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Early Studies of Respiratory Disease Associations with Nicotine and Tobacco Use

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Decades of robust research have established that combustible tobacco product use has both short- and long-term harmful effects on lung health.[1] However, the potential harmful effect of newer noncombustible nicotine and tobacco products, either alone or in combination with combustible products, is not yet well understood. Recent and rapidly arising critical health events, such as e-cigarette or vaping product use-associated lung injury (EVALI) and the SARS-CoV-2 pandemic, highlight the importance of examining how tobacco and nicotine products may influence and interact with respiratory health. Understanding the short- and long-term health effects of tobacco and nicotine products is particularly relevant to the U.S. Food and Drug Administration (FDA), which has broad authority to regulate tobacco and nicotine product manufacturing, distribution, and marketing.[2] This Special Issue on respiratory disease associations with cigarettes and noncigarette nicotine and tobacco use includes a collection of multidisciplinary studies that begin to examine the effect of tobacco and nicotine use from the cellular level to patterns of use and symptomology at the population level.

Preclinical Toxicity Studies of Electronic Nicotine Delivery Systems and Constituents

Many e-liquids have been released commercially without extensive premarket toxicological testing. Moreover, many members of the general public perceive e-cigarettes as being safe because the majority of e-liquid constituents (with the exception of nicotine, which is generally considered to be highly addictive and toxic) have appeared on the Generally Regarded as Safe (GRAS) list, an FDA designation for food additives used for oral consumption. However, this fails to take into account several issues: (1) although e-liquid constituents are on the Generally Regarded as Safe list as individual constituents, possible polytoxicity is unaccounted for, and there may be interactions and synergy between compounds; (2) many Generally Regarded as Safe compounds were tested following oral consumption, often in rodents. E-liquids are typically inhaled, and the route of ingestion may alter toxicity; (3) the pharmacokinetics and pharmacodynamics of many of these compounds are poorly understood after vaping, and the concentrations that they reach in the lungs is unknown, which has obvious implications for toxicity; (4) these compounds may be chemically altered during the heating/vaping process which could also alter their toxicity and/or generate new chemical entities which are toxic.

In this issue, researchers have addressed preclinical toxicity. One of the problems is that given the large number of e-liquids that are commercially available, where should researchers start? Correia-Alvarez and colleagues[3] have performed high throughput screening on ~100 e-liquids and found that vanillin, benzyl alcohol, acetoin, cinnamaldehyde, and methylcyclopentenolone were associated with increased cellular toxicity, suggesting that these flavors constituents should be targeted for further, more detailed study. Similarly, Williams and colleagues[4] found that cytotoxic metals were found in a number of e-cigarette vapers. Importantly, these metals were present in both the e-liquids and came from the atomizers, suggesting that e-liquid toxicity can change during vaping. Similarly, Jabba and colleagues[5] found that reactive aldehydes, which are highly toxic and can form adducts with proteins and other biomolecules, were formed after vaping and that the toxicology was significantly different from the unvaped e-liquid. An advantage of in vitro studies is the higher throughput and the ability to focus on specific cellular pathways, often in real time. However, the lung is a multicellular organ, and cross-talk between cell types can occur. In this series, Ni and colleagues[6] found that e-cigarette vapor induced upper airway irritation in mice via activation of nociceptive chemosensory systems, which reminds us of the importance of studying integrative systems.

Respiratory Symptoms Associated With Electronic Nicotine Delivery Systems Use

The set of articles addressing respiratory symptoms associated with electronic nicotine delivery systems (ENDS) use present an

array of methodologies, including laboratory-based assessments of vaping; qualitative and mixed method approaches to understanding symptom reports; and large population-based surveys that include both self-reports of symptoms and biomarkers of tobacco-related toxicants. Most rely on self-report measures of symptoms, which may have their own set of limitations and biases. Yet symptom self-reports are still valuable, given that they are often more strongly associated with health-related quality of life than are measures of lung function.[7] The study by Soule and colleagues[8] used a combination of methodologies, including qualitative data and multidimensional scaling with concept mapping to identify clusters of symptoms that participants believe are related to e-cigarette use. Although many of the symptoms overlapped between e-cigarette and dual users of both e-cigarettes and combustible cigarettes, understanding more about whether users distinguish unique symptoms associated with vaping may help to inform motivational messages and future interventions.

Cassidy and colleagues[9] used observational measures of vaping topography to examine whether different vaping topography variables were associated with the severity of respiratory symptoms. The authors found that none of the specific topography variables predicted symptom severity, and neither was e-cigarette dependence associated with symptom severity. By far, combustible cigarette smoking was the primary driver of higher levels of respiratory symptoms. Their study points to the potential continued harms of dual use on respiratory symptoms if smokers continue to use combustible cigarettes.

Dai and Khan[10] examined the association between baseline urinary biomarkers of exposure to tobacco-related toxicants and subsequent self-reports of respiratory symptoms, using data from 2014–2015 (Wave 2) of the Population Assessment of Tobacco and Health (PATH) Study. Several of the baseline biomarkers were prospectively associated with subsequent respiratory symptoms. Although both exclusive e-cigarette and polytobacco e-cigarette users had a higher prevalence of subsequent respiratory symptoms than did the nontobacco users, the polytobacco e-cigarette users had substantially higher concentrations of the clinically relevant biomarkers than did the exclusive e-cigarette users. As with the other studies in this series, it was challenging to isolate e-cigarette users who had no prior combustible cigarette history, and thus, some elevated symptoms and biomarkers may be residually related to prior combustible use. But the magnitude of the difference between the biomarkers of current exclusive e-cigarette and polytobacco e-cigarette users further highlights the continued harms of combustible tobacco use.

E-cigarette users frequently use multiple products that may exacerbate or add on to any respiratory symptoms that result from e-cigarettes alone. Polysubstance use may include not only other combustible tobacco products, but increasingly, marijuana products, which may be either concurrently vaped or smoked. Xie and Li[11] used 2016–2018 (Wave 4) PATH Study data to examine the cross-sectional association of e-cigarette use, with or without marijuana, and self-reported respiratory symptoms among adults. They found that adults who vaped with marijuana had an increased association with some respiratory symptoms. Although these findings are suggestive of increased respiratory symptoms from the couse of marijuana and nicotine vaping, there is a strong need to further examine these associations with measures that are better able to distinguish between forms of marijuana use and patterns of co-use with e-cigarettes (eg, in the same device, or using different devices/products, or during the same event).

Wheezing Symptoms and Patterns of Tobacco Use in the United States

A subset of studies using national population-based survey items explored associations among the use of different tobacco products and self-reported wheezing symptoms. Cross-sectional analyses conducted by Schneller and colleagues[12] found cigarette smoking and polytobacco use had strong associations with ever and past 12-month wheezing among US adults in 2015–2016 (Wave 3) of the PATH Study. Although ENDS use did show some associations with wheezing in adjusted models, when models were stratified by past cigarette smoking the association between ENDS and wheezing appeared to be attributable to previous cigarette smoking. ENDS users who were former smokers had significantly higher odds of reporting ever wheezing in the past, as well as in the past 12 months, when compared with noncurrent users who never smoked cigarettes. The authors also noted that there were few current users of cigars and ENDS who had never used cigarettes. These findings reinforce the need for fully powered longitudinal studies that can tease apart the unique health effects of individual tobacco product use and how they intersect with the long-lasting deleterious health outcomes of past and current cigarette smoking.

Li and colleagues[13] observed a dose–response pattern in frequency of vaping occurrences with wheezing and whistling in the chest among US adults in 2016–2018 (Wave 4) PATH Study data. The authors acknowledged that a large proportion of vapers were dual users of electronic nicotine products and cigarettes, and therefore, it was difficult to tease out the potential impact of cigarettes and other confounding variables.

Although longitudinal data are accumulating, these initial exploratory studies help inform hypotheses to test and highlight the importance of clear definitions of use and consideration of sample selection so that results can be interpreted in context, as well as compared across studies. These preliminary studies on wheezing also demonstrate the importance of accounting for previous cigarette use and looking specifically at the frequency of use as a necessary step toward unraveling the health effects of multiple tobacco product use.

Commentaries on Respiratory Health Events

Recent national and global events with EVALI and the SARS-CoV-2 pandemic have propelled the public health community to act swiftly and push forward with testing hypotheses to understand the role of tobacco use in respiratory diseases. Samet[14] contributed a timely commentary summarizing what is known to date regarding the potential role tobacco and nicotine use may have on increasing risk of infection and poor outcomes from COVID-19, as well as the hypothesis that nicotine may reduce the likelihood of SARS-CoV-2 infection. The piece emphasizes a need for timely evidence, but more importantly, high-quality rigorous investigations that test hypotheses.

Illustrating the significant impact of rigorous coordinated data collection and hypothesis testing during a respiratory disease outbreak, King and colleagues[15] from the Centers for Disease Control describe the evidence-based approach used to identify the primary cause of EVALI and the actions taken to curb the outbreak. Hypotheses that need further testing are described that may inform efforts to prevent future EVALI cases and better understand the long-term impact of EVALI at the individual and population levels.

Both the EVALI outbreak and the COVID-19 pandemic have focused the public health, and specifically, the tobacco regulatory science community more acutely on the importance of understanding environmental insults to our lung health and the need for rigorous and rapid research to inform policy and practice decisions in a timely manner. These events also point to the need to better understand mechanisms of action and agents of disease and injury that could be targets of preventive, precautionary actions. Prospective longitudinal studies are clearly needed to disentangle directions of effects and longer-term consequences. These recent events present compelling reasons to push for greater cross-site collaboration and data harmonization to ensure better-powered studies and attaining more generalizable and robust conclusions in shorter time frames that could drive relevant policy and practice actions.

Summary

This collection of multidisciplinary studies on tobacco/e-cigarette use and respiratory disease provides insight to inform new hypotheses in an emerging field. It will likely take decades to accumulate robust evidence to fully understand the impact of e-cigarette use and other nicotine product use on lung health. These early studies are foundational and will set the stage for additional larger studies and provide direction for study designs. Clearly, there is a need for better measurement and isolation of agents and effects (eg, separating dual vs single users). Accumulating evidence will help guide health practice and communication and provide foundational evidence to inform policies such as potential bans on specific flavors and constituents in tobacco and nicotine products. Preliminary results from these studies signal associations with e-cigarette use respiratory outcomes that need further study. The preclinical/toxicology studies, in which e-cigarette vapor effects could be more effectively isolated than in the human studies, provide a compelling case for further investigations in humans that can better untangle the effects of vaping from combustible use. A salient theme throughout the studies in this collection, however, is that toxicity and respiratory symptoms associated with cigarette smoking continue to be clear and profound. Practice and policies to reduce combustible smoking remain an unequivocal priority that is essential to promoting lung health and reducing tobacco-related death and disease.

Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at https://academic.oup.com/ntr.

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Declaration of Interests

None declared.

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