



What Will Uncontrolled Asthma Cost in the United States?

Asthma is characterized by variable levels of chronic airway inflammation and episodes of cough, wheeze, chest tightness, and difficulty breathing. The public health impact of asthma in the United States is substantial. In 2017, there were more than 25 million people in the United States with asthma, including more than 6 million children (1). Although many individuals are symptom-free and able to control their asthma by appropriately using prescribed medications and avoiding asthma triggers, millions have inadequate asthma control.

In 2010, on average, 38% of children and 50% of adults with asthma had uncontrolled asthma symptoms (2). Uncontrolled asthma reduces the quality of life of people with asthma and those who care for them, results in missed school or work, and increases the risk and severity of asthma exacerbation. In 2017, more than 11 million people reported having at least one asthma exacerbation in the last 12 months, and there were 1.8 million emergency department visits, nearly 200,000 hospitalizations, and about 3,500 deaths (2).

In this context, the study entitled “The Projected Economic and Health Burden of Uncontrolled Asthma in the United States,” published in this issue of the *Journal* by Yaghoubi and colleagues (pp. 1102–1112), provides important new information (3). The authors examined national and state-level projections of the economic burden (healthcare costs = direct costs and the cost of missed work = indirect cost or productivity loss) and health burden (quality-adjusted life-years) as a result of uncontrolled asthma from 2019 to 2038 in adults and adolescents aged ≥ 15 years in the United States. The authors used the Asthma Control Test (ACT) to separate people with asthma into two groups: those who have controlled and those who have uncontrolled asthma.

The methods used in the paper by Yaghoubi and colleagues set up a new approach in estimating the burden of asthma by separating the part of the total burden that can be reduced through cost-effective asthma management strategies. Unsurprisingly, people with uncontrolled asthma usually have more emergency department visits, more hospitalizations, more missed school or work days, and generally lower quality of life. Moreover, the average cost of asthma for patients with uncontrolled asthma is significantly higher than for patients with controlled asthma (4).

Previous studies on the cost of asthma primarily focused on estimating the added cost of having asthma of any level of control over having no asthma (5–8). Although such information presents a more complete estimate of the economic burden of asthma,

preventing or curing asthma is not currently possible. Because asthma management programs’ goal is to bring asthma symptoms under control, a counterfactual should be asthma that is controlled. Another important feature of the paper is an estimation of the projected added cost of uncontrolled asthma for the next 20 years based on several dedicated sources of data (3). The projection of the cost of uncontrolled asthma provides important information for policy makers and asthma management programs that should help develop and implement long-term asthma control strategies for the population with uncontrolled asthma.

Yaghoubi and colleagues estimate that the direct costs of asthma in adolescents and adults in the United States during the next 20 years is likely to be over \$1.5 trillion. During this 20-year-period, the authors also estimate that there will be 175 million person-years with uncontrolled asthma. If all those people with uncontrolled asthma in the United States can achieve and maintain asthma control, the authors estimate saving about \$300 billion in direct costs and \$660 billion in indirect costs, and recovering 15,462 quality-adjusted life-years (3).

Several limitations should be considered when interpreting the study results. Most notably, the authors acknowledge that their projections assume neither change in the prevalence of asthma nor in widespread implementation of effective asthma strategies that reduce the proportion of people with uncontrolled symptoms. In other words, the analyses ignore the possibility for potential changes in ambient and indoor environment linked to lung disease and the adoption and expansion of novel therapies and nonclinical asthma interventions that over the next two decades may significantly affect large populations with uncontrolled asthma. Also, the analyses do not include information about children with asthma who are younger than 15 years old or the consequences on those who care for them, such as poor sleep or days of lost work. It is therefore possible that the authors have overestimated or underestimated the costs of uncontrolled asthma. A potential next step could be to estimate the excess healthcare utilization, costs, and quality-adjusted life-years of individuals across different levels of asthma control (e.g., well-controlled asthma [ACT scores, 20–25] vs. not well-controlled asthma [ACT scores, 16–19], or well-controlled asthma vs. poorly controlled asthma [ACT scores, 5–15]). Such information would help to quantify savings according to changes in the proportion of people whose asthma is improved from poorly controlled asthma to not well-controlled asthma or to well-controlled asthma. The authors’ approach to estimating excess costs is based on the information from previous literature. Another potentially promising approach could be the use of econometric methods for estimating incremental cost of having uncontrolled asthma, similar to the methods used in the studies on the cost of asthma (5–8).

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Notwithstanding these considerations, the answer to the question “What will uncontrolled asthma cost in the United States?” by Yaghoubi and colleagues is clear: Too much. ■

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Endothelial Cell Death in Emphysema: More Sugarcoating Needed?

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide (1). The main risk factor for COPD in developed countries is smoking cigarettes. Inhaling cigarette smoke (CS) leads to different pulmonary pathologies, including emphysema, which contributes significantly to the poorly reversible airflow obstruction that is characteristic of COPD (2). The proteinase/antiproteinase hypothesis for emphysema development was formulated in the 1960s and postulates that CS increases the lung burden of proteinases to exceed the lung antiproteinase defense (2). However, in 2000, the “vascular hypothesis” emerged based on studies showing that 1) pharmacologic inhibition of VEGF (vascular endothelial growth factor) signaling via its receptors on endothelial cells (ECs), which is a crucial prosurvival pathway in these cells, leads rapidly to emphysema development in rats (3); and 2) pulmonary EC death occurs in COPD lungs associated with reduced lung levels of VEGF and its receptors (3). The vascular hypothesis proposes that components of CS that are absorbed into the circulation trigger apoptosis of pulmonary ECs (a key component of the alveolar septae), causing destruction of the alveolar walls (3).

Increased intracellular levels of ceramide (a second-messenger glycolipid molecule) were later linked to alveolar septal cell apoptosis

in animal models of emphysema and human emphysematous lungs (4). Ceramide sits at a central hub that determines cell death or survival. Proapoptotic ceramide is enzymatically synthesized from serine and palmitoyl-CoA (coenzyme A) or is generated by enzymatic cleavage of sphingomyelin (a cell membrane component) or other pathways (Figure 1A). Cell survival is promoted when intracellular ceramide levels are reduced by the conversion of ceramide to sphingosine-1-phosphate or metabolites of ceramide that have been glycosylated (glycosphingolipids [GSLs], including glucosylceramide [GlcCer]) by the actions of GCS (glucosylceramide synthase) (5, 6) (Figure 1A). The GCS–GlcCer pathway has not been robustly evaluated in the pathogenesis of emphysema, but it has the potential to contribute, as *Gcs*^{−/−} mice die before birth from massive apoptosis (7), and GlcCer mediates the prosurvival effects of VEGF on ECs partly by inhibiting autophagy-mediated cell death (8).

Autophagy is a normal homeostatic process by which organelles, proteins, and other cellular components (cargo) are recycled in several steps (autophagic flux; Figure 1B). Autophagosomes are assembled from invaginations of cellular membranes into which cargo is loaded from the cytosol. Loaded autophagosomes fuse with lysosomes, leading to acidification of the resulting autolysosomes and this permits degradation of the cargo by acidic proteinases such as cathepsin B (9). mTOR (mammalian target of rapamycin) is a negative regulator of autophagy (9), whereas endoplasmic reticulum (ER) stress promotes autophagy by inhibiting mTOR activation. However, when autophagic flux is excessive or impaired, this results in autophagic cell death (10). CS exposure triggers autophagy in various cells, and excessive autophagy-mediated cell death is linked to emphysema development (11).

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