S.C.'s research was supported by the National Cancer Institute of the National Institutes of Health (NIH) and FDA Center for Tobacco Products (CTP) under Award Number 2U54CA229974. G.C. is a salaried employee of Rose Research Center (RRC). This study was not funded by nor commissioned by any other entities. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the Food and Drug Administration.

	Tobacco Industry	E-cigarette and Nicotine Product Industry	Pharma Industry
The work being presented has received funding or other means of support from any of the following sources:	NO	NO	NO
Any of the authors have received funding (including consultancy) from any of the following sources in the past 5 years:	YES	YES	YES

Observational studies of exposure to tobacco and nicotine products: Best practices for maximizing statistical precision and accuracy

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SRNT 2025

Summary

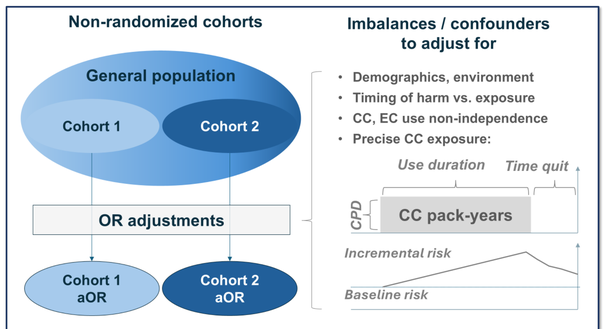
Significance: Observational studies of exposure can provide unique insights into the health impact of real-world product use. However, these non-randomized studies involve exposure to multiple tobacco products, utilize heterogeneous cohorts and are subject to confounding which can limit precision and accuracy.

Methods: The ROBINS framework for minimizing statistical bias was used to identify tobacco-product specific factors impacting precision and accuracy of tobacco and nicotine products. These considerations were then applied to a cohort of 107 studies identified in a recent meta-analysis (Glantz et al., 2024), with a specific focus on those studies pertaining to cardiovascular disease (CVD) and stroke risk.

Results: The ROBINS framework-informed factors spanned cohort selection, comprehensive exposure characterization, and outcome metric specification. Regarding outcome metrics, the referenced meta-analysis had reported the odds ratios (OR) associated with electronic cigarette use (EC use) vs. combusted cigarette (CC) use. This ratio (OR EC / OR CC) measures risk from all sources, including background non tobacco-use demographic and environmental risks, along with incremental risk associated with tobacco use. We now report the tobacco product-specific risk reduction associated with EC use vs. CC use, using the more precise outcome metric 1 - [(OR EC – 1.0) / (OR CC – 1.0)]. This incremental risk reduction, reflecting the aORs reported in the primary references, was 63% for CVD*, 70% for stroke, and 77%, 57%, 32%, and 7% for COPD, asthma, oral disease, and metabolic disease, respectively. Regarding exposure characterization, of the 15 unique references cited for CVD and stroke, 5 did not adjust for imbalances in pack-years of smoking CC in the EC group, and 10 counted outcome harm events which occurred before the EC exposure, which may have impacted precision and accuracy of results. Furthermore, 2 studies utilized a case-control cohort design (requiring independence of EC and CC use), and subsequently reported that CC had no risk (*CVD risk reduction was 85% with these two studies excluded).

Conclusions: These results are consistent with EC having both risk-reducing and risk-inducing effects They also highlight the prevalence of imprecision of exposure and risk characterization in observational studies. These results suggest opportunities for future studies to more precisely and accurately measure the health effects of alternative tobacco products.

Disclosures: S.C. has no disclosures to declare. G.C. is an employee of Rose Research Center (RRC). RRC is an independent contract research organization that performs studies pertaining to smoking cessation and tobacco harm reduction, whose founder invented the nicotine patch and did the early research leading to varenicline. Other research support: National Institute on Drug Abuse; Global Action to End Smoking, Inc. (formerly Foundation for a Smoke-Free World, Inc.), a US nonprofit 501(c)(3) private foundation; Nicotine BRST LLC; JUUL Labs; Altria; Embera Neurotherapeutics, Inc.; Otsuka Pharmaceutical; Swedish Match, Philip Morris International. G.C. was previously a Principal Scientist at JUUL Labs. He also was employed at Nektar Therapeutics, whose pipeline included an inhaled NRT. Stock holdings in Qnovia, a developer of an inhaled NRT, and JUUL Labs. Beyond RRC, none of these companies funded nor commissioned this study.



EC cohort	Most precise and accurate comparator*	Inaccurate comparator*
EC Use, CC Never-Use	Never tobacco-users ✓ Balanced: 1-99 CC uses	
CC → EC Switchers	Former CC, never EC ✓ Balanced: CC pack-years ✓ Balanced: CC time quit	Never-tobacco
EC + CC Dual-Use	Current CC, never EC ✓ Balanced: CC pack-years	Never-tobacco

*Most precise comparator for isolating impact of EC use

Graphical Abstract

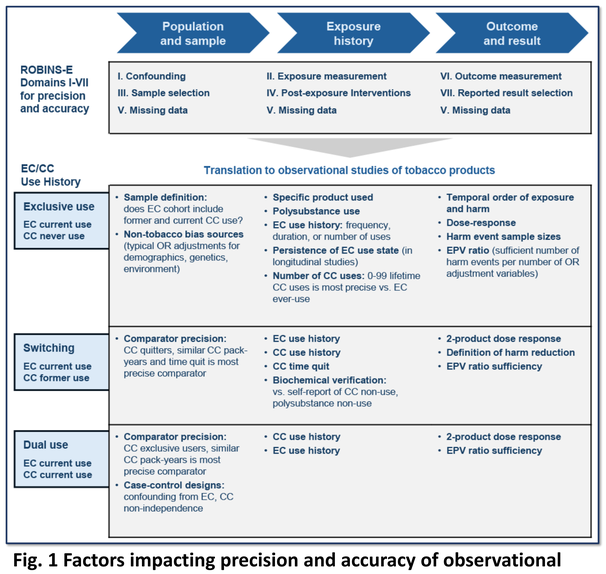


Fig. 1 Factors impacting precision and accuracy of observational studies of exposure to EC

Peer-reviewed paper now available
Cohen, G., and Cook, S. (2025).
iScience, 28 (3), 111985
doi.org/10.1016/j.isci.2025.111985

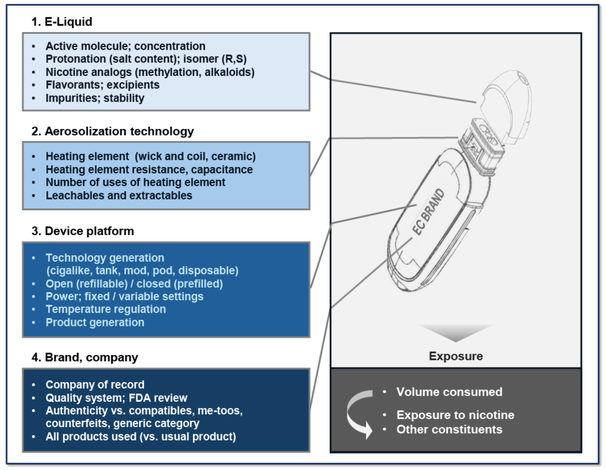


Fig.2 EC product characteristics impacting exposure

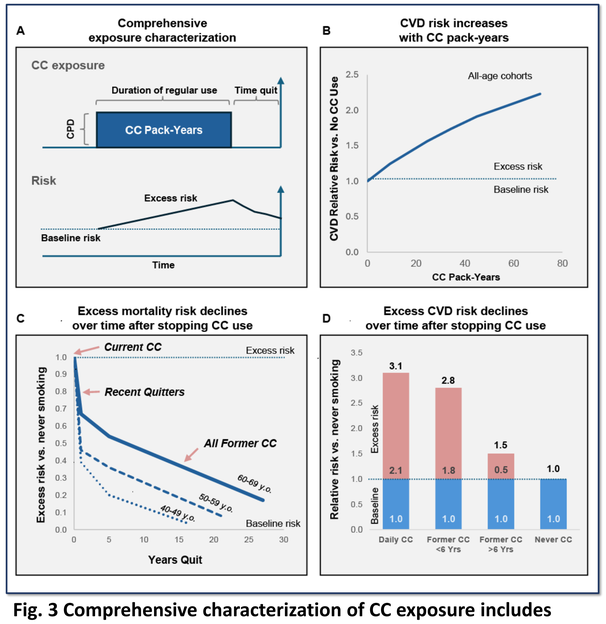


Fig. 3 Comprehensive characterization of CC exposure includes intensity, duration and timing of use

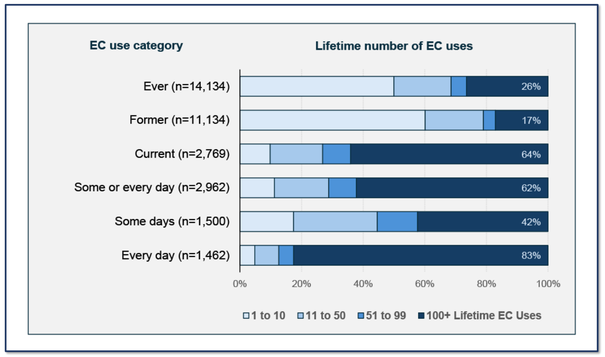


Fig.4 Lifetime number of EC uses, stratified by EC use category (PATH, Wave 6)

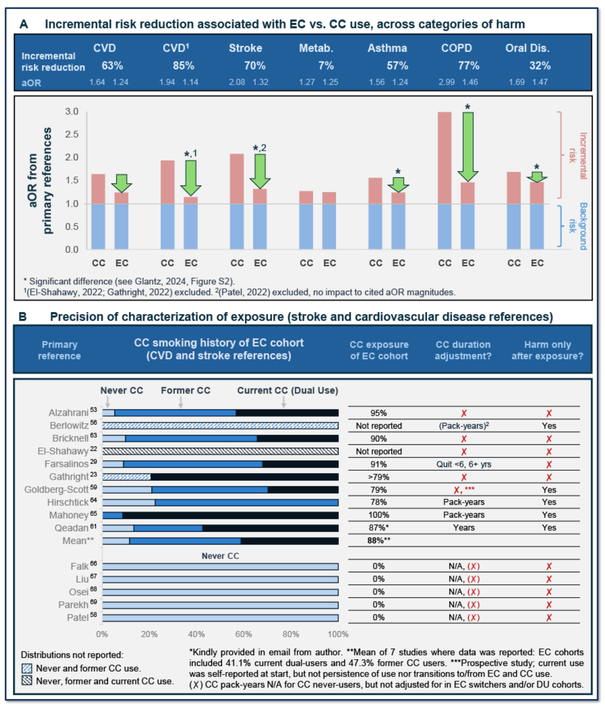


Fig.5 Characterization of risk associated with EC use (case study)

Highlights

- **Confounding often limits precision and accuracy of e-cigarette observational studies**
- **Precise characterization of exposure includes duration, intensity, and recency of use**
- **Comparisons of e-cigarette use vs. non-use should precisely balance cigarette exposure**
- **Non-independence of e-cigarette and cigarette use can invalidate case-control analyses**