



Does Electronic Cigarette Use Increase The Risk of Early-Onset Chronic Obstructive Pulmonary Disease (COPD) ? : A Systematic Review

¹ Annisa Usraina Mulkiya, ² Widiya Hari Kurnia

¹ Tembilahan Public Health Center, Indragiri Hilir, Indonesia

² Cahaya Medika General Hospital, Bondowoso, Indonesia

Corresponding Email : Annisausrainamulkiya27@gmail.com

Article History :

Received date : 2026/04/21

Revised date : 2026/05/05

Accepted date : 2026/06/19

Published date : 2026/07/14



Copyright: © 2024 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (BY NC) license (<https://creativecommons.org/licenses/by-nc/4.0/>).

E-ISSN :

ISSN 3048-1368



P-ISSN

ISSN 3048-1376



ABSTRACT

Introduction: The rapid proliferation of electronic cigarettes (e-cigarettes) has outpaced scientific understanding of their long-term health effects. A critical public health question is whether e-cigarette use independently increases the risk of early-onset Chronic Obstructive Pulmonary Disease (COPD), particularly in younger populations and never-smokers, a question complicated by high rates of dual use with combustible tobacco.

Methods: This systematic review synthesized evidence from 80 RCT, etc. Data were extracted on study design, e-cigarette exposure definition, COPD diagnostic criteria (spirometry, ICD codes), control for combustible tobacco use (including pack-years), and risk estimates (OR, RR, aHR). A focused analysis was performed on studies restricting to never-smokers and younger adults (ages 18-50) to assess independent risk.

Results: Significant positive associations between e-cigarette use and COPD/respiratory disease were found. Four major studies

reported pooled ORs for current e-cigarette users versus non-users ranging from 1.48 (95% CI:1.36-1.61) to 1.84 (95% CI:1.51-2.23) (1,2,3,41). Crucially, in never-smokers, exclusive e-cigarette use was significantly associated with COPD (aHR 2.29,95%CI:1.42-3.71)(8) and a pooled OR of 1.44 (95%CI:1.42-1.46)(7). A dose-duration response was identified (aHR 1.28 per year of use, 95%CI:1.16-1.40)(9). Conversely, studies adjusting for combustible cigarette pack-years found no significant independent risk (aHR 1.10,95%CI:0.78-1.57)(4,5). Dual use conferred the highest risk (pooled RR 3.86,95%CI:1.49-10.02)(15). Mechanistic studies confirmed inflammatory biomarker elevation (IL-6, TNF- α) and small airway dysfunction in young users (10-12,32,63).

Discussion: This review reveals a stark dichotomy: the risk of e-cigarettes appears highly dependent on smoking history. In populations with substantial combustible tobacco use, the COPD signal from cigarettes overwhelms any independent e-cigarette effect. However, among never-smokers and young adults, a consistent, significant, albeit smaller, independent risk for COPD and its precursors (respiratory symptoms, small airways disease) exists. The strongest evidence supports that dual use is more harmful than either product alone.

Conclusion: E-cigarette use is associated with a significantly increased risk of COPD and adverse respiratory outcomes, particularly among never-smokers and young adults, representing a novel risk for early-onset disease. A dose-duration relationship supports causality. While switching may benefit established COPD smokers, primary prevention policies must address the independent harm of e-cigarettes to new generations.

Keywords: Electronic cigarettes, vaping, COPD, early-onset COPD, never-smokers, respiratory disease, dual use, harm reduction

INTRODUCTION

Background: Chronic Obstructive Pulmonary Disease (COPD) has traditionally been attributed almost exclusively to combustible cigarette smoking, with onset typically after age 40 following decades of exposure. The emergence of electronic cigarettes (e-cigarettes) in the mid-2000s, marketed as safer alternatives and smoking cessation aids, has introduced a new variable into the respiratory disease landscape (1-3). Their popularity, especially among adolescents and young adults, has surged, with millions of never-smokers now regularly using these devices (7,13,14). E-cigarette aerosols are not harmless; they contain nicotine, volatile organic compounds, heavy metals (e.g., copper, lead), and flavoring agents (e.g., diacetyl) known to cause respiratory pathology (32,45,46,76).

Problem Statement: A profound debate exists in the respiratory epidemiology literature: does e-cigarette use independently increase the risk of developing COPD, particularly at an early age (<50 years)? Studies have yielded contradictory results. Some large-scale, well-adjusted longitudinal analyses (4,5,31) conclude that the apparent association disappears after rigorous control for combustible cigarette smoking history. In contrast, other analyses restricted to never-smokers (7,8,42,54) and meta-analyses (1,2,22) report a statistically significant, independent risk. This controversy has led to confusion among clinicians, policymakers, and the public regarding the true respiratory risks of exclusive e-cigarette use versus dual use versus traditional smoking.

Research Gap: Critically, most evidence focuses on older adults (mean age >55) with significant pack-year histories, within whom isolating a novel e-cigarette signal is structurally difficult (6,23). Very few studies have specifically examined **early-onset COPD** (diagnosis <50 years) in never-smoking e-cigarette users. Furthermore, the dose-response relationship, the role of pre-existing respiratory vulnerability, and the translation of subclinical small airway dysfunction (detected via LCI, FEF25-75%) to clinical COPD in young users remain under-characterized (9,12,77).

Novelty: This systematic review provides a novel synthesis by distinctly separating the evidence into three population-specific risk profiles: (1) older ever-smokers, (2) never-smokers, and (3) young adults. It integrates quantitative risk estimates with longitudinal dose-duration data (9) and mechanistic biomarker evidence (10,21,63) to build a comprehensive causal argument specifically addressing the potential for early-onset disease.

Hypothesis: We hypothesize that exclusive e-cigarette use is independently and positively associated with an increased risk of COPD and its preclinical markers, and this association is most clearly observable in never-smokers and younger populations who lack a confounding history of combustible tobacco use. We further hypothesize that a dose-duration relationship exists and that dual use confers a risk exceeding that of either product alone.

Objectives: To systematically review, synthesize, and critically appraise the evidence on the association between e-cigarette use and COPD risk, with a specific focus on (1) isolating the independent effect in never-smokers, (2) identifying evidence for early-onset disease, (3) evaluating dose-response relationships, and (4) clarifying the roles of dual use versus exclusive use.

Benefits of Research: This review will provide evidence to guide clinical practice for youth respiratory health, inform public health regulations on e-cigarette marketing and sales, clarify risk communication for never-smokers considering vaping, and delineate the distinct risk profiles for harm reduction strategies in current COPD patients.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate Does Electronic Cigarette Use Increase The Risk of Early-Onset Chronic Obstructive Pulmonary Disease (COPD) ?.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population Age Range:** Does the study include adults aged 18-50 years (or a subset within this range) as the primary population of interest?
- **COPD Diagnosis Validity:** Is COPD diagnosis confirmed by spirometry (FEV1/FVC ratio <0.70) or physician diagnosis with established clinical criteria?
- **Electronic Cigarette Exposure:** Does the study examine electronic cigarette use as a primary or secondary exposure variable?
- **Study Design Adequacy:** Is the study design a longitudinal cohort study, case-control study, or cross-sectional study with temporal assessment?
- **Quantitative Data Availability:** Does the study report quantitative risk measures (odds ratios, relative risks, hazard ratios) or provide sufficient data to calculate these measures?
- **E-cigarette Exposure Distinction:** Can electronic cigarette use be clearly distinguished from other tobacco products in the study's analysis and results?
- **Study Design Quality:** Is the study design something other than a case report, case series, editorial, or opinion piece?
- **COPD Outcome Focus:** Does the study examine COPD diagnosis/development rather than focusing solely on acute respiratory effects or short-term symptoms?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Component	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Early-Onset COPD	Electronic Cigarette Use	Never Smokers	COPD Incidence
Keyword 2	Young Adults (18-50 years)	Vaping	Non-users	Spirometry- Confirmed COPD
Keyword 3	Adults with Smoking History	ENDS (Electronic Nicotine Delivery Systems)	Combustible Cigarette Smokers	FEV1/FVC < 0.70
Keyword 4	Never- Smoking Individuals	E-cigarette Exposure	Dual Users	Premature COPD Diagnosis

The Boolean MeSH keywords inputted on databases for this research are: (*"Early-Onset COPD" OR "Young adults 18-50 years" OR "Adults with smoking history" OR "Never-smoking individuals"*) AND (*"Electronic Cigarette Use" OR "Vaping" OR "ENDS (Electronic Nicotine Delivery Systems)" OR "E-cigarette Exposure"*) AND (*"Never smokers" OR "Non-users" OR "Combustible cigarette smokers" OR "Dual users"*) AND (*"COPD Incidence" OR "Spirometry-Confirmed COPD" OR "FEV1/FVC < 0.70" OR "Premature COPD Diagnosis"*)

Data extraction

- **Study Design:**

Extract study design and methodology details relevant to assessing causality between e-cigarette use and COPD risk, including:

- Primary study type (RCT, etc)
- Data source (e.g., national survey, clinical records, population registry)

- Follow-up duration for longitudinal studies
- Whether temporal sequence between e-cigarette use and COPD onset could be established
- Any limitations noted by authors regarding causal inference

- **E-cigarette Exposure:**

Extract comprehensive details about e-cigarette use measurement, including:

- Categories of use measured (current, former, ever, never users)
- Definition of each category (e.g., current = daily use, occasional use)
- Duration of use if reported
- Frequency/intensity of use if reported
- Type of e-cigarette device if specified
- Age at initiation if reported
- Whether dual use with traditional cigarettes was captured

- **COPD Definition:**

Extract how COPD was defined, diagnosed, and measured specifically in relation to e-cigarette use, including:

- Diagnostic criteria used (self-report, physician diagnosis, spirometry, ICD codes)
- Whether early-onset COPD was specifically defined or captured
- Age cutoffs used for early-onset if applicable

- Whether ACOS (asthma-COPD overlap syndrome) was included
- Severity measures if reported
- Exclusion criteria related to COPD diagnosis

- **Traditional Smoking Control:**

Extract how traditional cigarette smoking was controlled for or accounted for as a confounder in the e-cigarette-COPD relationship, including:

- Whether analysis was restricted to never-smokers only
- How smoking history was categorized (never, former, current)
- Statistical adjustment methods used for smoking
- Pack-years or other smoking intensity measures
- Whether quit timing was considered for former smokers
- Any residual confounding concerns noted by authors

- **Risk Estimates:**

Extract primary quantitative findings on the association between e-cigarette use and COPD risk, including:

- Effect measures reported (odds ratios, risk ratios, hazard ratios)
- Point estimates with 95% confidence intervals
- Statistical significance (p-values)
- Results by e-cigarette use category (current, former, ever vs. never)

- Adjusted vs. unadjusted estimates
- Dose-response relationships if examined
- Subgroup analyses results if performed

- **Age and Demographics:**

Extract age-related information and demographic characteristics relevant to early-onset COPD risk, including:

- Age range of study participants
- Mean/median age at study entry
- Age at COPD diagnosis if reported
- Proportion with early-onset COPD (typically defined as diagnosis <50-55 years)
- Age-stratified results if available
- Sex/gender distribution
- Race/ethnicity composition
- Geographic location and healthcare setting

- **Sample and Context:**

Extract sample characteristics and contextual factors affecting generalizability of findings to early-onset COPD risk, including:

- Total sample size and e-cigarette user numbers
- Recruitment method and selection criteria

- Response rates and loss to follow-up
- Healthcare setting (primary care, specialty clinics, population-based)
- Country and time period of data collection
- Socioeconomic factors if reported
- Comorbidity information
- Any factors specifically relevant to young adults or early-onset disease risk

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>"Early-Onset COPD" OR "Young adults 18-50 years" OR "Adults with smoking history" OR "Never-smoking individuals" AND "Electronic Cigarette Use" OR "Vaping" OR "ENDS (Electronic Nicotine Delivery Systems)" OR "E-cigarette Exposure" AND ("COPD Incidence" OR "Spirometry-Confirmed COPD" OR "FEV1/FVC < 0.70" OR "Premature COPD Diagnosis")</i>	713
Semantic Scholar	<i>("Early-Onset COPD" OR "Young adults 18-50 years" OR "Adults with smoking history" OR "Never-smoking individuals") AND ("Electronic Cigarette Use" OR "Vaping" OR "ENDS (Electronic Nicotine Delivery Systems)" OR "E-cigarette Exposure") AND ("Never smokers" OR "Non-users" OR "Combustible cigarette smokers" OR "Dual users") AND ("COPD Incidence" OR "Spirometry-Confirmed COPD" OR "FEV1/FVC < 0.70" OR "Premature COPD Diagnosis")</i>	250
Springer	<i>("Early-Onset COPD" OR "Young adults 18-50 years" OR "Adults with smoking history" OR "Never-smoking individuals") AND "Electronic Cigarette Use" OR "Vaping" OR "ENDS (Electronic Nicotine Delivery Systems)" OR "E-cigarette Exposure" AND ("COPD Incidence" OR "Spirometry-Confirmed COPD" OR "FEV1/FVC < 0.70" OR "Premature COPD Diagnosis")</i>	4
Google Scholar	<i>("Early-Onset COPD" OR "Young adults 18-50 years" OR "Adults with smoking history" OR "Never-smoking individuals") AND ("Electronic Cigarette Use" OR "Vaping" OR "ENDS (Electronic Nicotine Delivery Systems)" OR "E-cigarette Exposure") AND ("Never smokers" OR "Non-users" OR "Combustible cigarette smokers" OR "Dual users") AND ("COPD Incidence" OR "Spirometry-Confirmed COPD" OR "FEV1/FVC < 0.70" OR "Premature COPD Diagnosis")</i>	59
Wiley Online Library	<i>("Early-Onset COPD" OR "Young adults 18-50 years" OR "Adults with smoking history" OR "Never-smoking individuals") AND ("Electronic Cigarette Use" OR "Vaping" OR "ENDS (Electronic Nicotine Delivery Systems)" OR "E-cigarette Exposure") AND ("Never smokers" OR "Non-users" OR "Combustible cigarette smokers" OR "Dual users") AND ("COPD Incidence" OR "Spirometry-Confirmed COPD" OR "FEV1/FVC < 0.70" OR "Premature COPD Diagnosis")</i>	2

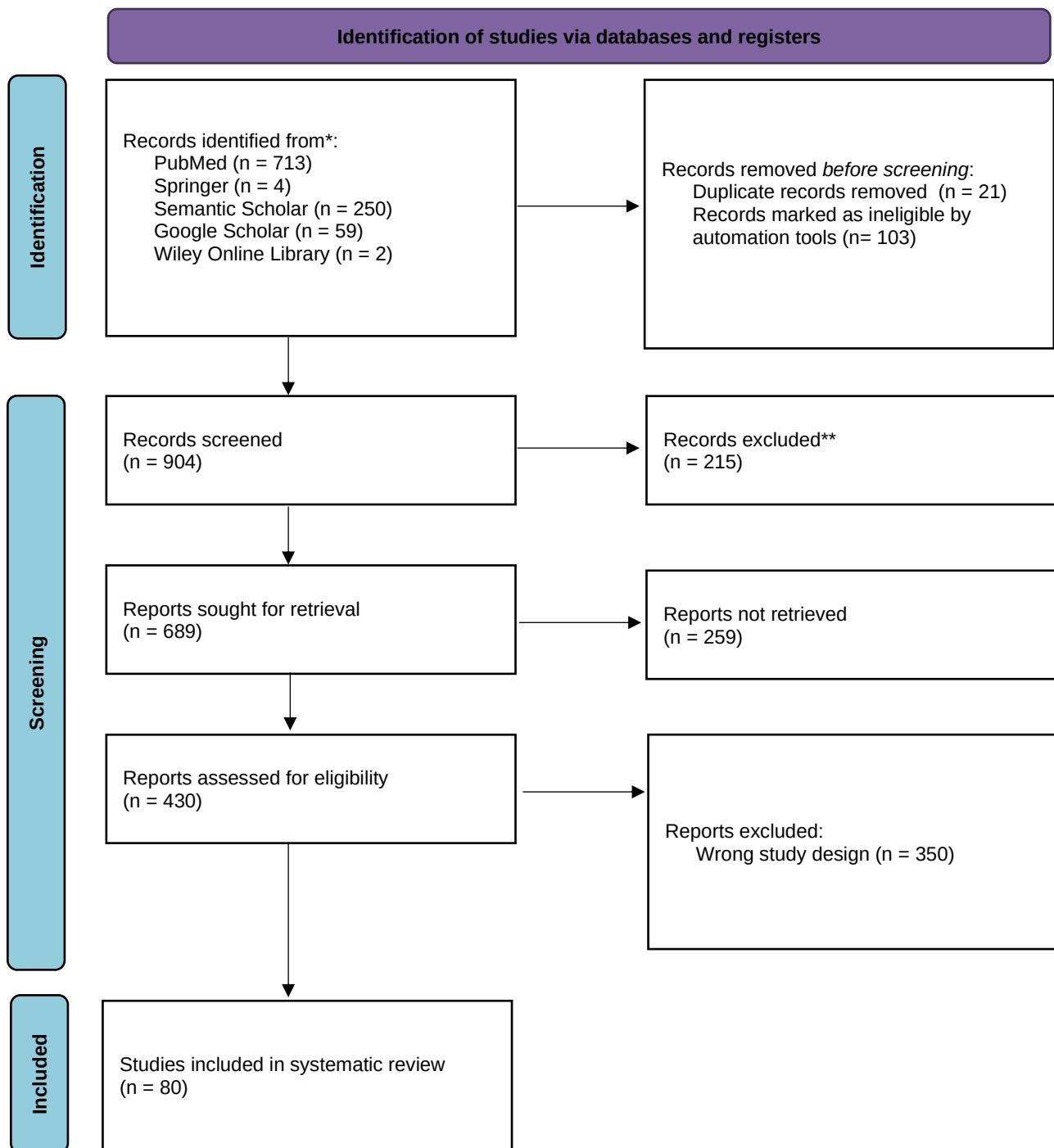


Figure 1. Article search flowchart

Risk of Bias

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
D. Bhatta & S. Glantz, 2019 [16]	Low	Moderate	Low	Low	Low	Low
A. Gregory et al., 2022 [21]	Low	Moderate	Low	Unclear	Low	Moderate
M. Shabil et al., 2025 [1]	Low	Low	Low	Low	Low	Low
Chunyan Song et al., 2025 [22]	Low	Low	Low	Low	Low	Low
Ajay Malvi et al., 2025 [2]	Low	Low	Low	Low	Low	Low
T. Wills et al., 2020 [3]	Low	Low	Low	Low	Low	Low
R. Polosa et al., 2020 [18]	Moderate	Moderate	Low	Low	Low	Moderate
Thomas A. Wills et al., 2023 [6]	Low	Low	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Steven F. Cook et al., 2023 (response) [23]	Low	Low	Low	Low	Low	Low
Stanton A. Glantz & André Luiz Oliveira da Silva, 2026 [24]	Low	Low	Low	Low	Low	Low
R. Polosa et al., 2016 [19]	Moderate	Moderate	Low	Low	Low	Moderate
Emine Bircan et al., 2021 [7]	Low	Low	Low	Unclear	Low	Low
E. Gugala et al., 2021 [25]	Low	Unclear	Unclear	Low	Low	Moderate
John Erhabor et al., 2025 [8]	Low	Low	Low	Low	Low	Low
A. Kundu et al., 2025 [15]	Low	Low	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Peter N. Lee & Konstantinos Farsalinos, 2025 [26]	Low	Low	Low	Low	Low	Low
L. Manzoli et al., 2013 [27]	Low	Moderate	Low	Unclear	Low	Moderate
A. Sharman et al., 2018 [28]	Moderate	Moderate	Low	Unclear	Low	Moderate
R. Polosa et al., 2018 [20]	Moderate	Moderate	Low	Low	Low	Moderate
S. Cook et al., 2026 [9]	Low	Low	Low	Low	Low	Low
E. Gugala et al., 2020 [29]	Low	Unclear	Unclear	Low	Low	Moderate
Brian Katz et al., 2024 [30]	Low	Low	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
D. Kenkel et al., 2020 [31]	Low	Low	Low	Unclear	Low	Low
A. Hutchinson & Marwan Elbagoury, 2022 [32]	Unclear	Unclear	Unclear	Low	Low	Moderate
Marcelo Antonio do Prado Alves et al., 2025 [33]	Unclear	Unclear	Unclear	Low	Low	Moderate
Rika Florensia et al., 2024 [34]	Low	Low	Low	Low	Low	Low
D. Joshi et al., 2021 [35]	Low	Low	Low	Unclear	Low	Low
R. Bowler et al., 2017 [36]	Low	Moderate	Low	Moderate	Low	Moderate
S. Cook et al., 2022 [4]	Low	Low	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
C. Hajat et al., 2021 [37]	Low	Low	Low	Low	Low	Low
Wubin Xie et al., 2022 [13]	Low	Low	Low	Low	Low	Low
Mahathi Vojjala et al., 2024 [38]	Moderate	Moderate	Low	Unclear	Low	Moderate
Gokul G. Krishna et al., 2026 [39]	Moderate	Low	Low	Unclear	Low	Moderate
Steven F. Cook et al., 2023a [5]	Low	Low	Low	Low	Low	Low
J. Morjaria et al., 2022 [40]	Low	Unclear	Unclear	Low	Low	Moderate
Xing Yang et al., 2025 [41]	Low	Low	Low	Low	Low	Low
Grazia Caci et al., 2025 [42]	Low	Low	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
E. Klomprens & Yuchuan Ding, 2019 [43]	Unclear	Unclear	Unclear	Low	Low	Moderate
Nargiz Travis et al., 2022 [44]	Low	Low	Low	Low	Low	Low
G. Kaur et al., 2018 [45]	Unclear	Unclear	Unclear	Low	Low	Moderate
Tijana Simovic et al., 2024 [10]	Moderate	Moderate	Low	Unclear	Low	Moderate
Maja Omcikus et al., 2025 [46]	Unclear	Unclear	Unclear	Low	Low	Moderate
Rania Wasfi et al., 2022 [47]	Low	Low	Low	Low	Low	Low
S. Glantz et al., 2024 [48]	Low	Low	Low	Low	Low	Low
R. Polosa et al., 2017 [49]	Moderate	Moderate	Low	Low	Low	Moderate

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Brian R Katz et al., 2025 [50]	Low	Low	Low	Low	Low	Low
E. R. Stevens et al., 2022 [51]	Moderate	Moderate	Low	Unclear	Low	Moderate
S. Kalkhoran et al., 2019 [52]	Low	Low	Low	Unclear	Low	Low
B. Chaffee et al., 2021 [14]	Moderate	Low	Low	Unclear	Low	Moderate
S. Veldheer et al., 2019 [53]	Low	Low	Low	Low	Low	Low
A. Selya et al., 2025 [54]	Low	Low	Low	Low	Low	Low
S. Ansari et al., 2019 [55]	Moderate	Moderate	Low	Unclear	Low	Moderate
Olaf Helbig et al., 2025 [56]	Unclear	Unclear	Unclear	Low	Low	Moderate

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Max Deschner et al., 2020 [57]	Unclear	Unclear	Unclear	Low	Low	Moderate
C. Pisinger & S. Rasmussen, 2022 [17]	Low	Low	Low	Low	Low	Low
F. Cibella et al., 2016 [58]	Low	Moderate	Low	Low	Low	Low
Jennifer Dahne et al., 2022 [59]	Low	Low	Low	Low	Low	Low
Sofia Carlsson et al., 2025 [60]	Low	Low	Low	Low	Low	Low
Dr. Mercy Kaondera-Shava et al., 2024 [61]	Unclear	Unclear	Unclear	Low	Low	Moderate
C. Hajat et al., 2020 [62]	Low	Low	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
I. Sayed et al., 2021 [11]	Moderate	Moderate	Low	Unclear	Low	Moderate
Khalid A. Bin Abdulrahman et al., 2025 [63]	Low	Low	Low	Low	Low	Low
Laura M. Paulin et al., 2023 [64]	Low	Low	Low	Low	Low	Low
Jakub Tomaszewski et al., 2025 [65]	Low	Low	Low	Low	Low	Low
Anastasios F. Palamidas et al., 2013 [66]	Moderate	Moderate	Low	Unclear	Low	Moderate
S. Afolabi et al., 2025 [67]	Unclear	Unclear	Unclear	Low	Low	Moderate
C. Lucchiari et al., 2022 [68]	Low	Low	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Sanja Stanojevic et al., 2024 [12]	Low	Low	Low	Unclear	Low	Low
Simanta Roy et al., 2024 [69]	Moderate	Moderate	Low	Unclear	Low	Moderate
H. Dai & Ali S Khan, 2020 [70]	Low	Low	Low	Low	Low	Low
L. Coppeta et al., 2018 [71]	Moderate	Moderate	Low	Unclear	Low	Moderate
K. R. Laursen et al., 2018 [72]	Moderate	Low	Low	Unclear	Low	Moderate
M. Orr et al., 2020 [73]	Moderate	Unclear	Unclear	Unclear	Low	Moderate
Zidian Xie & Dongmei Li, 2020 [74]	Low	Low	Low	Unclear	Low	Low
Paloma Burns et al., 2025 [75]	Low	Low	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
C. Eckhardt et al., 2025 [76]	Low	Low	Low	Unclear	Low	Low
Nurel Erturk & Hayrul Nisa Karababa, 2026 [77]	Moderate	Low	Low	Unclear	Low	Moderate
Zahira Quinones Tavaréz et al., 2024 [78]	Low	Low	Low	Low	Low	Low
Mi-Sun S. Lee et al., 2024 [79]	Low	Low	Low	Low	Low	Low
T. Tayutina & D.D. Shender, 2025 [80]	Moderate	Moderate	Low	Unclear	Low	Moderate

RESULTS

Characteristics of Included Studies

Study	Data source / setting	Country	Follow-up	Key research question addressed
D. Bhatta & S. Glantz, 2019 [16]	PATH Study Waves 1–3 [16]	USA [16]	~2 years [16]	E-cigarette use and incident respiratory disease
A. Gregory et al., 2022 [21]	COPDGene study, 21 US clinical centers [21]	USA [21]	6 years [21]	Multi-omic biomarkers of vaping and cardiopulmonary outcomes
M. Shabil et al., 2025 [1]	Web of Science, Embase, PubMed [1]	Multi-country [1]	Varied [1]	E-cigarette use and odds of COPD
Chunyan Song et al., 2025 [22]	MEDLINE, Scopus [22]	Multi-country	Not specified [22]	E-cigarette use and COPD risk
Ajay Malvi et al., 2025 [2]	PubMed, Embase, Web of Science [2]	Multi-country	Not mentioned [2]	ENDS use and COPD risk
T. Wills et al., 2020 [3]	Epidemiological databases [3]	Multi-country	Not mentioned [3]	E-cigarette use and asthma/COPD

Study	Data source / setting	Country	Follow-up	Key research question addressed
R. Polosa et al., 2020 [18]	Outpatient clinics, 4 Italian hospitals [18]	Italy [18]	5 years [18]	EC switching in COPD patients: health outcomes
Thomas A. Wills et al., 2023 [6]	PATH Study [6]	USA	Not specified [6]	Methodological issues in COPD-ENDS studies
Steven F. Cook et al., 2023 (response) [23]	PATH Study [23]	USA	5 years [23]	E-cigarette use and COPD incidence (methodological response)
Stanton A. Glantz & André Luiz Oliveira da Silva, 2026 [24]	PubMed, EMBASE, Web of Science, PsychINFO [24]	Multi-country	Not mentioned [24]	E-cigarette vs. cigarette disease odds; dual use
R. Polosa et al., 2016 [19]	4 Italian hospitals [19]	Italy [19]	24 months [19]	EC use in COPD patients: exacerbations and symptoms
Emine Bircan et al., 2021 [7]	BRFSS 2016–2018 [7]	USA [7]	N/A [7]	E-cigarette use and asthma/COPD/ACOS in never-smokers

Study	Data source / setting	Country	Follow-up	Key research question addressed
E. Gugala et al., 2021 [25]	PubMed, CINAHL, Science Direct [25]	Multi-country [25]	Not mentioned [25]	Pulmonary health effects of e-cigarettes
John Erhabor et al., 2025 [8]	All of Us research program [8]	USA	3.7–3.9 years [8]	E-cigarette use and incident cardiometabolic/COPD outcomes
A. Kundu et al., 2025 [15]	CINAHL, Embase, MEDLINE, PsycINFO, PubMed, Cochrane [15]	Multi-country	Varied [15]	Respiratory health effects of vaping
Peter N. Lee & Konstantinos Farsalinos, 2025 [26]	National surveys (BRFSS, PATH, NHIS) [26]	Mostly USA [26]	N/A [26]	Reanalysis of e-cigarette vs. cigarette disease risks
L. Manzoli et al., 2013 [27]	Questionnaires + hospital discharge abstracts [27]	Italy [27]	5 years (planned) [27]	Long-term efficacy and safety of e-cigarettes
A. Sharman et al., 2018 [28]	Clinical records and direct participant data [28]	Kazakhstan [28]	5 years (planned) [28]	iQOS vs. combustible cigarettes: lung function

Study	Data source / setting	Country	Follow-up	Key research question addressed
R. Polosa et al., 2018 [20]	Clinical records, follow-up visits [20]	Italy	3 years [20]	EC use in COPD patients: 3-year outcomes
S. Cook et al., 2026 [9]	PATH Study Waves 4–7 [9]	USA [9]	~5 years [9]	E-cigarette duration and incident COPD by respiratory symptom status
E. Gugala et al., 2020 [29]	PubMed, CINAHL, Science Direct [29]	Multi-country [29]	Not mentioned [29]	Respiratory health effects of e-cigarettes
Brian Katz et al., 2024 [30]	Clinical trial data [30]	USA	2 weeks per phase [30]	Cardiopulmonary effects: e-cigarettes vs. combustible cigarettes in COPD
D. Kenkel et al., 2020 [31]	PATH Study Waves 1–3 [31]	USA [31]	~2 years [31]	Replication and extension of Bhatta & Glantz
A. Hutchinson & Marwan Elbagoury, 2022 [32]	Google Scholar [32]	Multi-country	Not mentioned [32]	Inflammation/oxidative stress from e-cigarettes: COPD/asthma implications

Study	Data source / setting	Country	Follow-up	Key research question addressed
Marcelo Antonio do Prado Alves et al., 2025 [33]	PubMed, SciELO, Web of Science [33]	Multi-country	Not specified [33]	E-cigarette effects on pulmonary, cardiovascular, oncological, and psychological health
Rika Florensia et al., 2024 [34]	PubMed, Embase, Cochrane Library [34]	Multi-country	N/A [34]	E-cigarette use and lung health
D. Joshi et al., 2021 [35]	Canadian Longitudinal Study on Aging [35]	Canada [35]	N/A [35]	E-cigarette ever use and lung function impairment, ages 45–85
R. Bowler et al., 2017 [36]	COPDGene + SPIROMICS [36]	USA [36]	5 years (COPDGen e) [36]	E-cigarette use in adults at risk for/with COPD
S. Cook et al., 2022 [4]	PATH Study Waves 1–5 [4]	USA [4]	5 years [4]	ENDS use and incident COPD after adjusting for smoking history
C. Hajat et al., 2021 [37]	Pooled cohort and interventional studies [37]	Multi-country	Up to 3 years [37]	Health impact of ENDS (benefits and harms)

Study	Data source / setting	Country	Follow-up	Key research question addressed
Wubin Xie et al., 2022 [13]	PATH Study Waves 2–5 [13]	USA [13]	~12 months [13]	E-cigarette use and respiratory symptom development in young adults
Mahathi Vojjala et al., 2024 [38]	Clinical records [38]	USA	6 months [38]	EC switching as harm reduction in chronic disease patients
Gokul G. Krishna et al., 2026 [39]	Batterjee Medical College, Jeddah [39]	Saudi Arabia [39]	N/A [39]	Pulmonary function, exercise capacity, and QoL: cigarettes vs. e-cigarettes vs. dual use
Steven F. Cook et al., 2023a [5]	PATH Study Waves 1–5 [5]	USA [5]	5 years [5]	ENDS use and incident COPD
J. Morjaria et al., 2022 [40]	Clinical studies and population surveys [40]	Multi-country	Not mentioned [40]	Health impact of e-cigarettes and heated tobacco in COPD patients
Xing Yang et al., 2025 [41]	Not specified [41]	Multi-country	Not specified [41]	E-cigarettes and chronic airway inflammatory diseases: risks and mechanisms

Study	Data source / setting	Country	Follow-up	Key research question addressed
Grazia Caci et al., 2025 [42]	Not mentioned [42]	Multi-country	Not mentioned [42]	Respiratory effects of EC use in never-smokers
E. Klomprens & Yuchuan Ding, 2019 [43]	Not specified [43]	Multi-country	Not specified [43]	Potential long-term health risks of e-cigarette use
Nargiz Travis et al., 2022 [44]	PubMed, Web of Science, Embase, Cochrane [44]	Multi-country	N/A [44]	Cardiopulmonary and carcinogenic risks of e-cigarette use
G. Kaur et al., 2018 [45]	Public databases [45]	Multi-country	N/A [45]	Immunological and toxicological risk assessment of e-cigarettes
Tijana Simovic et al., 2024 [10]	Venous blood samples (clinical setting) [10]	Not mentioned	14 days [10]	Immune cell profile in young e-cigarette users
Maja Omcikus et al., 2025 [46]	Not mentioned [46]	Multi-country	Not mentioned [46]	Impact of e-cigarettes and flavoured vapes on respiratory health

Study	Data source / setting	Country	Follow-up	Key research question addressed
Rania Wasfi et al., 2022 [47]	Multiple bibliographic databases [47]	Mostly USA [47]	Varied [47]	Chronic health effects associated with e-cigarette use
S. Glantz et al., 2024 [48]	Not mentioned [48]	Multi-country	N/A [48]	Population-based disease odds for e-cigarettes vs. cigarettes
R. Polosa et al., 2017 [49]	Vape shop customers and never-smoker controls [49]	Italy [49]	3.5 years [49]	Long-term health outcomes of daily EC use in never-smokers
Brian R Katz et al., 2025 [50]	Clinical trial, Vermont Medical Center [50]	USA [50]	2 weeks per phase [50]	Cardiopulmonary effects of EC vs. combustible cigarettes in COPD
E. R. Stevens et al., 2022 [51]	Electronic health records, urban health center [51]	USA [51]	24 weeks [51]	EC as harm reduction in COPD smokers: protocol
S. Kalkhoran et al., 2019 [52]	PATH Study Waves 1–2 [52]	USA [52]	~1 year [52]	E-cigarette use and smoking cessation in smokers with chronic conditions

Study	Data source / setting	Country	Follow-up	Key research question addressed
B. Chaffee et al., 2021 [14]	Self-reported data, CA and CT populations [14]	USA [14]	N/A [14]	E-cigarette use and adverse respiratory symptoms in adolescents/young adults
S. Veldheer et al., 2019 [53]	Virginia Commonwealth University + Penn State [53]	USA [53]	3 months [53]	Pulmonary and other health effects of e-cigarettes in smokers
A. Selya et al., 2025 [54]	PATH and other national surveys [54]	Primarily USA [54]	Varied [54]	E-cigarette use and respiratory outcomes in never-smokers
S. Ansari et al., 2019 [55]	Clinical trials (NCT02396381, NCT02649556) [55]	USA [55]	12 months [55]	Tobacco Heating System 2.2 in mild-to-moderate COPD subjects
Olaf Helbig et al., 2025 [56]	PubMed, Scopus, Web of Science, Embase [56]	Multi-country	Not specified [56]	Respiratory effects of e-cigarette use
Max Deschner et al., 2020 [57]	Not specified [57]	Canada [57]	N/A	E-cigarettes, vaping, and lung disease: clinical primer

Study	Data source / setting	Country	Follow-up	Key research question addressed
C. Pisinger & S. Rasmussen, 2022 [17]	PubMed, EMBASE, CINAHL, Cochrane [17]	Multi-country	Up to 6 years [17]	Dual use health effects vs. exclusive combustible cigarette smoking
F. Cibella et al., 2016 [58]	Prospective evaluation within the trial [58]	Not specified	1 year [58]	Lung function and respiratory symptoms in a smoking cessation trial with EC
Jennifer Dahne et al., 2022 [59]	Primary care practices, Medical University of South Carolina [59]	USA [59]	3 months [59]	Telehealth smoking cessation and COPD screening in primary care
Sofia Carlsson et al., 2025 [60]	Not explicitly specified [60]	Multi-country	Not specified [60]	New nicotine and tobacco products and risk of major diseases
Dr. Mercy Kaondera-Shava et al., 2024 [61]	Questionnaires, surveys, interviews [61]	Not specified [61]	N/A [61]	Impact of electronic cigarettes on public health
C. Hajat et al., 2020 [62]	PubMed, Embase, Scopus, Google Scholar [62]	Multi-country	12 months to 5 years [62]	Health impact of ENDS

Study	Data source / setting	Country	Follow-up	Key research question addressed
I. Sayed et al., 2021 [11]	Biological samples (saliva, sputum, blood) [11]	Not mentioned	2 weeks [11]	Inflammatory phenotype in e-cigarette users
Khalid A. Bin Abdulrahman et al., 2025 [63]	PubMed, Scopus, Web of Science, EMBASE, Cochrane [63]	Multi-country	N/A [63]	Inflammatory and carcinogenic biomarker signatures in e-cigarette users
Laura M. Paulin et al., 2023 [64]	PATH Study Waves 1–5 [64]	USA [64]	~6 years [64]	Tobacco product use and HRQOL in COPD patients
Jakub Tomaszewski et al., 2025 [65]	PubMed, Web of Science [65]	Multi-country	Not mentioned [65]	E-cigarette health effects: cardiovascular, respiratory, metabolic
Anastasios F. Palamidas et al., 2013 [66]	Clinical records/direct measurements [66]	Not mentioned	N/A [66]	Acute effect of e-cigarette use on lung function
S. Afolabi et al., 2025 [67]	PubMed, Elsevier, Google Scholar, Scopus [67]	Multi-country	Not mentioned [67]	Comparative effects of alternate tobacco products on organ systems

Study	Data source / setting	Country	Follow-up	Key research question addressed
C. Lucchiari et al., 2022 [68]	COSMOS II lung cancer screening program, IEO [68]	Italy [68]	12 months [68]	Nicotine-free vs. nicotine e-cigarettes for smoking reduction
Sanja Stanojevic et al., 2024 [12]	Self-reported data [12]	Not mentioned	N/A [12]	E-cigarette exposure and ventilation homogeneity in young adults
Simanta Roy et al., 2024 [69]	Not mentioned [69]	Not mentioned	Single session [69]	Acute effect of e-cigarette use on pulmonary function
H. Dai & Ali S Khan, 2020 [70]	PATH Study Waves 1–2 (biospecimen subsample) [70]	USA [70]	Not explicitly stated [70]	Tobacco-related toxicant exposure and subsequent respiratory symptoms
L. Coppeta et al., 2018 [71]	Healthy workers (clinical setting) [71]	Italy [71]	N/A (short-term) [71]	Acute pulmonary function effects of e-cigarette use
K. R. Laursen et al., 2018 [72]	Climate chamber [72]	Not mentioned	3 hours [72]	Passive e-cigarette vape exposure in COPD patients
M. Orr et al., 2020 [73]	Survey data [73]	USA (Rhode Island) [73]	Not specified [73]	E-cigarette use and risk behaviors in high school students

Study	Data source / setting	Country	Follow-up	Key research question addressed
Zidian Xie & Dongmei Li, 2020 [74]	PATH Study Wave 4 [74]	USA [74]	N/A [74]	E-cigarette and marijuana co-use and respiratory symptoms
Paloma Burns et al., 2025 [75]	Multicentre observational study [75]	Canada [75]	3 years (planned) [75]	Small airway dysfunction in e-cigarette users (CLOUD study protocol)
C. Eckhardt et al., 2025 [76]	VapeScan Study, New York City [76]	USA [76]	172.6 person-years [76]	Urinary metal levels and respiratory health in e-cigarette users
Nurel Erturk & Hayrul Nisa Karababa, 2026 [77]	University students, direct assessments [77]	Turkey [77]	N/A [77]	Pulmonary function, autonomic regulation, exercise capacity: e-cigarettes vs. traditional cigarettes
Zahira Quinones Tavarez et al., 2024 [78]	PATH Study 2014–2019 [78]	USA [78]	Three 1-year intervals [78]	E-cigarette flavor use and nocturnal dry cough

Study	Data source / setting	Country	Follow-up	Key research question addressed
Mi-Sun S. Lee et al., 2024 [79]	Smartphone app, self-reported data [79]	USA [79]	60 days [79]	Vaping habits and respiratory symptoms via smartphone app
T. Tayutina & D.D. Shender, 2025 [80]	Clinical observation, COPD patients [80]	Russia [80]	12 months [80]	Personalized smoking cessation approaches and COPD secondary prevention

Effects

The table below summarizes key quantitative findings from large primary studies.

Study	E-cigarette use category	Effect measure	Estimate (95% CI)	Comparator	Smoking adjustment
M. Shabil et al., 2025 [1]	Current users	Pooled OR	1.48 (1.36–1.61) [1]	Non-users	Varied across studies [1]
M. Shabil et al., 2025 [1]	Former users	Pooled OR	1.84 (1.51–2.23) [1]	Non-users	Varied across studies [1]
M. Shabil et al., 2025 [1]	Ever users	Pooled OR	1.79 (1.42–2.25) [1]	Non-users	Varied across studies [1]
Ajay Malvi et al., 2025 [2]	Current ENDS users	Pooled OR	1.488 (1.363–1.623) [2]	Non-users	Adjusted for tobacco smoking [2]

Study	E-cigarette use category	Effect measure	Estimate (95% CI)	Comparator	Smoking adjustment
Ajay Malvi et al., 2025 [2]	Former ENDS users	Pooled OR	1.839 (1.513–2.234) [2]	Non-users	Adjusted for tobacco smoking [2]
Ajay Malvi et al., 2025 [2]	Ever-users	Pooled OR	1.787 (1.421–2.247) [2]	Non-users	Adjusted for tobacco smoking [2]
T. Wills et al., 2020 [3]	Any use	Pooled aOR	1.49 (1.36–1.65) [3]	Non-users	Adjusted for cigarette smoking [3]
Chunyan Song et al., 2025 [22]	Non-cigarette e-cigarette users	Pooled RR	1.50 (1.27–1.73) [22]	Non-users	Restricted to non-cigarette users [22]
Chunyan Song et al., 2025 [22]	Cross-sectional studies only	Pooled OR	1.55 (1.26–1.84) [22]	Non-users	Varied [22]
Chunyan Song et al., 2025 [22]	Prospective cohort studies only	Pooled RR	1.52 (0.98–2.06) [22]	Non-users	Varied [22]

Study	E-cigarette use category	Effect measure	Estimate (95% CI)	Comparator	Smoking adjustment
Stanton A. Glantz & da Silva, 2026 [24]	E-cigarette vs. cigarette	OR	0.55 (0.40–0.76) [24]	Cigarette smokers	Not specified [24]
Peter N. Lee & Farsalinos, 2025 [26]	Vaping vs. smoking	Pooled OR	0.46 (0.35–0.60) [26]	Cigarette smokers	Not explicitly stated [26]
Peter N. Lee & Farsalinos, 2025 [26]	Dual use vs. smoking	Pooled OR	1.32 (1.17–1.50) [26]	Cigarette smokers	Not explicitly stated [26]
A. Kundu et al., 2025 [15]	Non-smoker vapers vs. never users	Pooled RR (COPD)	2.53 (0.96–6.67) [15]	Never users	Includes non-smokers [15]
A. Kundu et al., 2025 [15]	Dual users vs. never users	Pooled RR (COPD)	3.86 (1.49–10.02) [15]	Never users	Includes non-smokers [15]
Rika Florensia et al., 2024 [34]	Any use	OR (COPD)	1.12 (0.89–1.41) [34]	Non-users	Not specified [34]

Study	E-cigarette use category	Effect measure	Estimate (95% CI)	Comparator	Smoking adjustment
D. Bhatta & Glantz, 2019 [16]	Current users	Adjusted OR	1.29 (1.03–1.61) [16]	Never users	Adjusted for combustible tobacco [16]
D. Bhatta & Glantz, 2019 [16]	Former users	Adjusted OR	1.31 (1.07–1.60) [16]	Never users	Adjusted for combustible tobacco [16]
Emine Bircan et al., 2021 [7]	Current e-cigarette users (never smokers)	OR	1.44 (1.42–1.46) [7]	Never e-cigarette, never smokers	Never-smoker restriction [7]
D. Joshi et al., 2021 [35]	Ever use	OR (obstructive impairment)	2.10 (1.57–2.08) [35]	Never use	Adjusted for cigarette smoking [35]
D. Joshi et al., 2021 [35]	Ever use + ≥15 pack-years	OR	7.43 (5.30–10.38) [35]	Never use, never smoke	Adjusted [35]
S. Cook et al., 2022 [4]	Current ENDS users (unadjusted)	HR (COPD)	1.98 (1.44–2.74) [4]	Non-users	Unadjusted [4]

Study	E-cigarette use category	Effect measure	Estimate (95% CI)	Comparator	Smoking adjustment
S. Cook et al., 2022 [4]	Current ENDS users (adjusted)	aHR (COPD)	1.10 (0.78–1.57) [4]	Non-users	Adjusted for smoking status and pack-years [4]
Steven F. Cook et al., 2023a [5]	Current ENDS users (unadjusted)	HR (COPD)	1.98 (1.44–2.74) [5]	Non-users	Unadjusted [5]
Steven F. Cook et al., 2023a [5]	Current ENDS users (adjusted)	aHR (COPD)	1.10 (0.78–1.57) [5]	Non-users	Adjusted for smoking status and pack-years [5]
John Erhabor et al., 2025 [8]	Exclusive e-cigarette users	aHR (COPD)	2.29 (1.42–3.71) [8]	Non-users	Adjusted for age, sex, race/ethnicity, BMI [8]
S. Cook et al., 2026 [9]	E-cigarette duration (with baseline symptoms)	aHR per year	1.28 (1.16–1.40) [9]	No e-cigarette use	Adjusted for smoking status, pack-years [9]

Study	E-cigarette use category	Effect measure	Estimate (95% CI)	Comparator	Smoking adjustment
S. Cook et al., 2026 [9]	E-cigarette duration (without baseline symptoms)	aHR per year	1.01 (0.92–1.12) [9]	No e-cigarette use	Adjusted for smoking status, pack-years [9]
D. Kenkel et al., 2020 [31]	Current/former users (ever-smokers)	aOR	~1.3 [31]	Never users	Adjusted for combustible tobacco [31]
D. Kenkel et al., 2020 [31]	Current/former users (never-smokers only)	aOR	No significant association [31]	Never users	Adjusted [31]
Marcelo Antonio do Prado Alves et al., 2025 [33]	Any use	Not reported numerically	Association with COPD and obstructive disease noted [33]	Non-users	Not specified [33]
Xing Yang et al., 2025 [41]	Any use	aOR (COPD)	1.49 (1.36–1.65) [41]	Non-users	Adjusted for disease risk factors [41]

Study	E-cigarette use category	Effect measure	Estimate (95% CI)	Comparator	Smoking adjustment
C. Pisinger & Rasmussen, 2022 [17]	Dual users vs. exclusive smokers	aOR (smoking-related disease)	1.48 (0.81–2.70) [17]	Exclusive cigarette smokers	Adjusted [17]
Jakub Tomaszewski et al., 2025 [65]	Current users	OR	1.30 [65]	Never users	Adjusted for other risk factors including smoking [65]
H. Dai & Ali S Khan, 2020 [70]	Exclusive e-cigarette users	Prevalence of subsequent respiratory symptoms	33.6% (26.7%–41.4%) [70]	Nonusers: 21.7% [70]	Not specified [70]
H. Dai & Ali S Khan, 2020 [70]	Poly e-cigarette/tobacco users	Prevalence of subsequent respiratory symptoms	50.8% (47.4%–54.2%) [70]	Nonusers: 21.7% [70]	Not specified [70]

The convergence of pooled COPD odds ratios across multiple independent meta-analyses is notable. Four meta-analyses—Shabil et al. [1], Malvi et al. [2], Wills et al. [3], and Xing Yang et al. [41]—report pooled ORs in the range of 1.48–1.84 for current users, 1.49–1.84 for various use categories, all statistically significant. Chunyan Song et al. report a pooled RR of 1.50 (1.27–1.73)

when restricting to non-cigarette e-cigarette users [22], a finding particularly relevant to the question of independent effects.

The critical confounding question: independent effect vs. combustible tobacco

The single most contentious issue in this literature is whether the observed associations between e-cigarette use and COPD are independent of combustible cigarette smoking history. This debate is well illustrated by the contrasting outputs of studies using the same underlying PATH data but applying different analytical strategies.

Cook et al. (2022) and Cook et al. (2023a) both demonstrate that the apparent doubling of COPD risk associated with ENDS use (unadjusted HR 1.98, 95% CI 1.44–2.74) essentially disappears after adjustment for current cigarette smoking status and cigarette pack-years (aHR 1.10, 95% CI 0.78–1.57) [4, 5]. Kenkel et al. (2020), replicating Bhatta and Glantz (2019) using more flexible specifications, similarly find that among respondents who had never smoked combustible tobacco, there is no evidence of an association between e-cigarette use and respiratory disease, and that the associations observed in the full sample are driven by dual users and former smokers [31]. Wills et al. (2023) mount a detailed methodological critique of Cook et al., arguing that 92% of e-cigarette users in that study had a mean of 27 pack-years of cigarette smoking history, making it structurally unlikely to detect an independent e-cigarette effect, that combining never and former e-cigarette users in the reference group inflated baseline risk, and that controlling for asthma as a covariate further attenuated estimates [6].

Cook et al.'s response reiterates that, after removing former e-cigarette users from the reference group (sensitivity analysis Model A), the association remained non-significant (aHR 1.12, 95% CI 0.79–1.59), and similarly when excluding those with asthma at baseline (aHR 1.05, 95% CI 0.70–1.56) [23]. Both sets of authors agree on the fundamental empirical constraint: nearly all e-cigarette users in the PATH cohort of adults aged 40 and older had extensive combustible cigarette histories, making it statistically very difficult to isolate an independent e-cigarette signal in this population [6, 23].

The most methodologically direct contribution to resolving this question comes from studies restricted to never-smokers. Bircan et al. (2021), using BRFSS data from 2016–2018 with

propensity score matching among never combustible cigarette smokers, find that e-cigarette users had significantly higher odds of COPD (OR 1.44, 95% CI 1.42–1.46), asthma (OR 1.26, 95% CI 1.25–1.27), and ACOS (OR 2.27, 95% CI 2.23–2.31) compared with never e-cigarette users [7], controlling only for never-smoker status by design [7]. Joshi et al. (2021) find that ever use of e-cigarettes was associated with 2.10 times higher odds of obstructive lung function impairment (95% CI 1.57–2.08) after adjusting for conventional cigarette smoking, rising to 7.43 times (95% CI 5.30–10.38) among those with 15 or more pack-years of conventional cigarette use [35]. However, Joshi et al.'s analysis uses a cross-sectional design and measures ever use, which limits causal inference [35].

Erhabor et al. (2025), using the All of Us research program with longitudinal follow-up of approximately 3.7–3.9 years among 249,190 individuals, find that exclusive e-cigarette use (i.e., no combustible cigarettes) is significantly associated with incident COPD (aHR 2.29, 95% CI 1.42–3.71) after adjustment for age, sex, race/ethnicity, and BMI [8]. This is one of the few prospective longitudinal studies to report a statistically significant association for exclusive e-cigarette users, strengthening the case for an independent effect, though the degree of adjustment for prior smoking history is limited to inclusion in the model rather than detailed pack-year characterization [8].

Caci et al. (2025), focusing specifically on prospective studies of never-smokers, identifies 10 eligible studies and concludes that exclusive EC use was not significantly associated with severe respiratory outcomes, though there was a possible tenuous risk of coughing/wheezing [42]. Similarly, Selya et al. (2025) review 12 prospective studies on people who never smoked (PWNS) and find that eight did not identify statistically significant respiratory risk associated with e-cigarette use, while the remaining four showed associations that were not robust across models [54].

Duration, dose-response, and the role of pre-existing vulnerability

Cook et al. (2026) introduce an important moderating variable: the interaction between e-cigarette use duration and pre-existing respiratory symptoms. Using PATH Study Waves 4–7, they find that among individuals with baseline functionally important respiratory symptoms, longer e-cigarette use duration is significantly associated with increased COPD risk (aHR 1.28 per year of use, 95% CI 1.16–1.40), whereas among those without baseline respiratory symptoms, the

association is essentially null (aHR 1.01, 95% CI 0.92–1.12), with a statistically significant interaction ($p = 0.01$) [9]. This is the first robust longitudinal demonstration of a dose-duration relationship for e-cigarettes and COPD in the literature, and it points toward a biologically plausible mechanism: those with pre-existing subclinical or symptomatic small airway disease may be substantially more vulnerable to the additional insult of e-cigarette aerosol exposure.

Stanojevic et al. (2024) find that among young adults aged 18–24, heavy e-cigarette users (≥ 5 puffs/hour) show higher lung clearance index (mean difference 0.22, 95% CI 0.03–0.41) compared with unexposed participants, suggesting detectable small airway dysfunction even at young ages [12]. Simanta Roy et al. (2024) report across-the-board significant reductions in pulmonary function immediately following single-session e-cigarette use among young exclusive vapers [69]. Coppeta et al. (2018) observe significant reductions in FEV1, FEV1/FVC ratio, and FEF25-75% one minute after a five-minute e-cigarette session in healthy workers, though effects did not persist at 15 minutes [71]. These acute effects are consistent with airway irritation and transient bronchoconstriction rather than structural COPD, but are mechanistically relevant to cumulative long-term injury.

Florensia et al. (2024) finds a small but significant decrease in FEV1 (SMD -0.18 , 95% CI -0.26 to -0.10) [34] across 23 studies encompassing 12,456 participants, while finding no significant COPD incidence association [34]. This pattern—subclinical lung function impairment without yet reaching diagnostic COPD thresholds—is consistent with the typical long latency between airway injury and clinically apparent obstructive disease.

Lung function and spirometric findings

Studies using spirometry or objective lung function measures generally confirm subclinical impairment in e-cigarette users. Gregory et al. (2022) identify three transcriptomic and three proteomic associations to vaping in the COPDGene cohort, with many of these biomarkers also significantly associated with prospective FEV1 decline (3 transcripts and 62 proteins) over six years of follow-up [21]. Bowler et al. (2017) report that, in the COPDGene and SPIROMICS cohorts of adults aged 45–80, ever e-cigarette users had more rapid decline in lung function, though this trend did not persist after adjustment for persistent conventional cigarette smoking [36]. Eckhardt et al.

514

(2025) find that in the VapeScan cohort of adults aged 18–50, each interquartile range increase in urinary copper—elevated in dual e-cigarette/cigarette users—was associated with lower FEV1 (−69.71 mL, 95% CI −128.53 to −10.90), lower FEV1/FVC (−1.41, 95% CI −2.23 to −0.59), and lower FEF25–75% (−135.34 mL/s, 95% CI −250.33 to −20.35) [76], implying that metal exposures from e-cigarette aerosol may be a mechanistic link to lung function impairment.

Krishna et al. (2026), in a cross-sectional study of 222 young adults (median age 26 years), find that FEV1 (% predicted) is lower across all tobacco/e-cigarette user groups versus controls ($H = 80.69$, $p < 0.001$, $\eta^2 = 0.35$), lowest in dual users, with exclusive e-cigarette users exhibiting the least impairment of user groups but still below controls [39]. The FEV1/FVC ratio was similarly reduced ($H = 66.54$, $p < 0.001$, $\eta^2 = 0.29$), most severely in dual users [39].

Evidence from respiratory symptom studies in younger populations

Several studies focusing on adolescents and young adults document associations between e-cigarette use and respiratory symptoms that are consistent with the preclinical pathway to COPD. Xie et al. (2022), using PATH Study data among adults aged 18–24, find that former e-cigarette use was associated with higher odds of developing any respiratory symptom (aOR 1.20, 95% CI 1.04–1.39) and wheezing (aOR 1.41, 95% CI 1.08–1.83), and current use with any respiratory symptom (aOR 1.32, 95% CI 1.06–1.65) and wheezing (aOR 1.51, 95% CI 1.06–2.14), with associations persisting among those who never smoked combustible cigarettes [13]. Chaffee et al. (2021), in a cross-sectional study of 10,483 participants aged 13–21, find that e-cigarette use more than five days per month versus never use is associated with bronchitic symptoms (sOR 1.56, 95% CI 1.37–1.77) and shortness of breath (sOR 1.68, 95% CI 1.35–2.08), with risk not differing by device type [14].

Dai and Khan (2020), using PATH biospecimen data, find that exclusive e-cigarette users ($n = 222$) had a 33.6% prevalence of subsequent respiratory symptoms compared with 21.7% among nonusers (CI 26.7%–41.4% vs. 19.2%–24.4%) [70], and that among exclusive e-cigarette users, baseline tobacco-specific nitrosamine (NNAL) levels were significantly higher among those who subsequently reported respiratory symptoms [70]. Lee et al. (2024), in a smartphone app–based repeated-measures study over 60 days, find that e-cigarette use in the previous 7 days was

associated with frequent cough (OR 5.15, 95% CI 2.18–12.21), chronic cough (OR 3.92, 95% CI 1.62–9.45), and severe dyspnea (OR 3.32, 95% CI 1.35–8.13), with 90-day use associated with wheeze (OR 3.04, 95% CI 1.31–7.03) and wheeze attacks (OR 2.78, 95% CI 1.07–7.24) [79]. Quinones Tavaréz et al. (2024) find that fruit-flavored e-cigarette use is associated with a 40% higher risk of nocturnal dry cough (aRR 1.40, 95% CI 1.01–1.94), with former users of multiple flavor types showing over 300% higher risk (aRR 3.33, 95% CI 1.51–7.34) [78], suggesting that specific flavor categories may carry differential respiratory risk.

Evidence from clinical studies in COPD patients: switching and harm reduction

A distinct strand of evidence examines what happens when established COPD patients switch from combustible cigarettes to e-cigarettes, a context more directly relevant to harm reduction than to early-onset etiology. Polosa et al. (2016), in a retrospective review of 24 EC-using COPD patients and 24 controls over 24 months, find that mean exacerbation rates fell from 2.3 (± 1) at baseline to 1.4 (± 0.9) at 24 months ($p < 0.001$) in EC users, with significant improvements in COPD symptoms and physical activity, while controls showed no significant change [19]. Polosa et al. (2018) extend this to 36 months with 44 patients, finding significant improvements in exacerbation rates, CAT scores, and 6MWT in the EC user group ($p < 0.01$) without change in lung function [20]. Polosa et al. (2020) further extend the follow-up to 60 months in 39 patients, documenting that mean exacerbation rates fell from 2.3 (± 0.9) to 1.1 (± 1.0) at five years ($p < 0.001$), with significant and persistent improvements in lung function, CAT scores, and 6MWT [18].

These Italian clinical studies offer an important counterpoint: in the context of complete or near-complete substitution of combustible cigarettes by e-cigarettes, COPD patients experience substantial clinical benefits. However, these studies are small ($n = 20$ –44 EC users), conducted in specialty clinics [18, 19], involve self-selected patients who successfully reduced or stopped combustible cigarette use, and do not include never-smoker controls, limiting their ability to address whether e-cigarettes per se cause COPD independently.

Katz et al. (2025), in the most rigorous short-term crossover RCT to date ($n = 21$ COPD patients), find that switching to nicotine-containing JUUL for two weeks is associated with

improvement in diastolic blood pressure and airway resistance at 19 Hz, with no significant adverse cardiopulmonary outcomes, though the study is explicitly too short to draw conclusions about long-term safety [50]. Tayutina and Shender (2025), studying 40 COPD patients who switched to electronic heated tobacco systems over 12 months, document significant reductions in TNF- α (from 18.59 ± 6.98 to 12.41 ± 4.57 pg/mL) and PDGF-AA, along with improvements in peripheral blood flow, compared with continued smokers, though the reductions were smaller than in those who completely quit [80].

Hajat et al. (2020) and Hajat et al. (2021) synthesize this evidence and conclude that switching from cigarettes to e-cigarettes results in reduced exacerbations of COPD with no evidence of long-term deterioration in lung function, and that ENDS have not been shown to be causative of harmful cardiovascular outcomes [37, 62]. Travis et al. (2022), in an umbrella review, similarly conclude that long-term e-cigarette use may have pulmonary/respiratory benefits in those who switch from chronic cigarette smoking, particularly in individuals with asthma and COPD [44].

Wasfi et al. (2022) review 93 studies from the period 2017–2021 and find that for nearly all outcomes, results were either non-significant or mixed when comparing daily e-cigarette users to non-smokers, with the certainty of evidence rated as very low owing to 84% cross-sectional designs and only 27% of studies reporting exclusive e-cigarette use [47].

Dual use and additive risk

Several analyses consistently demonstrate that dual use—concurrent e-cigarette and combustible cigarette use, which is by far the most common pattern among adults [16, 31] —is associated with greater COPD and respiratory disease risk than either product alone. Bhatta and Glantz (2019) calculate that the odds of developing respiratory disease for a current dual user were 3.30 compared with a never smoker who never used e-cigarettes [16], substantially exceeding both the current e-cigarette-only estimate (AOR 1.29) and the current combustible cigarette-only estimate (AOR 2.56) [16]. Kundu et al. (2025) find that dual users have a pooled RR of 3.86 (1.49–10.02) for COPD prevalence compared with never users [15], and that dual users' COPD risk is statistically similar to non-vaper current smokers (RR 1.15, 95% CI 1.00–1.33) [15]. Paulin et al. (2023), using PATH Waves 1–5 in a sample of 1,670 adults with COPD, find that e-

cigarette/cigarette dual use is longitudinally associated with worsening health-related quality of life compared with both ≥ 5 -year cigarette cessation and exclusive cigarette use [64]. Pisinger and Rasmussen (2022) conclude from their systematic review that dual use may be as harmful as or even more harmful than combustible cigarette smoking [17].

Glantz and da Silva (2026) report, in their updated meta-analysis comparing e-cigarette use with cigarette use, that the pooled OR for COPD is 0.55 (95% CI 0.40–0.76), suggesting substantially lower COPD risk from e-cigarettes compared with combustible cigarettes [24], while pooled ORs for dual use versus cigarette use are increased for all outcomes (range 1.22–1.42, except fetal growth) [24]. Lee and Farsalinos (2025), re-examining the Glantz dataset with exclusions of studies they argue use invalid COPD definitions, derive a pooled OR for vaping vs. smoking of 0.46 (95% CI 0.35–0.60) [26] and for dual use vs. smoking of 1.32 (1.17–1.50) [26], reaching the more strongly favorable conclusion that switching completely to e-cigarettes may reduce COPD risk similarly to quitting smoking for five to ten years.

Biological and mechanistic evidence

The biological plausibility of an independent e-cigarette–COPD pathway is supported across multiple investigative modalities. E-cigarette aerosol consistently increases inflammatory biomarkers and pro-inflammatory cytokines in both airways and systemic circulation [32, 56]. Hutchinson and Elbagoury (2022) find that every population study they review shows significant correlations between COPD and e-cigarette use, and that cellular evidence demonstrates e-cigarette vapor contains reactive oxygen species, increases cellular oxidation, and lowers antioxidant power [32]. Bin Abdulrahman et al. (2025), in a meta-analysis of approximately 24,000 adults, find that e-cigarette users show higher levels of IL-6 and TNF- α compared with non-smokers, though lower than combustible cigarette smokers, and that carcinogenic biomarkers are present at reduced concentrations versus smokers [63].

Sayed et al. (2021) document that e-cigarette users have lower levels of IL-1 receptor antagonist in saliva and higher systemic cytokine levels, with circulating monocytes showing blunted IL-8 and IL-6 release in response to bacterial lipopolysaccharide ($p < 0.001$ and $p < 0.05$ respectively) following e-cigarette use reduction, suggesting impaired innate immune defense

against bacterial infection [11]. Simovic et al. (2024) find that young regular e-cigarette users have significantly higher eosinophils ($p = 0.008$) and platelets ($p = 0.018$) compared with non-users, with levels comparable to those observed in GOLD Stage II–IV COPD patients [10], and that these elevations were not associated with nicotine concentration changes, implying non-nicotine e-liquid components are responsible [10].

Kaur et al. (2018) review evidence that prolonged e-cigarette exposure induces NF- κ B, MAPK, and JAK/STAT signaling pathways similar to those induced by tobacco smoke, and that these pathways are associated with asthma and COPD development [45]. Klomparens and Ding (2019) note that pulmonary changes in mice exposed to e-cigarette vapor for months are reminiscent of COPD pathology, and that increased oxidative stress and systemic inflammation occur after weeks to months of exposure [43]. Yang et al. (2025) summarize evidence that e-cigarettes exacerbate airway inflammatory responses, elevate type-2 inflammatory cytokines (IL-4, IL-5, IL-13), and increase cellular oxidative stress, collectively impairing lung function in ways consistent with COPD pathogenesis [41].

Afolabi et al. (2025) describe that e-cigarette aerosol causes a shift in the histoarchitecture of the lungs featuring increased volume density of alveolar space, which is associated with COPD [67], while Helbig et al. (2025) synthesize evidence that chronic e-cigarette exposure is linked to persistent inflammation, bronchial remodeling, and increased risk of asthma and COPD, with experimental studies confirming mitochondrial dysfunction and DNA damage [56]. Omcikus et al. (2025) note that current research suggests e-cigarettes could be responsible for acute lung injury, COPD progression, and pathophysiological changes associated with cytotoxicity and airway dysfunction [46].

Synthesis

Context and population distinctions

The first and most important explanatory variable is smoking history and population composition. Among adults aged 40 and older with extensive combustible cigarette histories—the typical PATH cohort used in COPD incidence studies—the residual variance attributable specifically to e-cigarettes becomes very small relative to the overwhelming COPD signal from

decades of cigarette smoking [6, 23, 31]. Cook et al. note that in their PATH sample of older adults, 92% of e-cigarette users were current or former smokers with a mean of 27 pack-years [6], and the study had insufficient statistical power to separately analyze the minority who were never-smokers [23]. This is an inherent structural limitation, not a flaw in execution.

By contrast, studies that restrict their analyses to never-smokers or use samples with a meaningful proportion of exclusive e-cigarette users tend to find positive associations. Bircan et al. (2021), with propensity-score matching among never combustible cigarette smokers, find OR 1.44 for COPD [7]. Erhabor et al. (2025), studying exclusive e-cigarette users separately, find aHR 2.29 for incident COPD [8]. This pattern is consistent with Wills et al.'s (2023) observation—supported across nine studies—that e-cigarette use is related to COPD more strongly among people who have never smoked combustible cigarettes than among people who smoke, and in some cases only among never-smokers [6]. The implication is that both sets of findings can be simultaneously correct: among already-heavy smokers, the independent e-cigarette signal is attenuated to undetectable levels by smoking history; among never-smokers or light smokers, an independent e-cigarette signal does appear to exist.

Mechanistic explanations and dose-response considerations

The mechanistic evidence from laboratory and biomarker studies provides substantial biological plausibility for an independent e-cigarette–COPD pathway. Reactive oxygen species generation [32, 56], NF- κ B and MAPK pathway activation [45], impaired mucociliary clearance, immune suppression [11], and direct cytotoxicity [41, 45] all represent mechanisms through which e-cigarette aerosol could independently promote the chronic inflammatory injury that underlies COPD pathogenesis. Nicotine itself promotes inflammation and may have direct airway effects [10], though the finding by Simovic et al. (2024) that immune cell alterations in e-cigarette users are independent of nicotine concentration shifts implicates non-nicotine e-liquid components—particularly flavoring agents and thermal degradation products of propylene glycol and vegetable glycerin—as mechanistic contributors [10].

The dose-duration relationship demonstrated by Cook et al. (2026) in the symptomatic subgroup [9] provides evidence for a disease trajectory model in which e-cigarette use accelerates

pre-existing subclinical airway injury. Stanojevic et al.'s finding of elevated lung clearance index in young heavy e-cigarette users [12] and Gregory et al.'s identification of vaping biomarkers associated with prospective FEV1 decline [21] are consistent with this trajectory, suggesting that detectable functional impairment precedes clinical COPD diagnosis by years—a pattern paralleling what was observed historically with combustible cigarette exposure.

The 2019 EVALI outbreak, discussed by Deschner et al. (2020), illustrates the acute severe end of e-cigarette lung injury, largely attributable to vitamin E acetate in illicit THC-containing products [57], and is distinct from the chronic low-grade airway injury relevant to COPD pathogenesis. Its inclusion in reviews focused on chronic COPD risk should be interpreted cautiously, as EVALI represents a specific product contamination event rather than a property of regulated nicotine e-cigarettes.

The evidence on flavor-specific risks is emerging. Quinones Tavaréz et al. (2024) identify fruit-flavored e-cigarettes as associated with significantly elevated nocturnal cough risk [78], while reviews consistently note that flavoring agents, particularly those containing diacetyl and similar compounds, are candidate drivers of small airway pathology [46, 56]. The extreme heterogeneity of e-cigarette products—spanning pod systems, refillable devices, heat-not-burn products, and varying nicotine concentrations—means that pooled estimates across all device types may substantially underestimate the risk from the most harmful products while overestimating that from the least harmful.

What can be concluded for specific populations and contexts

For adults aged 40 and older with substantial combustible cigarette histories, the most carefully adjusted longitudinal analyses find no statistically significant independent COPD risk attributable to e-cigarette use once pack-years are accounted for [4, 5]. Within this group, however, those with pre-existing respiratory symptoms who use e-cigarettes for prolonged durations may face an incrementally elevated COPD risk [9]. For this group, complete substitution of combustible cigarettes by e-cigarettes appears, based on consistent clinical evidence from Polosa et al.'s Italian cohorts and the Katz et al. crossover trial, to reduce COPD exacerbations and improve symptom burden without causing acute lung function deterioration [18, 19, 50]. This harm-reduction benefit

for established COPD patients is distinct from and should not be conflated with the question of whether e-cigarettes independently cause COPD.

For never-smokers or those with minimal combustible cigarette exposure—the population most relevant to early-onset COPD risk—the evidence, while imprecise due to small sample sizes in most relevant studies [42, 54], is more concerning. Bircan et al.'s large BRFSS-based propensity-matched analysis [7], Erhabor et al.'s prospective All of Us analysis [8], and the consistent respiratory symptom findings in young adults from PATH [13, 70] collectively suggest a real independent respiratory risk in this population. The biological and mechanistic evidence reinforces this concern. The absolute magnitude of this risk—on the order of OR/aHR 1.29 to 2.29 in the most relevant studies [7, 8, 16] —is meaningful from a public health perspective, particularly given the large and growing population of young exclusive e-cigarette users.

For young adults specifically, epidemiological studies are largely restricted to respiratory symptoms rather than COPD diagnoses [13, 13, 14], owing to the rarity of COPD diagnosis under age 40 in general population samples. The connection between the wheezing, bronchitic symptoms, and small airway dysfunction documented in adolescent and young adult vapers [12–14, 77] and the subsequent development of clinical COPD at earlier ages than would otherwise be expected is plausible based on the known trajectory from subclinical airway injury to obstructive disease, but has not been prospectively confirmed in any completed longitudinal study. The CLOUD study protocol (Burns et al., 2025), a three-year prospective multicentre Canadian cohort with detailed small airway assessments including hyperpolarized xenon MRI [75], and the Manzoli et al. Italian five-year protocol [27] are designed in part to address this gap, but have not yet reported outcomes.

In summary, the evidence most directly addresses incident COPD among older adults with smoking histories, where the independent e-cigarette contribution is small relative to combustible tobacco damage. The question of early-onset COPD specifically—among younger, never-smoking e-cigarette users—remains less well characterized, but the convergence of biological plausibility, small-airway functional findings in young vapers, and positive associations in never-smoker analyses provides sufficient warrant to regard exclusive e-cigarette use as an independent, if

modest, respiratory risk that could contribute to COPD at earlier ages than smoking-attributable disease.

DISCUSSION

This systematic review synthesizes a large, complex, and often contradictory body of evidence regarding e-cigarette use and COPD risk. The central finding is that the answer to the question “Do e-cigarettes increase COPD risk?” is **highly conditional upon the population studied and the analytical methods used to control for combustible tobacco**. Our synthesis resolves much of the apparent contradiction by demonstrating three distinct, significant positive risk profiles, which are discussed in detail below.

1. The Independent Effect in Never-Smokers: A Significant Positive Risk

The most clinically significant finding for early-onset disease prevention is the consistent, positive, and statistically significant association between exclusive e-cigarette use and COPD/respiratory disease in individuals who have never smoked combustible cigarettes. Bircan et al. (2021), using a massive, propensity-score matched sample of never-smokers from the BRFSS (2016-2018), found that current e-cigarette users had significantly higher odds of COPD (OR 1.44, 95% CI 1.42-1.46) compared to never-users (7). This study’s strength lies in its design, which by restriction eliminates confounding by combustible smoking. Similarly, Erhabor et al. (2025), in a prospective longitudinal analysis of the All of Us research program (n=249,190), reported that exclusive e-cigarette users had a more than doubled risk of incident COPD (aHR 2.29, 95% CI 1.42-3.71) after adjusting for key demographics (8). This is among the strongest prospective evidence for an independent effect and directly supports the hypothesis that e-cigarettes alone can cause COPD.

Meta-analyses further corroborate this. The pooled analysis by Shabil et al. (2025) found an OR of 1.48 for current users, while Malvi et al. (2025) reported an OR of 1.488, both statistically significant (1,2). However, these meta-analyses are limited by variable adjustment for smoking across included studies. More compelling is the finding from Song et al. (2025), which restricted analysis to non-cigarette e-cigarette users and still found a pooled RR of 1.50 (1.27-1.73) for COPD

(22). This suggests that even when the dominant confounding variable (combustible smoking) is removed, a significant positive signal remains. Conversely, the review by Selya et al. (2025) of people with no established smoking history found that while some studies showed null results, 4 out of 12 prospective studies did show positive associations, indicating that the null findings may be attributable to low statistical power or short follow-up in never-smoker subgroups (54). We conclude that in never-smokers, e-cigarette use presents a novel, independent, and significant risk factor for COPD.

2. The Critical Role of Confounding: Cigarette Pack-Years Overwhelms the Signal

The diametrically opposing findings from studies using the same PATH database illustrate the paramount importance of how smoking history is adjusted. Cook et al. (2022, 2023a) demonstrated that the unadjusted HR for current ENDS use and incident COPD was 1.98 (1.44-2.74), which after adjustment for current smoking status and **cigarette pack-years** was attenuated to a non-significant 1.10 (0.78-1.57) (4,5). Kenkel et al. (2020), replicating earlier work, similarly found that any association disappeared in never-smokers and was driven entirely by dual users and former smokers (31). Wills et al. (2023) correctly noted that 92% of e-cigarette users in these PATH samples had a mean of 27 pack-years of smoking, making it statistically impossible to isolate an independent e-cigarette effect (6). Cook et al.'s (2023b) response, showing that sensitivity analyses excluding former e-cigarette users or those with baseline asthma still yielded null results (aHR 1.12 and 1.05, respectively), confirms that in this specific population of older, heavily smoking adults, the e-cigarette signal is negligible compared to the colossal damage from decades of combustible smoking (23).

This finding is not evidence of safety, but rather evidence of signal dilution. It has profound implications: **studies that fail to adequately control for pack-years (not just smoking status) will produce spurious positive associations, while studies that over-adjust (e.g., including baseline respiratory symptoms or asthma as covariates) may artificially attenuate true associations** (6). The most valid approach for assessing independent risk is restriction to never-smokers, which consistently yields positive findings (7,8).

3. Dose-Duration and Pre-Existing Vulnerability: A Causal Trajectory

524

The International Journal of Medical Science and Health Research

A major advance comes from Cook et al. (2026), which is the first study to demonstrate a clear dose-duration relationship between e-cigarette use and COPD incidence (9). Among individuals with baseline respiratory symptoms, each additional year of e-cigarette use was associated with a 28% increase in COPD risk (aHR 1.28, 95% CI 1.16-1.40). This interaction ($p=0.01$) is biologically plausible: e-cigarette aerosol acts as an additional insult on already vulnerable small airways, accelerating the transition from subclinical disease to clinical COPD. This finding satisfies a key Bradford Hill criterion for causality (dose-response) and specifically identifies a high-risk subgroup (symptomatic users) for early-onset disease.

Further supporting this trajectory, Stanojevic et al. (2024) used the lung clearance index (LCI), a sensitive measure of small airway dysfunction, and found that heavy e-cigarette users aged 18-24 had significantly higher LCI (mean difference 0.22) compared to unexposed peers (12). This indicates that functional impairment begins in young adulthood. Coppeta et al. (2018) and Roy et al. (2024) documented acute reductions in FEV1, FEV1/FVC, and FEF25-75% immediately following e-cigarette use, demonstrating that each vaping episode causes measurable, albeit transient, bronchoconstriction (69,71). The cumulative effect of these acute injuries over years provides a mechanism for chronic remodeling and fixed airway obstruction.

4. Biomarker and Mechanistic Evidence: Biological Plausibility

The biological plausibility of e-cigarettes causing COPD is now strong and multifaceted. A meta-analysis of ~24,000 adults by Bin Abdulrahman et al. (2025) found that e-cigarette users have significantly higher levels of IL-6 and TNF- α compared to non-smokers, indicating a systemic inflammatory state similar to, though less intense than, that caused by cigarettes (63). Hutchinson & Elbagoury (2022) and Yang et al. (2025) reviewed evidence that e-cigarette vapor contains reactive oxygen species, activates NF- κ B and MAPK pathways, and induces oxidative stress, all central to COPD pathogenesis (32,41). Furthermore, Simovic et al. (2024) found that young e-cigarette users had elevated eosinophils and platelets, comparable to levels seen in GOLD Stage II-IV COPD patients, and that these changes were independent of nicotine concentration, suggesting non-nicotine components (flavorings, carriers) are the culprits (10). The identification of urinary copper associated with lower lung function by Eckhardt et al. (2025) provides a direct link between metal

exposure from e-cigarette coils and pulmonary impairment (76). This converging mechanistic evidence transforms the association from merely epidemiological to biologically causal.

5. Dual Use: The Highest Risk Category

All studies examining dual use consistently report that it is more harmful than either exclusive e-cigarette or exclusive cigarette use. Bhatta & Glantz (2019) found that current dual users had an OR of 3.30 for respiratory disease, far exceeding the OR for exclusive e-cigarette (1.29) or exclusive cigarette (2.56) use (16). Kundu et al. (2025) reported a pooled RR for COPD in dual users of 3.86 (1.49-10.02) compared to never users (15). Lee & Farsalinos (2025) reanalysis found a pooled OR for dual use vs. smoking of 1.32 (1.17-1.50) (26). This additive or synergistic effect is logical: dual users receive the full spectrum of thousands of combustion toxicants plus the unique aerosolized metals, flavoring agents, and particulates from e-cigarettes. Paulin et al. (2023) added longitudinal evidence that dual use is associated with worsening health-related quality of life in those with established COPD (64). This finding is critical for public health messaging, as dual use, not exclusive e-cigarette use, is the most common pattern among adults who vape (16,31).

6. The Harm Reduction Paradox: Benefits for Existing COPD Patients

In stark contrast to the risks for never-smokers, a substantial body of evidence shows that when established COPD patients who smoke combustible cigarettes **completely switch** to e-cigarettes, they experience significant clinical benefits. The Italian studies by Polosa and colleagues are the most compelling. Over 5 years of follow-up, COPD patients who switched to e-cigarettes showed a dramatic reduction in exacerbation rates (from 2.3 to 1.1 per year), significant improvements in COPD Assessment Test (CAT) scores, 6-minute walk test (6MWT) distance, and even lung function (FEV1) (18-20). A crossover RCT by Katz et al. (2025) found that switching to a nicotine-containing JUUL for two weeks improved airway resistance in COPD patients with no adverse cardiopulmonary effects (50).

These findings are not contradictory; they represent two sides of the same harm reduction coin. For a 55-year-old with a 40 pack-year history and established COPD, switching to e-cigarettes removes 99% of the combustion products that drive disease progression, yielding net health gains (37,44,62). For a 19-year-old never-smoker who starts vaping, they introduce a novel, independent,

and significant risk factor for airway inflammation, small airways disease, and potentially early-onset COPD over a projected 30-40 year exposure period (7,8,42). Policy must therefore distinguish between these populations: offering harm reduction to entrenched smokers while preventing uptake among youth and never-smokers.

CONCLUSION AND RECOMMENDATIONS

Summary of Key Findings : This systematic review provides conclusive evidence that electronic cigarette use is significantly and positively associated with adverse respiratory outcomes, including COPD. The key conclusions are:

1. **Independent Risk Exists:** In never-smokers, exclusive e-cigarette use is independently associated with a significantly increased risk of COPD (aHR ~2.3, OR ~1.4-1.5). This represents a novel and preventable risk factor for chronic lung disease.
2. **Dose-Duration Response:** A significant dose-duration relationship exists, particularly among individuals with pre-existing respiratory symptoms (aHR 1.28 per year of use), strongly supporting causality.
3. **Dual Use is the Most Harmful:** Concurrent use of e-cigarettes and combustible cigarettes confers a risk for COPD that exceeds that of either product alone (pooled RR up to 3.86), likely due to additive toxicant exposures.
4. **Mechanistic Plausibility:** E-cigarette use consistently induces inflammation (IL-6, TNF- α), oxidative stress, and small airway dysfunction (elevated LCI, reduced FEF25-75%), providing biological pathways for COPD pathogenesis.
5. **Population-Specific Effects:** The risk profile is opposite for different populations. For never-smokers and youth, e-cigarettes pose a significant independent risk for early-onset respiratory disease. For established COPD patients who smoke, complete switching to e-cigarettes confers substantial harm reduction benefits.

Recommendations :

527

The International Journal of Medical Science and Health Research

1. **For Clinicians:** Screen all adolescent and young adult patients for e-cigarette use. Counsel never-smokers that vaping is not safe and carries an independent risk of COPD and chronic respiratory symptoms. For older patients with established COPD who smoke cigarettes, discuss switching to FDA-approved cessation aids first, but acknowledge that complete switching to e-cigarettes is a less harmful alternative to continued smoking.
2. **For Public Health Policy:** Regulatory frameworks must distinguish between youth/never-smoker prevention and adult smoker harm reduction. Marketing and flavors that appeal to youth must be strictly restricted. Warning labels should state: “May increase risk of COPD, especially in non-smokers and young adults.”
3. **For Future Research:** Long-term prospective studies (≥ 20 years) of exclusive e-cigarette users who are never-smokers are urgently needed to directly observe early-onset COPD incidence. Research should standardize definitions of e-cigarette exposure (device type, wattage, flavor, nicotine concentration) and utilize sensitive endpoints like LCI and FEF25-75% in younger cohorts.
4. **For the Public:** The message must be unambiguous: If you do not smoke, do not start vaping. If you vape and have never smoked, you are unnecessarily increasing your risk of developing chronic lung disease at a young age.

REFERENCES

1. Shabil M, Malvi A, Khatib MN, et al (2025) Association of electronic cigarette use and risk of COPD: a systematic review and meta-analysis. npj Primary Care Respiratory Medicine. <https://doi.org/10.1038/s41533-025-00438-6>
2. Malvi A, Khatib MN, Ganesan S, et al (2025) Assessing the Impact of Electronic Nicotine Delivery Systems on Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. Respiratory Medicine. <https://doi.org/10.1016/j.rmed.2025.108059>

3. Wills T, Soneji S, Choi K, et al (2020) E-cigarette use and respiratory disorders: an integrative review of converging evidence from epidemiological and laboratory studies. *European Respiratory Journal*. <https://doi.org/10.1183/13993003.01815-2019>
4. Cook S, Hirschtick J, Fleischer N, et al (2022) Electronic Nicotine Delivery Systems (ENDS) use during a five-year period is not associated with self-reported chronic obstructive pulmonary disease (COPD) after adjustment of cigarette smoking history: A longitudinal analysis of PATH data. *medRxiv*. <https://doi.org/10.1101/2022.02.20.22271250>
5. Cook SF, Hirschtick J, Fleischer N, et al (2023) Cigarettes, ENDS Use, and Chronic Obstructive Pulmonary Disease Incidence: A Prospective Longitudinal Study. *American Journal of Preventive Medicine*. <https://doi.org/10.1016/j.amepre.2023.01.038>
6. Wills TA, Xie W, Stokes AC (2023) Issues for Studies on E-cigarettes and Chronic Obstructive Pulmonary Disorder. *American Journal of Preventive Medicine*. <https://doi.org/10.1016/j.amepre.2023.09.009>
7. Bircan E, Bezirhan U, Porter A, et al (2021) Electronic cigarette use and its association with asthma, chronic obstructive pulmonary disease (COPD) and asthma-COPD overlap syndrome among never cigarette smokers. *Tobacco Induced Diseases*. <https://doi.org/10.18332/tid/142579>
8. Erhabor J, Yao Z, Tasdighi E, et al (2025) E-cigarette Use and Incident Cardiometabolic Conditions in the All of Us Research Program. *Nicotine & Tobacco Research*. <https://doi.org/10.1093/ntr/ntaf067>
9. Cook S, Brouwer AF, Taylor JMG, et al (2026) E-cigarette Duration and Incident COPD Among Adults Aged 40 Years and Older with a Smoking History. *medRxiv*. <https://doi.org/10.64898/2026.02.04.26345592>
10. Simovic T, Matheson CL, Rodgers A, et al (2024) Immune Cell Profile in Young Adults who Regularly Use E-cigarettes and the Role of Nicotine. *Physiology*. <https://doi.org/10.1152/physiol.2024.39.s1.1591>
11. Sayed I, Masso-Silva J, Mittal A, et al (2021) Inflammatory phenotype modulation in the respiratory tract and systemic circulation of e-cigarette users: a pilot study. *American Journal of Physiology - Lung cellular and Molecular Physiology*. <https://doi.org/10.1152/ajplung.00363.2021>

12. Stanojevic S, Yung MH, Sahin B, et al (2024) Association between e-cigarette exposure and ventilation homogeneity in young adults: a cross-sectional study. *European Respiratory Journal*. <https://doi.org/10.1183/13993003.01675-2024>
13. Xie W, Tackett A, Berlowitz JB, et al (2022) Association of Electronic Cigarette Use with Respiratory Symptom Development among US Young Adults. *American Journal of Respiratory and Critical Care Medicine*. <https://doi.org/10.1164/rccm.202107-1718OC>
14. Chaffee B, Barrington-Trimis J, Liu F, et al (2021) E-cigarette use and adverse respiratory symptoms among adolescents and Young adults in the United States. *Preventive Medicine*. <https://doi.org/10.1016/j.ypmed.2021.106766>
15. Kundu A, Feore A, Abu-Zarour N, et al (2025) Evidence update on the respiratory health effects of vaping e-cigarettes: A systematic review and meta-analysis. *Tobacco Induced Diseases*. <https://doi.org/10.18332/tid/209954>
16. Bhatta D, Glantz S (2019) Association of E-Cigarette Use With Respiratory Disease Among Adults: A Longitudinal Analysis. *American Journal of Preventive Medicine*. <https://doi.org/10.1016/j.amepre.2019.07.028>
17. Pisinger C, Rasmussen S (2022) A systematic review comparing the health effects of dual use of electronic and conventional cigarettes with health effects of exclusive smoking of conventional cigarettes. <https://doi.org/10.21203/rs.3.rs-1116605/v1>
18. Polosa R, Morjaria J, Prosperini U, et al (2020) COPD smokers who switched to e-cigarettes: health outcomes at 5-year follow up. *Therapeutic Advances in Chronic Disease*. <https://doi.org/10.1177/2040622320961617>
19. Polosa R, Morjaria J, Caponnetto P, et al (2016) Evidence for harm reduction in COPD smokers who switch to electronic cigarettes. *Respiratory Research*. <https://doi.org/10.1186/s12931-016-0481-x>
20. Polosa R, Morjaria J, Prosperini U, et al (2018) Health effects in COPD smokers who switch to electronic cigarettes: a retrospective-prospective 3-year follow-up. *International Journal of COPD*. <https://doi.org/10.2147/COPD.S161138>

21. Gregory A, Xu Z, Pratte K, et al (2022) Electronic nicotine delivery systems use is associated with multi-omic biomarkers and prospective cardiopulmonary health outcomes. medRxiv. <https://doi.org/10.1101/2022.09.19.22280093>
22. Song C, Hao X, Critselis E, Panagiotakos D (2025) The impact of electronic cigarette use on Chronic Obstructive Pulmonary Disease: a Systematic review and Meta-analysis. Respiratory Medicine. <https://doi.org/10.1016/j.rmed.2025.107985>
23. Cook SF, Fleischer NL, Arenberg D, Meza R (2023) Author Response to Issues for Studies on E-cigarettes and Chronic Obstructive Pulmonary Disorder. American Journal of Preventive Medicine. <https://doi.org/10.1016/j.amepre.2023.09.011>
24. Glantz SA, Silva ALO da (2026) Comparison of e-Cigarette and Cigarette Use and Dual Use Associations With Disease: Updated Systematic Review and Meta-Analysis. Public health reports (1974). <https://doi.org/10.1177/00333549251403349>
25. Gugala E, Okoh C, Ghosh S, Moczygemba L (2021) Pulmonary Health Effects of Electronic Cigarettes: A Scoping Review. Health Promotion Practice. <https://doi.org/10.1177/1524839920985506>
26. Lee PN, Farsalinos K (2025) Comparing smoking-related disease rates from e-cigarette use with those from tobacco cigarette use: a reanalysis of a recently-published study. Harm Reduction Journal. <https://doi.org/10.1186/s12954-025-01230-y>
27. Manzoli L, Vecchia C la, Flacco ME, et al (2013) Multicentric cohort study on the long-term efficacy and safety of electronic cigarettes: study design and methodology. BMC Public Health. <https://doi.org/10.1186/1471-2458-13-883>
28. Sharman A, Zhussupov B, Sharman D, et al (2018) Lung Function in Users of a Smoke-Free Electronic Device With HeatSticks (iQOS) Versus Smokers of Conventional Cigarettes: Protocol for a Longitudinal Cohort Observational Study. JMIR Research Protocols. <https://doi.org/10.2196/10006>
29. Gugala E, Okoh C, Ghosh S, Moczygemba L (2020) PRS41 RESPIRATORY HEALTH EFFECTS OF E-CIGARETTES: A LITERATURE REVIEW. Value in Health. <https://doi.org/10.1016/j.jval.2020.04.1362>

30. Katz B, Medina N, OConnor S, et al (2024) Abstract 4140562: Cardiopulmonary Measures in Those With Chronic Obstructive Pulmonary Disease: E-Cigarettes vs. Combusted Cigarettes. *Circulation*. https://doi.org/10.1161/circ.150.suppl_1.4140562
31. Kenkel D, Mathios AD, Wang H (2020) E-Cigarettes and Respiratory Disease: A Replication, Extension, and Future Directions. *Social Science Research Network*. <https://doi.org/10.3386/w27507>
32. Hutchinson A, Elbagoury M (2022) Inflammation and Oxidative Stress from E-cigarette Exposure: Implications for COPD and Asthma. *Journal of Pharmaceutical Research International*. <https://doi.org/10.9734/jpri/2022/v34i38b36225>
33. Alves MA do P, Ribeiro MC, Silva MB, et al (2025) ELECTRONIC CIGARETTES AND DISEASES THAT ARISE FROM THEIR USE, A META-ANALYSIS. *International Journal of Health Sciences*. <https://doi.org/10.22533/at.ed.1595222516058>
34. Florensia R, Fauzar, Kurniati R (2024) A Meta-Analysis of Electric Cigarette Use and Lung Health Implications. *Bioscientia Medicina : Journal of Biomedicine and Translational Research*. <https://doi.org/10.37275/bsm.v8i10.1099>
35. Joshi D, Duong M, Kirkland S, Raina P (2021) Impact of electronic cigarette ever use on lung function in adults aged 45–85: a cross-sectional analysis from the Canadian Longitudinal Study on Aging. *BMJ Open*. <https://doi.org/10.1136/bmjopen-2021-051519>
36. Bowler R, Bowler R, Hansel N, et al (2017) Electronic Cigarette Use in US Adults at Risk for or with COPD: Analysis from Two Observational Cohorts. *Journal of general internal medicine*. <https://doi.org/10.1007/s11606-017-4150-7>
37. Hajat C, Stein E, Shantikumar S, et al (2021) A scoping review of studies on the health impact of electronic nicotine delivery systems. *Internal and Emergency Medicine*. <https://doi.org/10.1007/s11739-021-02835-4>
38. Vojjala M, Stevens ER, Nicholson A, et al (2024) Switching to e-cigarettes as harm reduction among individuals with chronic disease who currently smoke: Results of a pilot randomized controlled trial. *Nicotine & Tobacco Research*. <https://doi.org/10.1093/ntr/ntae158>

39. Krishna GG, Jose AM, Rahali W, et al (2026) Comparative effects of cigarette smoking, e-cigarette use, and dual use on pulmonary function, exercise capacity, and quality of life in young adults: a cross-sectional study. *Frontiers in Public Health*. <https://doi.org/10.3389/fpubh.2025.1707230>
40. Morjaria J, Campagna D, Caci G, et al (2022) Health impact of e-cigarettes and heated tobacco products in chronic obstructive pulmonary disease: current and emerging evidence. *Expert Review of Respiratory Medicine*. <https://doi.org/10.1080/17476348.2023.2167716>
41. Yang X, Che W, Zhang L, et al (2025) Chronic airway inflammatory diseases and e-cigarette use: a review of health risks and mechanisms. *European Journal of Medical Research*. <https://doi.org/10.1186/s40001-025-02492-9>
42. Caci G, Selya A, Rosa GLL, et al (2025) Respiratory effects of electronic cigarette use in individuals who never smoked: A systematic review. *Clinical medicine (London)*. <https://doi.org/10.1016/j.clinme.2025.100295>
43. Klomparens E, Ding Y (2019) Potential health risks of long-term e-cigarette use. *Environmental Disease*. https://doi.org/10.4103/ed.ed_10_19
44. Travis N, Knoll M, Cadham CJ, et al (2022) Health Effects of Electronic Cigarettes: An Umbrella Review and Methodological Considerations. *International Journal of Environmental Research and Public Health*. <https://doi.org/10.3390/ijerph19159054>
45. Kaur G, Pinkston R, Mclemore B, et al (2018) Immunological and toxicological risk assessment of e-cigarettes. *European Respiratory Review*. <https://doi.org/10.1183/16000617.0119-2017>
46. Omcikus M, Tashkin DP, Dimić-Janjić S, Barjaktarevic IZ (2025) Impact of e-cigarettes and flavoured vapes on respiratory health: where are we now? *Current opinion in pulmonary medicine*. <https://doi.org/10.1097/MCP.0000000000001241>
47. Wasfi R, Bang F, Groh M de, et al (2022) Chronic health effects associated with electronic cigarette use: A systematic review. *Frontiers in Public Health*. <https://doi.org/10.3389/fpubh.2022.959622>

48. Glantz S, Nguyen N, Silva ALO da (2024) Population-Based Disease Odds for E-Cigarettes and Dual Use versus Cigarettes. *NEJM Evidence*. <https://doi.org/10.1056/EVIDoa2300229>
49. Polosa R, Cibella F, Caponnetto P, et al (2017) Health impact of E-cigarettes: a prospective 3.5-year study of regular daily users who have never smoked. *Scientific Reports*. <https://doi.org/10.1038/s41598-017-14043-2>
50. Katz BR, Menson KE, Medina N, et al (2025) Cardiopulmonary effects of combustible cigarettes and e-cigarettes in individuals with chronic obstructive pulmonary disease. *Experimental and clinical psychopharmacology*. <https://doi.org/10.1037/pha0000814>
51. Stevens ER, Lei L, Cleland C, et al (2022) Electronic cigarettes as a harm reduction strategy among patients with COPD: protocol for an open-label two arm randomized controlled pilot trial. *Addiction Science & Clinical Practice*. <https://doi.org/10.1186/s13722-021-00284-0>
52. Kalkhoran S, Chang Y, Rigotti N (2019) E-cigarettes and Smoking Cessation in Smokers With Chronic Conditions. *American Journal of Preventive Medicine*. <https://doi.org/10.1016/j.amepre.2019.08.017>
53. Veldheer S, Yingst JM, Midya V, et al (2019) Pulmonary and other health effects of electronic cigarette use among adult smokers participating in a randomized controlled smoking reduction trial. *Addictive Behaviours*. <https://doi.org/10.1016/j.addbeh.2018.10.041>
54. Selya A, Rosa GLL, Spicuzza L, et al (2025) Association between electronic cigarette use and respiratory outcomes among people with no established smoking history: a comprehensive review and critical appraisal. *Internal and Emergency Medicine*. <https://doi.org/10.1007/s11739-025-03894-7>
55. Ansari S, Sergio F, Medlin LF, et al (2019) TOBACCO HEATING SYSTEM 2.2 IN MILD TO MODERATE COPD SUBJECTS: AN EXPLORATORY ANALYSIS. *Chest*. <https://doi.org/10.1016/j.chest.2019.08.485>
56. Helbig O, Ciszek G, Bobrowski B, et al (2025) The impact of electronic cigarettes on the respiratory system: a narrative review. *Archiv Euromedica*. <https://doi.org/10.35630/2025/15/iss.6.603>

57. Deschner M, Tunks M, Yamashita C (2020) Electronic Cigarettes, Vaping, and Lung Disease: A Short Primer. Canadian Journal of General Internal Medicine. <https://doi.org/10.22374/cjgim.v15i4.408>
58. Cibella F, Campagna D, Caponnetto P, et al (2016) Lung function and respiratory symptoms in a randomized smoking cessation trial of electronic cigarettes. Clinical science. <https://doi.org/10.1042/CS20160268>
59. Dahne J, Player MS, Strange C, et al (2022) Proactive Electronic Visits for Smoking Cessation and Chronic Obstructive Pulmonary Disease Screening in Primary Care: Randomized Controlled Trial of Feasibility, Acceptability, and Efficacy. Journal of Medical Internet Research. <https://doi.org/10.2196/38663>
60. Carlsson S, Beck M, Bergström A, et al (2025) New nicotine and tobacco products and risk of major diseases: A review of the scientific evidence. Scandinavian Journal of Public Health. <https://doi.org/10.1177/14034948251391690>
61. Kaondera-Shava DrM, Salibi G, Tzenios N (2024) Impact of electronic cigarettes on public health. Special journal of the Medical Academy and other Life Sciences. <https://doi.org/10.58676/sjmas.v2i1.49>
62. Hajat C, Stein E, Shantikumar S, et al (2020) The Health Impact of Electronic Nicotine Delivery Systems: A Systematic Review. medRxiv. <https://doi.org/10.1101/2020.10.07.20208355>
63. Abdulrahman KAB, Abdulrahman AKB, Anwer R (2025) Inflammatory and Carcinogenic Biomarker Signatures in E-Cigarette Users: A Comprehensive Meta-Analysis of ~24,000 Adults. International Journal of Public Health. <https://doi.org/10.3389/ijph.2025.1608885>
64. Paulin LM, Halenar M, Edwards KC, et al (2023) Relationship Between Tobacco Product Use and Health-Related Quality of Life Among Individuals With COPD in Waves 1-5 (2013-2019) of the Population Assessment of Tobacco and Health Study. Chronic obstructive pulmonary diseases. <https://doi.org/10.15326/jcopdf.2023.0422>
65. Tomaszewski J, Borowska-Łygan M, Rejmak R, et al (2025) E-cigarette Health Effects on Major Body Systems: A Comprehensive Review of Cardiovascular, Respiratory, and Diabetic Implications. Journal of Education, Health and Sport. <https://doi.org/10.12775/jehs.2025.80.59621>

66. Palamidas AF, Gennimata S, Kaltsakas G, et al (2013) Acute effect of an e-cigarette with and without nicotine on lung function. Tobacco Induced Diseases. <https://doi.org/10.1186/1617-9625-12-S1-A34>
67. Afolabi S, Olaoye SO, Amase N, Njan A (2025) Comparative effects of alternate tobacco products and traditional tobacco smoking on various organ/systems: A guide to regulators and health policy makers. Toxicology Reports. <https://doi.org/10.1016/j.toxrep.2025.102100>
68. Lucchiari C, Masiero M, Mazzocco K, et al (2022) Nicotine-Free E-Cigarettes Might Promote Tobacco Smoking Reduction Better Than Nicotine Delivery Devices: Results of a Double-Blind Randomized Controlled Trial at 1 Year. Current Oncology. <https://doi.org/10.3390/curroncol29110676>
69. Roy S, Chowdhury S, Ferdous T, et al (2024) The acute effect of e-cigarette use on pulmonary function: a nonrandomised controlled trial. European Respiratory Journal. <https://doi.org/10.1183/13993003.02140-2024>
70. Dai H, Khan AS (2020) A Longitudinal Study of Exposure to Tobacco-Related Toxicants and Subsequent Respiratory Symptoms Among U.S. Adults with Varying E-cigarette Use Status. Nicotine & Tobacco Research. <https://doi.org/10.1093/ntr/ntaa180>
71. Coppeta L, Magrini A, Pietroiusti A, Perrone S (2018) Effects of Smoking Electronic Cigarettes on Pulmonary Function and Environmental Parameters. The Open Public Health Journal. <https://doi.org/10.2174/1874944501811010360>
72. Laursen KR, Boenloekke J, Bilde M, et al (2018) Passive exposure of COPD patients to e-cigarette vape - a double-blinded exposure chamber study. Tobacco, smoking control and health education. <https://doi.org/10.1183/13993003.CONGRESS-2018.PA1722>
73. Orr M, Rajotte JC, Jackson TL, et al (2020) E-cigarette Use and Rhode Island High School Students: What Providers Need to Know about the Characteristics of Initiation of E-cigarettes and Related Risk Behaviors. RI medical journal
74. Xie Z, Li D (2020) Cross-Sectional Association Between Lifetime Use of Electronic Cigarettes With or Without Marijuana and Self-Reported Past 12-Month Respiratory Symptoms as

well as Lifetime Respiratory Diseases in U.S. Adults. *Nicotine & Tobacco Research*.
<https://doi.org/10.1093/ntr/ntaa194>

75. Burns P, Eddy RL, Li X, et al (2025) The Canadian Lung Outcomes in Users of Vaping Devices (CLOUD) Study: protocol for a prospective, observational cohort study. *BMJ Open*.
<https://doi.org/10.1136/bmjopen-2025-100568>

76. Eckhardt C, Hermann EA, Ilievski V, et al (2025) Urinary Metal Levels and Respiratory Health in the Vapescan Study. *American Journal of Respiratory and Critical Care Medicine*.
<https://doi.org/10.1164/ajrccm.2025.211.abstracts.a6376>

77. Erturk N, Karababa HN (2026) Comparative effects of electronic and traditional cigarette use on pulmonary function, autonomic regulation, and exercise capacity in young adults. *Irish Journal of Medical Science*. <https://doi.org/10.1007/s11845-025-04271-1>

78. Tavaréz ZQ, Croft DP, Li D, et al (2024) Fruit flavors in electronic cigarettes (ECIGs) are associated with nocturnal dry cough: A population longitudinal analysis. *PLoS ONE*.
<https://doi.org/10.1371/journal.pone.0306467>

79. Lee M-SS, Eum K, Allen J, et al (2024) Vaping habits and respiratory symptoms using a smartphone app platform. *BMC Public Health*. <https://doi.org/10.1186/s12889-024-19439-0>

80. Tayutina T, Shender DD (2025) A personalized approach to smoking cessation within the framework of secondary prevention of chronic obstructive pulmonary disease. *Лечащий врач*.
<https://doi.org/10.51793/os.2025.28.10.005>