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Center for the Assessment of Tobacco Regulations [CAsToR]

Health Effects of Electronic Cigarettes: an Umbrella Review and Methodological Considerations

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Conflicts of Interest

- **All authors have no competing interests to declare.**
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Goals

- To develop parameters for modeling, but required expertise beyond of our capabilities
- Expert elicitation also ruled, primarily due to concerns about the conflictual nature of the issues

Outline

- Aim of present work
- Methods used to conduct the umbrella review
- Results of the literature search in databases
- Key findings of the literature synthesis
- Methodological limitations of existing systematic reviews
- Limitations of the umbrella review
- Conclusions
- Recommendations for future research

Paper recently published in IJERPH

Aim of the Umbrella Review

- To summarize the evidence of e-cigarette (ECs) health effects from existing systematic reviews:
  - include cardiovascular, pulmonary, respiratory, and carcinogenic risks of e-cigarette (EC) use
  - distinguish between short-term and longer-term health effects
  - consider health effects in specific populations (e.g., people with asthma)
  - examine the effects by smoking status (tobacco-naïve EC users, EC-naïve smokers, dual EC and TC users, and former smokers who switched to EC use)
- To examine methodological limitations of existing systematic reviews.
- To provide recommendations for future research.

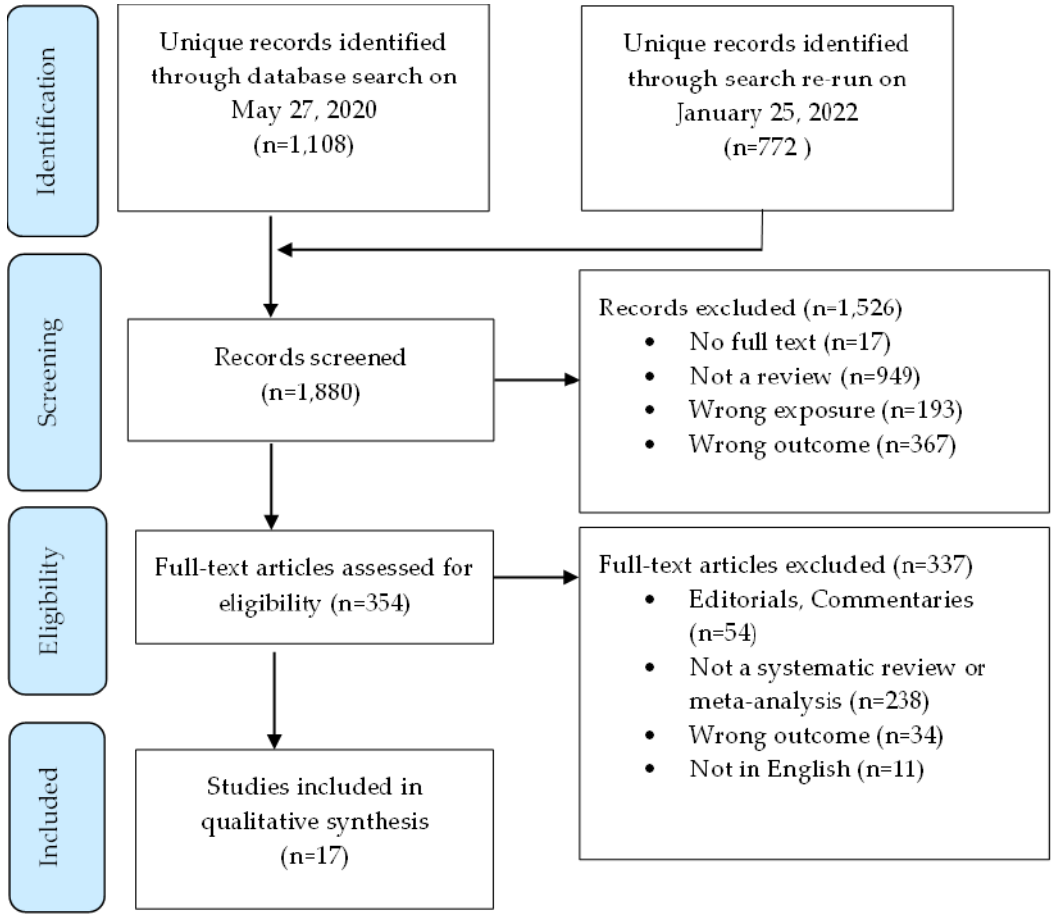
Methods

- Conducted in adherence with the guidelines for umbrella reviews and the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA)
- Review protocol registered with PROSPERO (Registration Number: CRD42021237878)
- Systematic reviews eligible for inclusion were appraised for methodological quality using the AMSTAR-2 quality appraisal tool

Results of the literature search

- Search in four databases: PubMed, Web of Science, Embase, and Cochrane Database of Systematic Reviews
- Through January 25, 2022
- Selection: published in English, must claim to be a systematic review
- Eligible: 17 systematic reviews, including 5 meta-analyses:
  - Cardiovascular outcomes = 11
  - Respiratory/Pulmonary = 13
  - Carcinogenic= 5

Figure 1. Flow diagram of the literature selection process



Key findings: Cardiovascular Health Effects

- Short-term effects: Reviewed evidence suggests the potential for cardiovascular harm of EC use through acute increases in heart rate, systolic and diastolic blood pressure, endothelial dysfunction, arterial stiffness, and biomarkers of oxidative stress. *The effects were seen both in cigarette smokers and non-smokers.*
- Longer-term effects: Evidence of the association of EC use and chronic changes in heart rate, blood pressure, cardiac geometry and function, and increased risk of cardiovascular events compared to non-use was insufficient.

Key findings: Pulmonary/Respiratory Health

- Short-term EC use was found to reduce lung defense mechanisms and impact lung function and overall peripheral airway resistance *both in smokers and non-smokers.*
- Long-term EC use was suggested to increase exacerbations in individuals with asthma.
- Switching from chronic cigarette smoking to long-term EC use showed a potential reduction in pulmonary/respiratory harm, especially in individuals with asthma and COPD.
- Evidence on the effects of *dual EC and cigarette use* compared to using one product alone is limited but suggests that EC use could be an independent risk factor contributing to respiratory harm.

Key findings: Carcinogenic effects

- Some evidence of potentially carcinogenic effects based on compounds found in human urine samples of EC users and likely increased risk of lung cancer in high-risk individuals based on in vitro studies.
- Limited evidence of mutagenic effects or DNA damage in humans and no evidence of an association between EC use and intermediate or long-term cancer endpoints.

Methodological Limitations of Systematic Reviews

The AMSTAR 2 checklist is comprised of 16 questions and includes seven critical domains, such as:

A registered review protocol

Adequacy of the literature search

Justification for the exclusion of individual studies

Risk of bias assessment

Appropriate statistical methods for combining results and investigating publication bias (for meta-analysis)

Consideration of potential biases when interpreting the results of individual studies.

- **Thirteen reviews (nearly 80%)** failed to report whether their methods were established in a written protocol prior to conducting the review
- **Nine reviews (nearly 50%)** failed to apply a comprehensive literature search strategy
- **Ten reviews (nearly 60%)** did not report any information on the conflict of interest/funding received by the authors of the included studies.
- **Nine reviews (nearly 50%)** failed to apply an appropriate technique for the systematic assessment of the quality and risk of bias of included studies was

- All five meta-analyses used appropriate methods for the statistical combination of results. However, one failed to apply a satisfactory technique to assess the quality and risk of bias of the included studies, one did not assess the risk of publication bias, and two did not assess the potential impact of the risk of bias in individual studies on the overall findings.

Further limitations of systematic reviews

- Overall underreporting of important information:
  - Data on the studied EC device types was missing in nine reviews
  - Data on e-liquid type (e.g., containing nicotine, flavor) was missing in ten reviews.
  - The smoking status of the studied individuals was reported only in ten reviews
  - The health status of studied individuals was reported only in seven reviews
- Often missing definition of “acute” outcomes or “short-term” EC use
- Missing or inconsistent definitions of “long-term” EC use, spanning from several days to several years.
- No reviews examined the health effects of the latest generation devices.
- Dependent on author’s claim that a systematic review was conducted

Limitations of the Umbrella Review

- The heterogeneity of the included reviews and meta-analyses precluded us from generating quantitative measures to compare the quality between reviews. Instead, we address the limitations of each systematic review based on the individual items of the tool.
- Our analysis included only those literature reviews that explicitly self-identified as systematic in the title, abstract, keyword, or methods. This method was selected as the most straightforward way to detect a systematic review but may have excluded some good-quality literature reviews.
- The insufficient reporting of the effect sizes across the included systematic reviews precluded us from summarizing the evidence in quantitative terms
- Original studies included in examined systematic reviews may have overlapped, thereby overrepresenting the findings of such studies in our umbrella review.

Conclusions

- Limited guidance for modeling, but still lacking esp. wrt prior smoking
- Overall poor reporting across systematic reviews presents an important limitation in the current research on EC health effects.
- Underreporting EC device and e-liquid types across most reviews limit the ability to compare health effects across different generations of EC devices and their e-liquid characteristics.
- Lack of reporting of the smoking status and health status of study participants presents another major limitation.
- Lack of clear definitions of “short-term” and “long-term” health outcomes further limit the comparability of results across reviews.

Recommendations for future research

- This umbrella review highlights the need for future systematic reviews with better adherence to established reporting guidelines.
- In addition, future systematic reviews should:
  - ✓ adhere to a consistent definition of the duration of EC exposure (i.e., explicitly defined acute and long-term use) and of the device and e-liquid type.
  - ✓ focus on the health effects of newer generation EC devices.
  - ✓ systematically report the smoking status of participants to distinguish the risks of vaping from those of smoking.
  - ✓ when possible, adjust for health status and a cumulative history of smoking.
  - ✓ focus on clinical trials to minimize the variability in product devices, e-liquids, individual product use patterns, and study designs across the included studies.
- Meeting each of these needs will ensure that the evidence of the health consequences of EC use is clear and reliable.

Thank you!

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