airways with higher BMI, and the amount of airway fat correlates with wall thickness and the number of inflammatory cells (13). Airway adipose tissue accumulation by itself may therefore partly explain some of the changes seen in asthma, including airway narrowing and remodeling. Future studies should examine whether excess visceral and/or pericardial fat in children denotes a phenotype of obesity that tends to accumulate adipose tissue in certain organs, including the airways. We must also learn whether certain adiposity distribution profiles have a more immediate proinflammatory effect on the lungs.

The BMI will certainly continue to play an important role in epidemiological studies of obesity (and consequently of obese asthma). But in the era of big data, detailed phenotyping, multiomics, gene editing, and machine-learning, we owe it to our patients to shift our focus to a more nuanced approach—one that better characterizes "obesity" and studies the specific profiles and characteristics of adipose tissue that lead to obese asthma. ∎

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🔓 Use of Modeling to Inform Tuberculosis Elimination Strategies

Although the United States reported its lowest number of tuberculosis (TB) diagnoses in 2018 (2.8 cases per 100,000 persons), the decline in TB incidence has slowed in recent years (1) and the current pace of this decline is too slow to reach the national goal of TB elimination (defined as an annual incidence of less than one case per 1 million population [2]) within this century.

In a study presented in this issue of the *Journal*, Menzies and colleagues (pp. 356–365) compared three epidemiologic models to analyze the potential impact of different interventions in California, where 82.6% of individuals with TB in 2018 were born outside of the United States (3). Although the authors credit the successful implementation of TB control principles (e.g., early detection of active TB disease and prompt initiation and completion of appropriate therapy) for reducing TB incidence to historic lows in the United States, all three models show that in the absence of additional interventions, these activities alone will not be enough to significantly reduce TB incidence in the United States in the coming decades.

The authors provide a thoughtful and nuanced discussion about the role and utility of modeling, and their use of multiple modeling methodologies in this study helps to strengthen the impact of results that are concordant across the models. However, the authors also note the inherent limitations of these models in the absence of more robust data. Such an approach can also help individuals involved in TB control programs and policy makers better understand the implications and potential applications of these findings within their own local context.

Across the models used in this analysis, recent transmission accounted for a small proportion of overall TB morbidity in California, and a scenario involving halting of future TB transmission led to a predicted reduction between 8.1% and 25.5% in new TB cases. For jurisdictions where TB incidence rates are elevated and TB outbreaks still occur (e.g., New York and Seattle), efforts to identify and interrupt TB transmission through contact investigations, outbreak detection and response, and community-based interventions that address barriers to diagnosis and preventive treatment remain a priority (4). However, as these models and others demonstrate, addressing domestic TB transmission alone will not negate the need for other strategies, and additional actions to address the community burden of latent TB infection (LTBI) are required to accelerate the pace of TB decline.

The halting of future importation of *Mycobacterium tuberculosis* had the highest predicted impact across models in this analysis, highlighting the importance of strengthening international TB screening and prevention programs. Activities to address TB among individuals who will become long-term residents in the United States are an important component of the national TB control strategy and are currently coordinated and organized through the CDC's Division of Global Migration and Quarantine. Expansion of overseas LTBI testing and possibly initiation of treatment for LTBI in selected groups should be considered (5). In addition, resources must also be allocated for follow-up care in destination jurisdictions to ensure that these individuals are linked to healthcare services after their arrival (6).

In the United States overall, non–U.S.-born persons accounted for 70% of TB cases in 2018, and it is estimated that up to 13 million live with LTBI (7). Comprehensive case management of persons with TB disease and their close contacts has been used effectively by domestic TB programs since the 1990s and must be continued, but it is also vital to engage non–U.S.-born communities in intensified yet culturally mindful TB prevention. The authors suggest that even short-term interventions targeting the reservoir of LTBI among non–U.S.-born persons will generate ongoing benefits in terms of reductions in TB cases and deaths. Similarly, a recent model to evaluate TB epidemiology in New York City showed that additional interventions among non–U.S.-born populations would have the greatest projected impact on furthering the decline of TB (8). With this understanding, an emphasis on enhanced testing and treatment for LTBI is now a core component of national, state, and local TB elimination strategies (9). Dedicated resources are required for this plan because it will include expanded surveillance, collaboration with local healthcare providers, and outreach to and engagement with affected communities. Individuals involved in public health programs can and must be data-driven and use their expertise to identify high-risk communities, understand how frequently testing and treatment for LTBI should occur, provide various types of additional robust information to enhance modeling and other practical analyses, engage healthcare providers, and advocate for innovation and a sustained political commitment to eliminate TB.

Because the models used by Menzies and colleagues are based on parameters of TB epidemiology in California, the implementation and impact of the intervention scenarios will be different in other parts of the United States. Strategies to reduce TB transmission, stem the importation of *M. tuberculosis*, and expand LTBI testing and treatment in high-risk communities must be adapted to reflect local resources and sociopolitical contexts. Understanding the dynamics of TB epidemiology is critical for tailoring decisions and prioritizing interventions at a local program level.

All of the scenarios in these models assume the presence of a political commitment to sustain funding for the current policies and practices of domestic TB control programs. Although the recent decline in TB incidence is remarkable, it is challenging for many local health departments to maintain their current priority activities, such as case management and contact investigations. We must support these core TB control activities, which are essential to cure patients with TB and protect the public. Furthermore, it is crucial to invest in research and superior diagnostics that can accurately predict who will progress to active TB disease (10), to identify shorter and better-tolerated LTBI regimens, and to use implementation science to improve the effectiveness of care. It will take a substantial commitment to accelerate the pace of TB elimination, and this commitment must be sustained if we are to reach our audacious goal in this century. ■

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Another Piece in the Estrogen Puzzle of Pulmonary Hypertension

Pulmonary arterial hypertension (PAH) affects predominantly women, yet women with PAH have better survival than men with PAH. Women have a more robust response to endothelin receptor antagonism, and treatment-associated improvements in right ventricular (RV) function account for survival differences between men and women with PAH (1, 2). Although female sex has been linked to the development of PAH, response to therapy, and better RV function, the role of estrogen in PAH is not completely understood (a comprehensive review of animal and human studies in this area is discussed by Hester and colleagues [3]). Higher levels of circulating 17β-estradiol (E2), the most potent estrogen, are associated with increased risk for PAH and more severe disease in both men and postmenopausal women (4–6), and variations in E2 metabolism influence the penetrance of heritable PAH (7). Although these human observations consistently demonstrate sexual dimorphism in PAH and suggest a critical role for E2 in pulmonary vascular disease, they have generated more questions than answers about the effect of E2 across the cardiopulmonary interface.

Experimental models of pulmonary hypertension (PH) have provided fundamental mechanistic insight; however, as in humans, these studies fall short in crossing the translational divide, and the estrogen puzzle of pulmonary vascular disease remains unsolved. In contrast to humans, female sex in hypoxia-induced and monocrotaline-induced PH (MCT-PH) models is protective. Endogenous and exogenous E2 has been shown to prevent, mitigate, and reverse PH in these models (8, 9). In MCT-PH, E2 is associated with increased nitric oxide and prostacyclin levels and decreased macrophage infiltration (10). In contrast, transgenic and Sugen-hypoxia (SuHx) models of PH demonstrate a female bias similar to humans, and as in humans, SuHx females have better RV function and improved survival compared with males (11–14). In the SuHx model, E2 promotes a proinflammatory and proangiogenic response but inhibits RV fibrosis, decreases collagen deposition in the myocardium, and increases proximal pulmonary artery (PA) compliance (12, 13).

These studies demonstrate that E2 may have differential effects on the pulmonary vasculature as compared with the RV, but the effects of E2 on RV afterload and on the mechanics of the pulmonary vasculature have not been studied.

In this issue of the Journal, Philip and colleagues (pp. 371–374) describe the effect of endogenous and exogenous E2 on the prevention of SuHx PH (15). Pulmonary vascular mechanics were compared in female rats with intact cyclical endogenous E2 and ovariectomized rats with and without exogenous E2 supplementation. Rats that received continuous exogenous E2 were protected from PH with similar levels of RV systolic pressure and intermediate and distal PA impedance compared with the intact and ovariectomized rats. Exogenous E2 prevented an increase in the transpulmonary gradient, preserved distal PA distensibility, and was associated with a 60% reduction in PA wall remodeling. Treatment with a rho kinase inhibitor in the absence of continuous exogenous E2 demonstrated that SuHx-induced increases in RV afterload were driven by vasoconstriction.

This carefully executed study not only adds new knowledge in its use of pulsatile pulmonary vascular mechanics as surrogates of RV afterload but also provides critical insight into the protective role of E2 on impedance, distensibility, and remodeling in the distal PA. The distinction between biologic endogenous E2 exposure in intact animals versus exogenous E2 treatment in ovariectomized animals is an important one, as is isolating vasoconstriction. The findings of this study mirror limited observational data in humans that exogenous hormone therapy may prevent PH in postmenopausal women with systemic sclerosis (16). Similarly, higher levels of E2 in hormone therapy users have been associated with better RV function in postmenopausal women without clinical cardiovascular disease (17).

What pieces remain to solve the estrogen puzzle in PAH? Results from the preventative strategy used here will need to be replicated in rescue experiments and compared in male animals and ideally in young and aged animals. Downstream genomic effects of E2 on biomechanics and cardiopulmonary function may also differ from nongenomic vasodilatory effects. Numerous human and experimental observations implicate female sex and E2 (as well as other sex hormones, their metabolism, receptor signaling, and sex chromosomes) in the pathogenesis of PAH. This study is a strong contribution to accumulating evidence of a pleiotropic role of E2 on tissues, which may explain the observed contradictions in animal