in-depth panel study of a relatively small group of children with asthma to evaluate the interactive effects of SHS and particulate matter air pollution, two common established environmental risk factors, on disease severity. In particular, they focused on how SHS

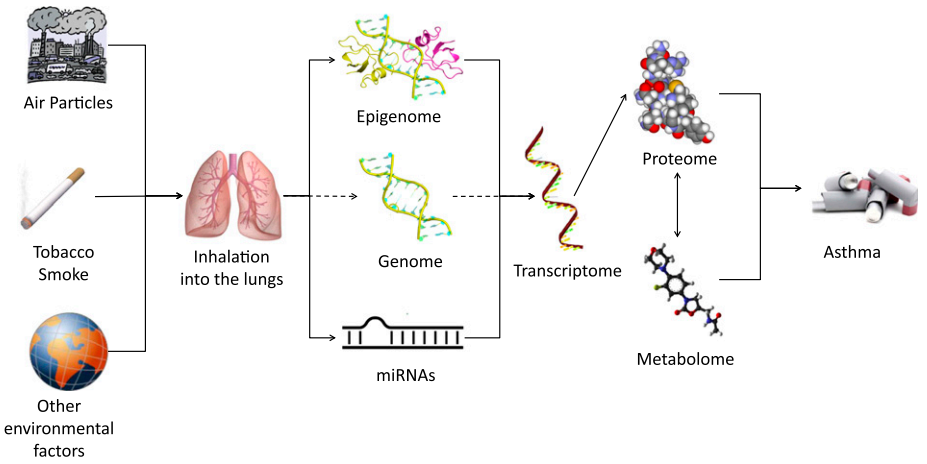

Figure 1. Potential biological mechanisms underlying the interactions of air particles and environmental tobacco smoke in determining asthma exacerbations.

exposure modified the effect of ambient pollution on asthma severity.

A strength in their analysis is use of objective measures of asthma severity and exacerbations –urinary levels of leukotriene E4 (LTE4, a biological marker associated with airway inflammation and bronchoconstriction) and the frequency of rescue albuterol inhaler use (logged electronically by the inhaler). Both LTE4 and albuterol use were higher on days with higher outdoor ambient $PM_{2.5}$ concentrations. However, the effects of PM were stronger on days when exposure to SHS, measured by same-day urinary cotinine concentrations, was low. The effect of PM on asthma severity could not be seen with high SHS exposure. The findings in the study were not as consistent year-to-year and across statistical models as would be preferred, but the results are of interest. They suggest that the effects of two common environmental exposures—in this case PM and SHS, which might be considered to act in a similar fashion—do not simply add on to each other. This finding may be particularly helpful to assess the actual impact of environmental triggers of asthma in real-life settings, where exposures typically occur in mixtures and combinations.

Aspects of the study design enhance the strength of the work. The repeated-measure design exploits the inherent variability of asthma phenotypes to evaluate time-varying environmental factors. Repeated laboratory assessment of biomarkers of both asthmatic inflammation and SHS probably reduces misclassification of both exposure and outcome, and hence increases our confidence in the results.

Why should exposure to SHS attenuate airway effects of ambient PM? Does tobacco smoke simply overwhelm the effect of PM and create a situation in which our observational methods simply are not sensitive enough to observe the more subtle effect exerted by ambient particles? If the two agents are acting to impact the same biological pathway(s), is one agent actually competing with the other or is a pathway merely saturated? If the two agents impact different (even subtly different) pathways, then one agent could reduce impact of the other through a variety of regulatory mechanisms at the cellular and molecular level. Rabinovitch and colleagues explain their findings by relying on the likely nonlinearity of the concentration–response function that includes both SHS and PM. This explanation is compelling, but is not related to the underlying biological processes that are involved.

The finding of an attenuation of the effects of air particles in the presence co-exposure to SHS raises questions regarding the mechanism underlying the cellular and molecular interactions between the two risk factors (Figure 1). Both particles and SHS, in addition to several other triggers of childhood asthma, are inhaled into the airways and initiate cascades that result in local and systemic oxidative stress and inflammation. Recent evidence has helped us to understand that environmental risk factors activate specific molecular mechanisms that contribute to these processes and lead to asthma exacerbation. Changes in the DNA sequence—which are relatively rare and tend to be permanent once they escape mechanisms for DNA repair—are not directly tied in with the mechanism underlying asthma triggering and exacerbation. Conversely, the levels and timing of expression of gene products—including mRNA and proteins—are highly sensitive to environmental challenges. In addition, recent investigations have identified changes in epigenetic mechanisms, including DNA methylation (6–10) and histone modifications (11), that control gene expression. The epigenome, together with microRNAs (miRNAs) (12, 13)—an emerging class of inhibitors of gene expression—appears exquisitely sensitive to environmental exposures and may also contribute to mediate rapid changes in gene expression (14, 15), as well as in protein activities and metabolite levels, that may parallel the fluctuating phenotypes typical of patients with asthma. Each of these molecular steps is potentially subject to saturation under the pressure of multiple environmental stimuli. Further investigations are warranted to identify which of those physiological and molecular mechanisms contribute to determine the dose–effect response profiles in the presence of multiple exposures.

Rabinovitch and colleagues have provided us with an intriguing piece of work that raises new questions regarding our understanding of the environmental determinants of asthma. The impact of environmental factors cannot be simply added together to understand disease risk. Unraveling the complex interplay of these factors will lead to more complete understanding of the genesis of asthma and the best way to reduce the burden of this often preventable disease.

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References

1. Prüss-Üstün A. Preventing disease through healthy environments: towards an estimate of the environmental burden of disease. Geneva: World Health Organization; 2006.
2. Asher MI, Stewart AW, Mallol J, Montefort S, Lai CK, Ait-Khaled N, Odhiambo J. Which population level environmental factors are associated with asthma, rhinoconjunctivitis and eczema? Review of the ecological analyses of isaac phase one. *Respir Res* 2010;11:8.
3. Patel MM, Miller RL. Air pollution and childhood asthma: recent advances and future directions. *Curr Opin Pediatr* 2009;21:235–242.
4. President's Task Force on Environmental Health Risks and Safety Risks to Children. Asthma and the environment: a strategy to protect children. Washington, DC: EPA/DHHS; 2000.
5. Rabinovitch N, Silveira L, Gelfand EW, Strand M. The response of children with asthma to ambient particulate is modified by tobacco smoke exposure. *Am J Respir Crit Care Med* 2011;184:1350–1357.
6. Baccarelli A, Wright RO, Bollati V, Tarantini L, Litonjua AA, Suh HH, Zanobetti A, Sparrow D, Vokonas PS, Schwartz J. Rapid DNA methylation changes after exposure to traffic particles. *Am J Respir Crit Care Med* 2009;179:572–578.
7. Tarantini L, Bonzini M, Apostoli P, Pegoraro V, Bollati V, Marinelli B, Cantone L, Rizzo G, Hou L, Schwartz J, *et al.* Effects of particulate matter on genomic DNA methylation content and inos promoter methylation. *Environ Health Perspect* 2009;117:217–222.
8. Madrigano J, Baccarelli A, Mittleman MA, Wright RO, Sparrow D, Vokonas PS, Tarantini L, Schwartz J. Prolonged exposure to particulate pollution, genes associated with glutathione pathways, and DNA methylation in a cohort of older men. *Environ Health Perspect* 2011;119:977–982.
9. Perera F, Tang WY, Herbstman J, Tang D, Levin L, Miller R, Ho SM. Relation of DNA methylation of 5′-cpg island of acsl3 to transplacental exposure to airborne polycyclic aromatic hydrocarbons and childhood asthma. *PLoS ONE* 2009;4:e4488.
10. Nadeau K, McDonald-Hyman C, Noth EM, Pratt B, Hammond SK, Balmes J, Tager I. Ambient air pollution impairs regulatory T-cell function in asthma. *J Allergy Clin Immunol* 2010;126:845–852.
11. Cantone L, Nordio F, Hou L, Apostoli P, Bonzini M, Tarantini L, Angelici L, Bollati V, Zanobetti A, Schwartz J, *et al.* Inhalable metal-rich air particles and histone h3k4 dimethylation and h3k9 acetylation in a cross-sectional study of steel workers. *Environ Health Perspect* 2011;119:964–969.
12. Bollati V, Marinelli B, Apostoli P, Bonzini M, Nordio F, Hoxha M, Pegoraro V, Motta V, Tarantini L, Cantone L, *et al.* Exposure to metal-rich particulate matter modifies the expression of candidate micrornas in peripheral blood leukocytes. *Environ Health Perspect* 2010;118:763–768.
13. Jardim MJ, Fry RC, Jaspers I, Dailey L, Diaz-Sanchez D. Disruption of microrna expression in human airway cells by diesel exhaust particles is linked to tumorigenesis-associated pathways. *Environ Health Perspect* 2009;117:1745–1751.
14. Baccarelli A, Bollati V. Epigenetics and environmental chemicals. *Curr Opin Pediatr* 2009;21:243–251.
15. Bollati V, Baccarelli A. Environmental epigenetics. *Heredity* 2010;105:105–112.

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Aging, Inflammation, and Emphysema

An enhanced or abnormal inflammatory response to the lungs to inhaled particles and gases, usually from cigarette smoke, is considered to be a general pathogenic mechanism in chronic obstructive pulmonary disease (COPD) (1). However, the mechanisms involved in the perpetuation of the inflammatory response in the lungs in patients who develop COPD, even after smoking cessation, are not fully established, and are key to our understanding of the pathogenic mechanisms in COPD and should be important for the development of new therapies for this condition.

There are a plethora of proposed mechanisms to account for the change from the "normal" inflammatory response in the lungs to cigarette smoke, which occurs in all smokers (2) to the enhanced or abnormal innate and adaptive immune responses in the lungs that characterize the development of COPD (3). A recent hypothesis derives from the association between chronic inflammatory diseases and an enhancement of the processes involved in aging as a novel mechanism in the pathogenesis of COPD (4). There is now good evidence linking mechanisms of enhanced or accelerated aging and COPD, particularly related to the pathogenesis of emphysema (5), which has been associated with markers of accelerated ageing in the lungs.

Telomere length provides a marker of biological age, at least at the cellular level, shorter telomeres indicating increased biological age. Oxidative stress and chronic inflammation enhance telomere shortening (6), as does exposure of lung cells to cigarette smoke (7), and there is a dose-dependent relationship between leukocyte telomere length and years smoked (8). Alveolar epithelial and pulmonary endothelial cells (9) and fibroblasts (10) from the lungs of patients with emphysema exhibit shorter telomeres, compared with those from subjects without emphysema. Recent data also indicate that telomeres in circulating leukocytes from patients with COPD are shorter, compared with control subjects in any age range (11, 12).

When telomeres reach a critical length, cell senescence is induced (13). Cell cycle progression is controlled via cyclin-dependent kinases (CDK) and their inhibitors such as $p16^{INK4a}$ and $p21^{Cip1/Waf1}$ (14). Thus, $p21^{Cip1/Waf1}$ can initiate senescence that is primarily telomere dependent, which is then maintained by $p16^{INK4a}$. Mice exposed to cigarette smoke *in vivo* and exposure of human cells *in vitro* increases the expression of $p21^{Cip1/Waf1}$ (15). Furthermore, endothelial cells and alveolar Type II cells in lungs of patients with emphysema have an increased expression of $p16^{INK4a}$ and $p21^{Cip1/Waf1}$ as markers of increased cellular senescence (9, 15).

Anti-aging molecules may influence the aging process and may have relevance in the pathogenesis of COPD. Metabolic nitocinamide adenine a nucleotide (NAD^+)-dependent histone/protein deacetylases (*sirtuins*) play an important role in a variety of processes, including stress resistance, metabolism, apoptosis, senescence, differentiation, and aging. Sirtuin I (SIRT-1) is essential for maintaining silent chromatin via the deacetylation of histones, but also regulates NF-κB–dependent transcription and cell survival in response to TNF-α. Environmental stress, such as cigarette smoke exposure, decreases SIRT-1 levels in both macrophages *in vitro* and rat lungs *in vivo*, associated with increased inflammatory cytokine expression (16). SIRT-1 has recently been shown to be reduced in lung cells from patients with COPD as a result of post-translational oxidative modification by cigarette smoke–derived components, leading to increased acetylation and enhanced inflammatory responses to cigarette smoke (17). Thus, SIRT-1 may have an important role in the regulation of inflammation in the lungs, as well as being involved in aging and in the pathogenic mechanisms in COPD.