E-Cigarette Collection

August 23, 2021

Topics covered

1. How are e-cigarettes regulated around the world?
2. What is the prevalence of e-cigarette use?
3. How effective are e-cigarettes at delivering nicotine?
4. Are e-cigarettes a gateway to smoking for youth and young adults?
5. Do e-cigarettes help people quit smoking?
6. What role do e-cigarettes play among populations with high smoking prevalence rates?
7. Should pregnant women who smoke use e-cigarettes?
8. What are the health effects of e-cigarettes?
9. Why is there debate over use of flavors in e-cigarettes?
10. How safe is exposure to second-hand aerosols from e-cigarettes?
11. Overall, what is the public health impact of e-cigarettes?
12. Using the evidence for decision-making

E-cigarettes are battery-powered devices that heat a liquid solution (often referred to as e-liquid or e-juice) of propylene glycol and/or vegetable glycerin to create an aerosol that is inhaled by the user. Typically, nicotine and flavors are added to the solution. There are various types of e-cigarettes. For example, some are disposable while others are refillable; some mimic cigarettes in the way they look; and others have advanced designs with variable voltage and resistance.

Other names for e-cigarettes include (but are not limited to): electronic nicotine delivery systems (ENDS), alternative nicotine delivery devices (ANDs), vape pens, vaping products, mods, pod mods and vapes. Despite the common use of terms like ENDS and ANDS, not all devices contain nicotine (particularly in countries where nicotine e-liquid is not permitted).

Using an e-cigarette is typically referred to as "vaping." It is also important to note that sometimes users of e-cigarettes refer to the device simply by its brand name (e.g., Juul or Puff bar) and refer to using the product similarly (e.g., Juuling).

People working in the nicotine and tobacco research field, as well as some health agencies, may hold strong (and often opposing) views about e-cigarettes, resulting in active debate. These debates typically center around differences in interpreting the limited existing evidence around: 1) the efficacy/effectiveness of e-cigarettes for smoking cessation; 2) their general safety, and what standard

to use to assess safety (e.g. whether or not to compare toxicity to that of cigarettes) ; and 3) whether e-cigarettes are a tobacco harm reduction measure, or a product that facilitates and exacerbates nicotine and tobacco use among youth and maintains addiction among existing tobacco users. It is therefore important that you bear this "diversity of opinion" in mind when critically appraising the e-cigarette literature. Some key papers to read regarding these perspectives are provided below:

- Balfour D, Benowitz N, Colby S, et al. Balancing Consideration of the Risks and Benefits of E-cigarettes. *American Journal of Public Health, 2021; pp. e1-e12.*

- Carroll DM, Denlinger-Apte RL, Dermody SS, et al. Polarization Within the Field of Tobacco and Nicotine Science and its Potential Impact on Trainees. *Nicotine & Tobacco Research, 2021. 23 (1): 36–39.*

- Beaglehole R, Bates C, Youdan B, Bonita R. Nicotine without smoke: fighting the tobacco epidemic with harm reduction. *Lancet. 2019 Aug 31;394(10200):718–20.*

The opinion piece below suggests a possible solution for managing research bias in a divisive environment:

- Munafò MR, West, R. E-cigarette research needs to adopt open science practices to improve quality. *Addiction*, 2020: 115 (1)

For resources related to critical appraisal, you may want to browse the SRNT-U Research Methodologies & Skills section (for example, the Literature Synthesis & Review subsection includes a link to an overview of critical appraisal of journal articles).

Although taking no position on e-cigarettes, SRNT-U leadership believes this is an important research topic. For this reason, we have selected a few key papers that we feel researchers new to the topic should be aware of, prior to more self-directed exploration of the e-cigarette literature. Readers may not always agree with the views presented in the papers below. Furthermore, the collection is by no means exhaustive.

1. How are e-cigarettes regulated around the world?

The World Health Organization (WHO) and the WHO Framework Convention on Tobacco Control (FCTC) have shaped a lot of e-cigarette policy, especially in low and middle income countries. The WHO's statement on e-cigarettes can be found here. However, regulatory approaches to the design, manufacture, distribution, availability, and marketing of e-cigarettes vary greatly around the world. We provide some examples of relevant papers on this topic but encourage you to explore the literature more fully yourself.

The first publication below highlights the extent of the regulatory variability, and the webinar provides an example of how one country has used the available evidence on e–cigarettes to inform government policy. The third item outlines how e-cigarettes are regulated under the jurisdiction of the US Food and Drug Administration. The last paper provides one example of the impact of the e-cigarette regulatory environment--in this case the focus is on smoking cessation.

- Kennedy RD, Awopegba A, De León E, et al. Global approaches to regulating electronic cigarettes. *Tobacco Control* 2017;26:440-445.

- SRNT Webinar: Evidence into policy: UK approach to e-cigarettes (2016, SRNT members only)

- Backinger CL, Meissner HI, Ashley DL. The FDA "Deeming Rule" and tobacco regulatory research. *Tobacco Regulatory Science* 2016 Jul; 2(3): 290–293. The FDA "Deeming Rule" can be found here.

- Yong H-H, Hitchman SC, Cummings KM, Borland R, Gravely SML, McNeill A, Fong GT. Does the regulatory environment for e-cigarettes influence the effectiveness of e-cigarettes for smoking cessation? Longitudinal findings from the ITC Four Country Survey. *Nicotine & Tobacco Research* 2017; 19(11): 1268–1276.

For other information related to e-cigarette regulation, you may want to browse SRNT-U's Policy Research and Tools & Resources sections. For example, the Policy Research Product Regulation subsection contains links to a recorded 2018 plenary lecture by then-FDA Commissioner Scott Gottlieb, addressing e-cigarette regulations among other topics. The Tools & Resources section (Resource Portals subsection) includes a link to the Institute for Global Tobacco Control, which maintains information about country regulations of e-cigarettes .

2. What is the prevalence of e-cigarette use?

Prevalence data for e-cigarette use is lacking for many countries. What data does exist is highly variable, and influenced by each country's policy environment (i.e., whether e-cigarettes with and/or without nicotine are permitted and accessible), the survey methodology employed, and the types of questions asked. When reviewing the literature, one should always check the definition of "e-cigarette use" used in each survey. For example,

- How is the term "current e-cigarette use" defined? It could be "used in the last 30 days" or it could be defined as "daily use."
- The presence or absence of nicotine is not always assessed explicitly in items that assess e-cigarette use behavior.
- Does the research question cover use of pod–based devices? As mentioned above, users of JUUL may not refer to the device as an e-cigarette, they simply call it "JUUL" and the act of using it as "JUULing". Therefore, they may answer "No" to the question "Have you used an e-cigarette in the last 30 days?"

Ideally, e-cigarette use should be assessed along with cigarette use and use of other tobacco products, in the same survey or study. Furthermore, measurement of "dual use" of both e-cigarettes with conventional cigarettes and/or other tobacco products should be undertaken. Four publications related to measurement of e-cigarette related constructs are listed below.

- Borland R, Murray K, Gravely S, et al. A new classification system for describing concurrent use of nicotine vaping products alongside cigarettes (so-called "Dual Use"): Findings from the ITC-4 country smoking and vaping Wave 1 survey. *Addiction* 2019 doi: 10.1111/add.14570. [subscription or payment required to read full text]

- Pearson JL, Hitchman SC, Brose LS et al. Recommended core items to assess e-cigarette use in population-based surveys. *Tobacco Control* 2018; 27; 341-346. [subscription or payment required to read full text]

- Weaver SR, Kim H, Glasser AM, et al. Establishing consensus on survey measures for electronic nicotine and non-nicotine delivery system use: Current challenges and considerations for researchers. *Addictive Behaviors*. 2018 Apr; 79: 203–212.

- Villanti AC, Pearson JL, Glasser AM, Johnson AL, Collins LK, Niaura RS, Abrams DB. Frequency of youth e-cigarette and tobacco use patterns in the U.S.: Measurement precision is critical to inform public health. *Nicotine & Tobacco Research* 2017; 19(11): 1345-1350.
    - Update to this paper found at: *Nicotine & Tobacco Research,* 2017; 19 (10): 1253–1254.

The subsequent papers/websites are examples of prevalence data from different countries, and populations of different ages.

Prevalence of e-cigarette use in youth and young adults:

- Hammond D, Rynard VL, Reid JL. Changes in prevalence of vaping among youths in the United States, Canada, and England from 2017 to 2019. *JAMA Pediatrics*; 2020. 174; 797–9.

- Glasser AM, Johnson AL, Niaura RS, et al. Youth Vaping and Tobacco Use in Context in the United States: Results from the 2018 National Youth Tobacco Survey. *Nicotine & Tobacco Research.* 2020 Jan 13. pii: ntaa010.

- Walker N, Parag V, Wong S, et al. Daily use of e-cigarettes and smoked tobacco in youth aged 14-15 years in New Zealand: findings from repeated cross-sectional studies (2014-2019). *Lancet Public Health 2020; Jan 21. pii: S2468-2667(19)30241-5.*

- Jarvis M, Jackson S, West R, Brown J. Epidemic of youth nicotine addiction? What does the National Youth Tobacco Survey 2017-2019 reveal about high school e-cigarette use in the USA? *Qeios* 2020; September. doi:10.32388/745076.5.

- Cullen KA, Ambrose BK, Gentzke AS, et al. Notes from the field: Use of electronic cigarettes and any tobacco product among middle and high school students - United States, 2011-2018. Morbidity and Mortality Weekly Report (US Centers for Disease Control and Protection). 2018;67(45):1276–1277.

- Kotz D, Böckmann M, Kastaun S. The use of tobacco, e-cigarettes, and methods to quit smoking in Germany—a representative study using 6 waves of data over 12 months (the DEBRA study). *Deutsches Ärzteblatt International* 2018; 115: 235–42.

- Bauld L, MacKintosh A, Eastwood B et al. Young people's use of e-cigarettes across the United Kingdom: Findings from five surveys 2015–2017. *International Journal of Environmental Research and Public Health* 2017;14(9):973.

Prevalence of e-cigarette use in adults:

- The English Smoking Toolkit regularly reports data on e-cigarette use in England.

- Laverty AA, Filippidis FT, Vardavas CI. Patterns, trends and determinants of e-cigarette use in 28 European Union Member States 2014-2017. *Preventive Medicine* 2018; 116: 13-18. [subscription or payment required to read full text]

- The US Behavioral Risk Factor Surveillance System has searchable data on e-cigarette use in the USA.

- Kotz D, Böckmann M, Kastaun S. The use of tobacco, e-cigarettes, and methods to quit smoking in Germany - a representative study using 6 waves of data over 12 months (the DEBRA study). *Deutsches Ärzteblatt International* 2018; 115: 235–42.

- Gravely, S, Driezen P, Ouimet J, et al. Prevalence of awareness, ever-use and current use of nicotine vaping products (NVPs) among adult current smokers and ex-smokers in 14 countries with differing regulations on sales and marketing of NVPs: cross-sectional findings from the ITC Project. *Addiction*, 2019; 114(6): 1060-1073.

For more data on prevalence of e-cigarette use, see SRNT-U's Tools & Resources section (Data & Statistics sub-section). Measures repositories can be found in the SRNT-U Tools & Resources section (Measures sub-section).

3. Are e-cigarettes a gateway to smoking for youth and young adults?

The majority of people who use tobacco start when they are teenagers or young adults. Consequently, strategies to prevent initiation of tobacco use are important, as are cessation interventions to help youth quit tobacco use.

What role do e-cigarettes play in this respect? Furthermore, what are the implications if youth who don't use tobacco start to vape (with or without nicotine) and what influence does nicotine have on

the developing brain? Examples of some relevant publications are given below (note, you may not always agree with the views held by the authors):

- Shahab L, Beard E, Brown J. Association of initial e-cigarette and other tobacco product use with subsequent cigarette smoking in adolescents: a cross-sectional, matched control study. *Tobacco Control* 2021; 30: 212–220. doi:10.1136/tobaccocontrol-2019-055283

- FDA Center for Tobacco Products Office of Science. Patterns of tobacco product use in the United States: transitions across three waves of the PATH study (2013-2016). *Tobacco Control 2020; 29 (3).*

- Chan GCK, Stjepanovic D, Lim C, Sun T, Shanmuga Anandan A, Connor JP, et al. Gateway or common liability? A systematic review and meta-analysis of studies of adolescent e-cigarette use and future smoking initiation. *Addiction*. 2020 Sep 4; https://doi.org/10.1111/add.15246]

- National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on the Review of the Health Effects of Electronic Nicotine Delivery Systems; Eaton DL, Kwan LY, Stratton K, editors. *Washington (DC): National Academies Press (US); 2018 Jan.*

- Etter, J-F. Gateway effects and electronic cigarettes. *Addiction* 2018; 113 (10). [subscription or payment required to read full text]

- Kozlowski LT, Warner E. Adolescents and e-cigarettes: Objects of concern may appear larger than they are. *Drug and Alcohol Dependence*, 2017; 174: 209-214. [subscription or payment required to read full text]

- Levy D, Warner, K, Cumming M, et al. Examining the relationship of vaping to smoking initiation among US youth and young adults: a reality check. *Tobacco Control* 2018: doi: 10.1136/tobaccocontrol-2018-054446.

- Soneji S, Barrington-Trimis JL, Wills TA, et al. Association between initial use of e-cigarettes and subsequent cigarette smoking among adolescents and young adults: a systematic review and meta-analysis. *JAMA Pediatrics*, 2017; 171(8), 788-797.

4. How effective are e-cigarettes at delivering nicotine?

Many factors can influence nicotine delivery, uptake and bio-availability when vaping. These factors include the characteristics of the device, how the device is used and the components or characteristics of the e-liquid. For these reasons, nicotine content alone is an unreliable predictor of nicotine delivery and absorption by the user. The review article below provides a summary of the issues.

- DeVito EE, Krishnan-Sarin S. E-cigarettes: Impact of E-Liquid Components and Device Characteristics on Nicotine Exposure**.** *Current Neuropharmacology* 2018; 16(4): 438-459.

This paper below highlights how different e-cigarettes can deliver very different levels of nicotine.

- Hajek P, Pittaccio K, Pesola F, et al. Nicotine delivery and users' reactions to Juul compared with cigarettes and other e-cigarette products. *Addiction*. 2020; Jan 29.

5. Do e-cigarettes help people quit smoking?

E-cigarettes are a harm reduction measure in that they can deliver nicotine in the absence of tobacco smoke. There are many surveys and observational studies providing evidence about the impact of e-cigarette use on tobacco use, and how people may use e-cigarettes to help them switch away from tobacco use. The highest quality evidence around the efficacy and effectiveness of e-cigarettes for smoking cessation is obtained using a clinical trial design. To date, few randomized controlled clinical trials of e-cigarettes have been conducted that had ≥ six-month smoking abstinence as a primary outcome. Some of the key trials are listed below.

- Walker N, Parag V, Verbiest M, Laking G, Laugesen M, Bullen C. Nicotine patches used in combination with e-cigarettes (with and without nicotine) for smoking cessation: a pragmatic randomised trial. *Lancet Respiratory Medicin*e 2019 Published Online September 9, [subscription or payment may be required to read full text]

- Hajek P, Phillips-Waller A, Przulj D, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. *New England Journal of Medicine* 2019; 380: 629-637. [subscription or payment may be required to read full text]

- Bullen C, Howe C, Laugesen M, et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet* 2013;382:1629-37.

- Caponnetto P, Campagna D, Cibella F, et al. EffiCiency and safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: A prospective 12-month randomized control design study. *PLoS ONE* 2013;8:e66317.

There are also a number of systematic reviews of the evidence related to e-cigarettes for smoking cessation. Below we have referenced just one of the reviews: the Cochrane Review on this topic, given Cochrane methodology is internationally accepted as a robust process. There are other reviews that have differing search strategies and conclusions, and so careful comparison of the methodology used across reviews is advised.

The Cochrane Review on e-cigarettes is a 'living review' and in its last iteration concluded that based on current evidence "there is moderate-certainty evidence that ECs with nicotine increase quit rates compared to ECs without nicotine and compared to NRT. Evidence comparing nicotine EC with usual care/no treatment also suggests benefit but is less certain." The review came with a caveat, specifically "the main limitation of the evidence base remains imprecision due to the small number of RCTs, often with low event rates."

- Hartmann-Boyce J, McRobbie H, Lindson N, Bullen C, Begh R, Theodoulou A, Notley C, Rigotti NA, Turner T, Butler AR, Fanshawe TR, Hajek P. Electronic cigarettes for smoking cessation. *Cochrane Database of Systematic Reviews* 2020;

- Listen to the monthly 'Let's talk e-cigarettes' podcast, hosted by Jamie Hartmann-Boyce and Nicola Lindson of Oxford University and the Cochrane group (access via Oxford University, Apple Podcasts, or Spotify) to hear about the new studies that they are including in the Cochrane living review of e-cigarettes (plus interviews with study authors).

6. What role do e-cigarettes play among populations with high smoking prevalence rates?

Smoking rates remain disproportionately high among a number of population subgroups. These groups include (but are not limited to): some racial/ethnic populations, low socio-economic groups, and people with significant comorbidities and complex needs (such as those with mental health issues, and/or substance misuse). What role might e-cigarette play to help these populations switch away from tobacco use?

- Thomas DP, Lusis N, Van der Sterren AE, Borland R. Electronic Cigarette Use and Understanding Among a National Sample of Australian Aboriginal and Torres Strait Islander Smokers. *Nicotine & Tobacco Research.* 2019;21(10):1434-40. [subscription or payment required to view full text]

- Gentry S, Forouhi NG, Notley C. Are Electronic cigarettes an effective aid to smoking cessation or reduction among vulnerable groups? A systematic review of quantitative and qualitative evidence. *Nicotine & Tobacco Research* 2019: 21 (5); 602–616 [subscription or payment required to view full text]

- Giovenco DP, Spillane TE, Merizier M. Neighborhood Differences in Alternative Tobacco Product Availability and Advertising in New York City: Implications for Health Disparities. *Nicotine & Tobacco Research* 2019 Jun 21;21(7):896-902. [subscription or payment required to view full text]

- Friedman AS, Horn SJL. Socioeconomic Disparities in Electronic Cigarette Use and Transitions from Smoking. *Nicotine & Tobacco Research* 2018 Jun 16. [subscription or payment required to view full text]

- Harlow A, Stokes A, Brooks D. Socio-economic and racial/ethnic differences in e-cigarette uptake among cigarette smokers: Longitudinal analysis of the Population Assessment of Tobacco and Health (PATH) study. *Nicotine & Tobacco Research* 2018 Jul 7. [subscription or payment required to view full text]

- Carroll DM, Wagener, TL, Peck, JD, Brame LS, Thompson DM, Stephens LD, Campbell JE, Beebe LA. Biomarkers of Exposure in ENDS Users, Smokers, and Dual Users of American

Indian Descent. *Tobacco Regulatory Science* 2018; 4 (2): 3-15(13). [subscription or payment required to view full text]

- Webb Hooper M, Kolar SK. Racial/Ethnic Differences in Electronic Cigarette Use and Reasons for Use among Current and Former Smokers: Findings from a Community-Based Sample. *International Journal of Environmental Research and Public Health* 2016 Oct 14;13(10). pii: E1009.

- Spears CA, Jones DM, Weaver SR, Pechacek TF, Eriksen MP. Use of Electronic Nicotine Delivery Systems among Adults with Mental Health Conditions, 2015. *International Journal of Environmental Research and Public Health* 2016 Dec 23;14(1). pii: E10. doi: 10.3390/ijerph14010010.

7. Should pregnant women who smoke use e-cigarettes?

Smoking during pregnancy poses substantial risks to the unborn baby, and later, the infant. For these reasons stopping smoking as early in the pregnancy as possible is recommended. However, some pregnant women who smoke have tried numerous times to quit during their pregnancies but have been unsuccessful (despite psychosocial interventions). What further cessation support should be offered to these women?

Internationally, there is no consensus on whether smoking cessation pharmacotherapy should be offered to pregnant women who smoke. For instance, in some countries treatment guidelines recommend nicotine replacement therapy (NRT) be offered to pregnant women who smoke (given NRT is less harmful than smoking while pregnant), but only after they have been advised of the potential risks and benefits of NRT use (given the potential epigenetic effects of nicotine).

The debate is ongoing as to the use of e-cigarettes during pregnancy, given little is known about their use in this population or their impact on the unborn child. Articles relevant to this discussion are presented below. The last reference is the latest WHO recommendations regarding management of pregnant women who smoke.

- McDonnell BP, Dicker P, Regan CL. Electronic cigarettes and obstetric outcomes: a prospective observational study. *British Journal of Obstetrics and Gynecology.* 2020 May;127(6):750-756. doi: 10.1111/1471-0528.16110. [subscription or payment required to view full text]

- Cooper S, Orton S, Campbell KA, et al. Attitudes to e-cigarettes and cessation support for pregnant women from English stop smoking services: A mixed methods study. *International Journal of Environmental Research and Public Health* 2019: 16 (1);110.

- Kumar R, Gould GS. Tobacco harm reduction for women who cannot stop smoking during pregnancy—A viable option? *JAMA Pediatrics* 2019;173(7):615-616 [viewpoint]. [subscription or payment required to view full text]

- Whittington JR, Simmons PM, Phillips AM, et al. The use of electronic cigarettes in pregnancy. *Obstetrical & Gynecological Survey* 2018: 73(9); 544–549. [subscription or payment required to view full text]

- World Health Organization. WHO recommendations for the prevention and management of tobacco use and second-hand smoke exposure in pregnancy. Geneva. World Health Organization 2013. [page 50 onwards covers treatment]

8. What are the health effects of e-cigarettes?

When looking at papers on this topic, consider closely the type of study undertaken (e.g., is it chemical, toxicological, a cross-sectional survey, a cohort study, a trial) and the ability of the design to answer the "safety question." For example, two papers describing preclinical studies are presented below. Are these findings translatable to humans? The third paper provides an example of this argument (in relation to the second paper).

- Lee WH, Ong S-G, Zhou Y, et al. Modeling Cardiovascular Risks of E-Cigarettes With Human-Induced Pluripotent Stem Cell–Derived Endothelial Cells, *Journal of the American College of Cardiology* Jun 2019, 73 (21) 2722-2737

- Garcia-Arcos I, Geraghty P, Baumlin N, et al. Chronic electronic cigarette exposure in mice induces features of COPD in a nicotine-dependent manner. *Thorax* 2016;71:1119-1129.

- Shapiro SD, Kaynar AM. Electronic cigarettes: the lesser of two evils, but how much less? *Thorax* 2016;**71:** 1080-1081.[editorial]

When reading the literature around the health effects of e-cigarettes, also consider whether the study you are reading about is hypothesis-generating or hypothesis-proving (e.g., you can't prove causality with a cross-sectional study), and make sure you look for the *absolute* risk (relative risks, while informative, can be very misleading). Finally, consider whether the data presented relates to short-term or long–term risk. You may want to browse SRNT-U's Research Methodologies & Skills section for information on cross-sectional studies and on relative risk. The Quantitative Data Analysis & Statistics sub-section has links to material on these topics.

Below are four examples of research on carcinogen and toxicant exposure for e-cigarette users compared to users of nicotine replacement therapy or tobacco, highlighting the reduced risk of e-cigarettes compared to tobacco.

- Hatsukami D, Meier E, Lindgren BR, et al. A randomized clinical trial examining the effects of instructions for electronic cigarette use on smoking-related behaviors, and biomarkers of exposure. *Nicotine & Tobacco Research*. 2019 Dec 12. pii: ntz233. doi: 10.1093/ntr/ntz233.

- Goniewicz ML, Smith DM, Edwards KC, et al. Comparison of nicotine and toxicant exposure in users of electronic cigarettes and combustible cigarettes. *JAMA Network Open* 2018; 7; 1(8):e185937.

- Shahab L, Goniewicz ML, Blount BC, et al. Nicotine, carcinogen, and toxin exposure in long-term e-cigarette and nicotine replacement therapy users: a cross-sectional study. *Annals of Internal Medicine* 2017;166(6), 390-400. [requires subscription or payment to view full text]

- Chen J, Bullen C, Dirks K. A Comparative Health Risk Assessment of Electronic Cigarettes and Conventional Cigarettes. *International Journal of Environmental Research and Public Health.* 2017;14(4):382. doi:10.3390/ijerph14040382

The cardiovascular safety of nicotine is important to consider when using reduced harm tobacco products, such as nicotine replacement therapy, smokeless tobacco, and e-cigarettes. The papers below provides a good summary of this topic.

- George J, Hussain M, Vadiveloo T, Ireland S, Hopkinson P, Struthers AD, Donnan PT, Khan F, Lang CC. Cardiovascular effects of switching from tobacco cigarettes to electronic cigarettes. *Journal of the American College of Cardiology.* 2019 Dec 24;74(25):3112-3120. doi: 10.1016/j.jacc.2019.09.067.

- Benowitz NL, Burbank AD. Cardiovascular toxicity of nicotine: Implications for electronic cigarette use. *Trends in Cardiovascular Medicine* 2016; 26 (6): 515-523. [requires subscription or payment to view full text]

Studies included in the Cochrane review on "Electronic cigarettes for smoking cessation," did not detect any serious adverse events considered possibly related to e-cigarette use in adult smokers using the devices to quit.

- Hartmann-Boyce J, McRobbie H, Lindson N, Bullen C, Begh R, Theodoulou A, Notley C, Rigotti NA, Turner T, Butler AR, Fanshawe TR, Hajek P. Electronic cigarettes for smoking cessation. *Cochrane Database of Systematic Reviews* 2020.

There is an urgent need for e-cigarette studies that are large enough and long enough to assess the occurrence of uncommon serious adverse events and events with a long lead-time. One such study is highlighted below:

- Polosa R, Morjaria JB, Prosperini U, Busà B, Pennisi A, Malerba M, Maglia M, Caponnetto P. COPD smokers who switched to e-cigarettes: health outcomes at 5-year follow up. *Therapeutic Advances in Chronic Disease 2020, 11: 1–15.*

USA EVALI outbreak

Between August 2019 and January 2020, an outbreak of severe, acute respiratory failure (including deaths) potentially related to vaping was reported in the USA. These events are commonly referred to as EVALI or "electronic-cigarette, or vaping, product use-associated lung injury" and appear linked to vitamin E acetate in THC (Tetrahydrocannabinol) vapes. The papers below provide further details.

- Trivers KF, Watson CV, Neff LJ, Jones CM, Hacker K. Tetrahydrocannabinol (THC)-containing e-cigarette, or vaping, product use behaviors among adults after the onset of the 2019 outbreak of e-cigarette, or vaping, product use-associated lung injury (EVALI). *Addictive Behaviors.* 2021; 121: doi.org/10.1016/j.addbeh.2021.106990

- Blount BC, Karwowski MP, Shields PG, et al. Vitamin E Acetate in Bronchoalveolar-Lavage Fluid Associated with EVALI. *New England Journal of Medicine.* 2019; 382(8):697-705.

Two US government agencies continue to offer information and advice related to this outbreak: the US Food and Drug Administration (FDA) and the US Centers for Disease Control and Prevention (CDC).

9. Why is there debate over use of flavors in e-cigarettes?

Flavorings may be added to e-liquid to make e-cigarette use more pleasurable. Flavors may include (but are not limited to): tobacco, menthol, fruit, and sweet flavors. Two papers on consumer preference for e-liquid flavors are provided below:

- Zare S, Nemati M, Zheng Y. A systematic review of consumer preference for e-cigarette attributes: Flavor, nicotine strength, and type. *PLoS One* 2018;13(3):e0194145.

- Russell C, McKeganey N, Dickson T, Nides M. Changing patterns of first e-cigarette flavor used and current flavors used by 20,836 adult frequent e-cigarette users in the USA. *Harm Reduction Journal* 2018;15(1):33.

There is some debate over whether flavors should be used in e-cigarettes. This debate is primarily focused on three issues: 1) Are flavors important for helping cigarette smokers switch to e-cigarettes; 2) Do some flavors attract youth and young adults who have never used an e-cigarette or smoked tobacco, to initiate e-cigarette use; and 3) How safe are the flavoring chemicals used in e-liquids when they are heated and then inhaled (as occurs when used in e-cigarettes)?

Three papers on the toxicity assessment of flavors used in e-liquids are provided below.

- Farsalinos K, Lagoumintzis G. Toxicity classification of e-cigarette flavouring compounds based on European Union regulation: analysis of findings from a recent study. *Harm Reduction Journal* 2019 Jul 25;16(1):48

- Omaiye EE, McWhirter KJ, Luo W, Tierney PA, Pankow JF, Talbot P. High concentrations of flavor chemicals are present in electronic cigarette refill fluids. *Scientific Reports* 2019;9(1):2468.

- Varlet V, Farsalinos K, Augsburger M, Thomas A, Etter JF. Toxicity assessment of refill liquids for electronic cigarettes. *International Journal of Environmental Research and Public Health* 2015;12:4796–4815.

Some countries regulate whether flavors can be added to e-liquids. This information can be found in the SRNT-U Tools & Resources section (Resource Portals subsection) where there is a link to the Institute for Global Tobacco Control, which maintains information about country regulations of e-cigarettes .

10.How safe or hazardous is exposure to second-hand aerosols from e-cigarettes?

It's important when reading literature on this topic to first understand the difference between "side-stream smoke" (i.e., the smoke released into the environment from the end of a burning cigarette) and "mainstream smoke" (i.e., the smoke that is inhaled by a smoker and then exhaled into the environment)**.** The most toxic part of second-hand tobacco smoke exposure is side-stream smoke, as it contains ~75% of the nicotine and a majority of the tobacco-related toxicants and particles. E-cigarettes do not combust tobacco and therefore have no side-stream component. E-cigarette emissions only occur during active use and are only mainstream, i.e., they originate only from what is exhaled by the user. Most inhaled aerosol from an e-cigarette is absorbed by the body. The paper below provides a good summary of the pharmacokinetics of nicotine, propylene glycol and vegetable glycerin from e-cigarettes.

- St. Helen G, Havel C, Dempsey D, et al. Nicotine delivery, retention, and pharmacokinetics from various electronic cigarettes. *Addiction* 2016; 111(3): 535-544. [requires subscription or payment to view full text]

Given the above information, exhaled aerosol from an e-cigarette is very diluted. Below are examples of some key papers on second-hand exposure to aerosols from e-cigarettes. The first two papers below provide data on the gas phase (i.e., no particulates), the subsequent two papers (Martuzevicius et al and Tongke et al) on the "particulate" phase (i.e., droplets), and the last paper covers both phases.

- Martuzevicius D, Prasauskas T, Setyan A, et al. Characterization of the spatial and temporal dispersion differences between exhaled e-cigarette mist and cigarette smoke. *Nicotine & Tobacco Research*, 18 June 2018; nty121

- Liu J, Liang Q, Oldham MJ, et al. Determination of selected chemical levels in room air and on surfaces after the use of cartridge- and tank-based e-vapor products or conventional cigarettes. *International Journal of Environmental Research and Public Health* 2017, 14, 969.

- Zwack L, Stefaniak A, LeBouf R. Evaluation of chemical exposures at a vape shop. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. 2017.

- Tongke Z., Nguyen C., Che-Hsuan L, et al. Characteristics of second-hand electronic cigarette aerosols from active human use. *Aerosol Science and Technology* 2017; 51(12): 1368-1376.

- Ruprecht AA, De Marco C, Saffari A, et al. Environmental pollution and emission factors of electronic cigarettes, heat-not-burn tobacco products, and conventional cigarettes. *Aerosol Science and Technology* 2017; 51(6): 674-684.

The papers below also provide evidence of reduced second-hand exposure to nicotine from e-cigarettes, compared to tobacco cigarettes, as well as reduced lung cancer risk.

- Martín D, Peñín-Ibáñez M, González GA, et al. On the passive exposure to nicotine from traditional cigarettes versus e-cigarettes. *International Journal of Public Health Research* 2019; 7(1): 11-17

- Avino P, Scungio M, Stabile L, et al. Second-hand aerosol from tobacco and electronic cigarettes: Evaluation of the smoker emission rates and doses and lung cancer risk of passive smokers and vapers. *Science of the Total Environment* 2018;15(642):137-147. [requires subscription or payment to view full text]

Given the above information, do you think e-cigarettes should be included in indoor smoking bans? The paper below provides some points for you to consider.

- Wilson N, Hoek J, Thomson G, Edwards R. Should e-cigarette use be included in indoor smoking bans? *Bulletin of the World Health Organization*. 2017;95(7):540-541.

11.Overall, what is the public health impact of e-cigarettes?

There is a diversity of opinion about the overall population impact of e-cigarettes. Comprehensive evidence reviews from two different countries are provided below.

- McNeill A, Brose LS, Calder R, Simonavicius E & Robson D. Vaping in England: an evidence update, including vaping for smoking cessation, February 2021. A report commissioned by Public Health England. London: Public Health England, 2021.

- Public health consequences of e-cigarettes. National Academies of Sciences, Engineering, and Medicine. National Academies Press, 2018.

Evidence from modeling:
Current reports based on simulation modeling provide discordant predictions of the impact of e-cigarettes on population health. However, the studies differ in their population focus, modeling methods and structure, which could explain the different findings. The papers below provide examples of modeling data related to e-cigarettes (based on various scenarios) for three high-income countries: the USA, New Zealand, and the United Kingdom.

- Warner KE, Mendez D. E-cigarettes: Comparing the possible risks of increasing smoking initiation with the potential benefits of increasing smoking cessation. *Nicotine & Tobacco Research* 2019; 21(1): 41-47. [requires subscription or payment to view full text]

- Petrović-van der Deen FS, Wilson N, Crothers A, et al. Potential country-level health and cost impacts of legalizing domestic sale of vaporized nicotine products. *Epidemiology*.2019; 30(3): 396-404. [requires subscription or payment to view full text]

- Levy DT, Borland R, Lindblom EN, et al. Potential deaths averted in USA by replacing cigarettes with e-cigarettes. *Tobacco Control* 2018; 27**:** 18-25.

- Soneji SS, Sung HY, Primack BA, et al. Quantifying population-level health benefits and harms of e-cigarette use in the United States. *PLoS One* 2018; 13(3): e0193328.

- Levy DT, Borland R, Villanti AC, et al. The application of a decision-theoretic model to estimate the public health impact of vaporized nicotine product initiation in the United States. *Nicotine & Tobacco Research* 2017; 19(2): 149–59.

12.Using the evidence for decision-making

With so much published information on e-cigarettes, how does one synthesize this information in a meaningful way? For example, how do you identify research gaps or use the evidence to inform your own opinion or advice around use of e-cigarettes? In the lecture below, Professor Robert West (University College London, England) provides an example of data synthesis - he uses the APEASE criteria to evaluate the evidence around e-cigarettes as an intervention, by considering Acceptability, Practicability, Effectiveness, Affordability, Safety and Equity. Please note that this is a personal opinion piece and you may or may not agree with the statements made by the presenter.

- Keynote Lecture. SRNT-E Annual Meeting, Oslo, Norway 12.-14. September 2019. https://vimeo.com/361160577

Research around e-cigarettes is rapidly evolving, as are the devices themselves. With this in mind, please come back to SRNT-U on a regular basis to review this collection, as new information will be added as it becomes available.

If you feel a key paper is missing from this collection, please feel free to suggest additional content via email.

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