Table S1. Systematic search in databases showing number of articles found (Number of searched articles/duplicates/included in screening process)

First search: all studies published before 12.01.2021									
	PubMed		**EMBASE**		**Cinahl**		**Cochrane**		Total number / duplicates / included in screening process
Search words	#	Number of searched articles	#	Number of searched articles	#	Number of searched articles	#	Number of searched articles	
(Dual use) AND (E-cigarette OR e-cigarettes)	1	493	2	199	3	231	4	43	966 / 406 / 560
Second search: all studies published before 27.04.2021									
	PubMed		**EMBASE**		**Cinahl**		**Cochrane**		Total number / duplicates / included in screening process
Search words	#	Number of searched articles	#	Number of searched articles	#	Number of searched articles	#	Number of searched articles	
(Dual use) AND (Electronic cigarette OR Electrically heated cigarette OR Electronic nicotine delivery system OR Electronic nicotine delivery device)	5	596	6	292	7	119	8	50	1.057 / 906 / 151
Found in searched articles									4 / 0 / 4
Searched by hand									6 / 0 / 6

Search number

Table S2. Overview of the 45 studies excluded in full text review. All studies are divided into six exclusion criteria-categories.

Reference	Exclusion criteria
Abafalvi L, Pénzes M, Urbán R, Foley KL, Kaán R, Kispélyi B, Hermann P: Perceived health effects of vaping among Hungarian adult e-cigarette-only and dual users: a cross-sectional internet survey. *BMC public health* 2019, 19(1):302.	Comparison between EC and CC not possible
Bhatta DN, Glantz SA: Electronic Cigarette Use and Myocardial Infarction Among Adults in the US Population Assessment of Tobacco and Health. *J Am Heart Assoc* 2019, 8(12):e012317.	Article retracted
Brożek GM, Jankowski M, Zejda JE: Acute respiratory responses to the use of e-cigarette: an intervention study. *Scientific reports* 2019, 9(1):6844.	Comparison between EC and CC not possible
Carroll DM, Wagener TL, Stephens LD, Brame LS, Thompson DM, Beebe LA: The relationship between nicotine metabolism and nicotine and carcinogen exposure among American Indian commercial cigarette smokers and electronic nicotine delivery system users. *Addict Behav* 2019, 92:58-63.	Wrong outcome
Cassidy RN, Tidey JW, Colby SM: Exclusive e-cigarette users report lower levels of respiratory symptoms relative to dual e-cigarette and cigarette users. *Nicotine Tob Res* 2020.	Comparison between EC and CC not possible
Czoli CD, Fong GT, Goniewicz ML, Hammond D: Biomarkers of Exposure Among"Dual Users" of Tobacco Cigarettes and Electronic Cigarettes in Canada. *Nicotine Tob Res* 2019, 21(9):1259-1266.	Not real-world study
Doran N, Brikmanis K, Petersen A, Delucchi K, Al-Delaimy WK, Luczak S, Myers M, Strong D: Does e-cigarette use predict cigarette escalation? A longitudinal study of young adult non-daily smokers. *Prev Med* 2017, 100:279-284.	Wrong outcome
Doran N, Correa JB, Myers MG, Tully L: Associations Between Self-Reported and Biological Measures of Nicotine Consumption Among Young Adult Nondaily Cigarette Smokers. *Am J Addict* 2020.	Wrong outcome
D'Ruiz CD, Graff DW, Robinson E: Reductions in biomarkers of exposure, impacts on smoking urge and assessment of product use and tolerability in adult smokers following partial or complete substitution of cigarettes with electronic cigarettes. *BMC public health* 2016, 16:543.	Wrong outcome
D'Ruiz CD, O'Connell G, Graff DW, Yan XS: Measurement of cardiovascular and pulmonary function endpoints and other physiological effects following partial or complete substitution of cigarettes with electronic cigarettes in adult smokers. *Regulatory toxicology and pharmacology : RTP* 2017, 87:36-53.	Wrong outcome
Dunbar MS, Tucker JS, Ewing BA, Pedersen ER, Miles JN, Shih RA, D'Amico EJ: Frequency of E-cigarette Use, Health Status, and Risk and Protective Health Behaviors in Adolescents. *J Addict Med* 2017, 11(1):55-62.	Wrong outcome
Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V: Characteristics, Perceived Side Effects and Benefits of Electronic Cigarette Use: A Worldwide Survey of More than 19,000 Consumers. *International Journal of Environmental Research and Public Health* 2014, 11:18.	Comparison between EC and CC not possible
González-Roz A, MacKillop J: No evidence of differences in smoking levels, nicotine dependence, carbon monoxide or motivational indices between cigarette smokers and cigarette + e-cigarette dual users in two samples. *Addict Behav* 2021, 112:106543.	Wrong outcome
Jackson M, Singh KP, Lamb T, McIntosh S, Rahman I: Flavor Preference and Systemic Immunoglobulin Responses in E-Cigarette Users and Waterpipe and Tobacco Smokers: A Pilot Study. *Int J Environ Res Public Health* 2020, 17(2).	Not EC-CC dual use
Jacob P, St. Helen G, Yu L, Nardone N, Havel C, Cheung P, Benowitz NL: Biomarkers of Exposure for Dual Use of Electronic Cigarettes and Combustible Cigarettes: Nicotelline, NNAL, and Total Nicotine Equivalents. *Nicotine and Tobacco Research* 2020, 22(7):1107-1113.	Wrong outcome
Jain RB: Re-visiting serum cotinine concentrations among various types of smokers including cigarette only smokers: some new, previously unreported results. *Environ Sci Pollut Res Int* 2020.	Wrong outcome

Karasneh R, Al-Azzam S, Nusair M, Hawamdeh S: Perceptions, symptoms, and practices of electronic cigarette users: Descriptive analysis and validation of Arabic short form vaping consequences questionnaire. *PLoS One* 2021, 16(1):e0245443.	Comparison between EC and CC not possible
Kim J PhD MPH, Lee S: Daily Cigarette Consumption and Urine Cotinine Level between Dual Users of Electronic and Conventional Cigarettes, and Cigarette-Only Users. *J Psychoactive Drugs* 2020, 52(1):20-26.	Wrong outcome
Lechasseur A, Huppé C, Talbot M, Routhier J, Aubin S, Beaulieu M, Duchaine C, Marsolais D, Morissette M: Exposure to nicotine-free and flavor-free e-cigarette vapors modifies the pulmonary response to tobacco cigarette smoke in female mice. *American journal of physiology Cell physiology* 2020, 319:717-727.	Animal study
Lechner WV, Janssen T, Kahler CW, Audrain-McGovern J, Leventhal AM: Bi-directional associations of electronic and combustible cigarette use onset patterns with depressive symptoms in adolescents. *Prev Med* 2017, 96:73-78.	Wrong outcome
Lehmann K, Kuhn S, Reimer J: Electronic Cigarettes in Germany: Patterns of Use and Perceived Health Improvement. *Eur Addict Res* 2017, 23(3):136-147.	Comparison between EC and CC not possible
Majeed B, Linder D, Eissenberg T, Tarasenko Y, Smith D, Ashley D: Cluster analysis of urinary tobacco biomarkers among U.S. adults: Population Assessment of Tobacco and Health (PATH) biomarker study (2013-2014). *Preventive Medicine* 2020, 140 (no pagination).	Comparison between EC and CC not possible
Makena P, Liu G, Chen P, Yates CR, Prasad GL: Urinary Leukotriene E(4) and 2,3-Dinor Thromboxane B(2) Are Biomarkers of Potential Harm in Short-Term Tobacco Switching Studies. *Cancer Epidemiol Biomarkers Prev* 2019, 28(12):2095-2105.	Not EC-CC dual use
Makri OE, Pallikari A, Kagkelaris K, Mastronikolis SN, Karanasios G, Symeonidis C, Plotas P, Georgakopoulos CD: The Acute Effects of Electronic Cigarette Vaping and Tobacco Cigarette Smoking on Choroidal Thickness in Young, Healthy, Habitual, Dual Smokers. *Toxics* 2020, 8(4).	Comparison between EC and CC not possible
Marsden DG, Loukas A, Chen B, Perry CL, Wilkinson AV: Associations between frequency of cigarette and alternative tobacco product use and depressive symptoms: A longitudinal study of young adults. *Addict Behav* 2019, 99:106078.	Wrong outcome
Mohamed MHN, Rahman A, Jamshed S, Mahmood S: Effectiveness and safety of electronic cigarettes among sole and dual user vapers in Kuantan and Pekan, Malaysia: a six-month observational study. *BMC Public Health* 2018, 18(1):1028.	Comparison between EC and CC not possible
Nollen NL, Mayo MS, Clark L, Cox LS, Khariwala SS, Pulvers K, Benowitz NL, Ahluwalia JS: Tobacco toxicant exposure in cigarette smokers who use or do not use other tobacco products. *Drug Alcohol Depend* 2017, 179:330-336.	Not EC-CC dual use
O'Connell G, Graff DW, D'Ruiz C: Reductions in biomarkers of exposure (BoE) to harmful or potentially harmful constituents (HPHCs) following partial or complete substitution of cigarettes with electronic cigarettes in adult smokers. *Toxicology Mechanisms and Methods* 2016, 26(20):453-464.	Not real-world study
Park MB, Choi JK: Differences between the effects of conventional cigarettes, e-cigarettes and dual product use on urine cotinine levels. *Tob Induc Dis* 2019, 17:12.	Wrong outcome
Polosa R, Morjaria J, Caponnetto P, Caruso M, Strano S, Battaglia E, Russo C: Effect of smoking abstinence and reduction in asthmatic smokers switching to electronic cigarettes: evidence for harm reversal. *International journal of environmental research and public health* 2014, 11(5):4965-4977.	Comparison between EC and CC not possible
Polosa R, Morjaria JB, Caponnetto P, Prosperini U, Russo C, Pennisi A, Bruno CM: Evidence for harm reduction in COPD smokers who switch to electronic cigarettes. *Respiratory research* 2016, 17(1):166.	Comparison between EC and CC not possible
Polosa R, Morjaria JB, Prosperini U, Russo C, Pennisi A, Puleo R, Caruso M, Caponnetto P: Health effects in COPD smokers who switch to electronic cigarettes: a retrospective-prospective 3-year follow-up. *Int J Chron Obstruct Pulmon Dis* 2018, 13:2533-2542.	Comparison between EC and CC not possible
Pulvers K, Emami AS, Nollen NL, Romero DR, Strong DR, Benowitz NL, Ahluwalia JS: Tobacco Consumption and Toxicant Exposure of Cigarette Smokers Using Electronic Cigarettes. *Nicotine Tob Res* 2018, 20(2):206-214.	Comparison between EC and CC not possible
Rubinstein ML, Delucchi K, Benowitz NL, Ramo DE: Adolescent Exposure to Toxic Volatile Organic Chemicals From E-Cigarettes. *Pediatrics* 2018, 141(4).	Comparison between EC and CC not possible
Singh KP, Maremanda KP, Li D, Rahman I: Exosomal microRNAs are novel circulating biomarkers in cigarette, waterpipe smokers, E-cigarette users and dual smokers. *BMC Med Genomics* 2020, 13(1):128.	Not EC-CC dual use

Smith DM, Christensen C, van Bemmel D, Borek N, Ambrose B, Erives G, Niaura R, Edwards KC, Stanton CA, Blount BC *et al*: Exposure to Nicotine and Toxicants Among Dual Users of Tobacco Cigarettes and E-Cigarettes: Population Assessment of Tobacco and Health (PATH) Study, 2013-2014. *Nicotine Tob Res* 2021.	Comparison between EC and CC not possible
So CJ, Meers JM, Alfano CA, Garey L, Zvolensky MJ: Main and Interactive Effects of Nicotine Product Type on Sleep Health Among Dual Combustible and E-Cigarette Users. *Am J Addict* 2020.	Comparison between EC and CC not possible
Soule EK, Bode KM, Desrosiers AC, Guy M, Breland A, Fagan P: User-Perceived Negative Respiratory Symptoms Associated with Electronic Cigarette Use. *Nicotine & Tobacco Research* 2020, 22:S45-S53.	Comparison between EC and CC not possible
St Helen G, Liakoni E, Nardone N, Addo N, Jacob P, 3rd, Benowitz NL: Comparison of Systemic Exposure to Toxic and/or Carcinogenic Volatile Organic Compounds (VOC) during Vaping, Smoking, and Abstention. *Cancer Prev Res (Phila)* 2020, 13(2):153-162.	Comparison between EC and CC not possible
St Helen G, Nardone N, Addo N, Dempsey D, Havel C, Jacob P, 3rd, Benowitz NL: Differences in nicotine intake and effects from electronic and combustible cigarettes among dual users. *Addiction* 2020, 115(4):757-767.	Comparison between EC and CC not possible
Veldheer S, Yingst J, Midya V, Hummer B, Lester C, Krebs N, Hrabovsky S, Wilhelm A, Liao J, Yen MS *et al*: Pulmonary and other health effects of electronic cigarette use among adult smokers participating in a randomized controlled smoking reduction trial. *Addictive behaviors* 2019, 91:95-101.	Comparison between EC and CC not possible
Vora MV, Chaffee BW: Tobacco-use patterns and self-reported oral health outcomes: A cross-sectional assessment of the Population Assessment of Tobacco and Health study, 2013-2014. *J Am Dent Assoc* 2019, 150(5):332-344.e332.	Not EC-CC dual use
Wiener RC, Bhandari R: Association of electronic cigarette use with lead, cadmium, barium, and antimony body burden: NHANES 2015-2016. *J Trace Elem Med Biol* 2020, 62:126602.	Comparison between EC and CC not possible
Wiernik E, Airagnes G, Lequy E, Gomajee R, Melchior M, Le Faou AL, Limosin F, Goldberg M, Zins M, Lemogne C: Electronic cigarette use is associated with depressive symptoms among smokers and former smokers: Cross-sectional and longitudinal findings from the Constances cohort. *Addict Behav* 2019, 90:85-91.	Wrong outcome
Wong LP, Mohd Salim SN, Alias H, Aghamohammadi N, Hoe VCW, Isahak M, Ali Mohd M: The Association Between E-Cigarette Use Behaviors and Saliva Cotinine Concentration Among Healthy E-Cigarette Users in Malaysia. *J Addict Nurs* 2020, 31(2):102-109.	Wrong outcome

Table S3. Detailed overview of all 52 included studies investigating health effects of dual use.

First author, reference, year of publication, country	Conflict of interest	Method	Duration at follow-up	Numbers included, description of participants and use	Percent dual users in the study sample	Risk of bias	Major outcomes	Findings Adjusted analyses and odds ratio (aOR) shown (95%confidence intervals) if not mentioned otherwise	Overall finding: Dual use outcome
Akinkugbe A.A. (1) 2019 USA	None	Population-based survey (PATH) Cross-sectional data High participation rates	12 months (past year)	13,650 adolescents aged 12 to 17 years Past 30 days use 12,692 NU 221 EC 433 ESCC 196 DU	1.4% of all 66% of EC	Low risk of selection bias Risk of recall bias Weighted data Adjusted for 6 confounders	Self-reported past-year diagnosis with dental problems (told by health professional)	Ever users: Never use, ref =1 EC: 1.11 (0.79 to 1.55) ESCC: 1.50 (1.18 to 1.90) DU: 1.72 (1.24 to 2.38) Current/past 30 days users: Never use, ref =1 EC: 1.12 (0.90 to 1.38) ESCC: 1.34 (1.13 to 1.58) DU: 1.43 (1.22 to 1.67)	DU: higher odds of dental problems than ESCC, but SIGN. not tested
Bhatta D. N. (2) 2020 USA	None	Nationally representative, longitudinal cohort study (PATH) High participation rates	2 years retrospective respiratory disease	32,320 adults Never, former and current smokers and EC, DU Current use: every day or some days Only weighted numbers shown	78.6% of EC users at wave 1	Low risk of selection bias Risk of recall bias Weighted data Adjusted for 5 confounders	Self-reported respiratory disease (chronic obstructive pulmonary disease, chronic bronchitis, emphysema, or asthma)	The total adj. odds of developing respiratory disease for a current DU= 3.30 compared with a never smoker who never used EC Ref. never smoker who never used EC DU (with TP): aOR=3.04 DU (with CC): aOR=3.32 Current ESCC: aOR=2.56 (1.92, 3.41) Current EC: aOR=1.29 (1.03, 1.61)	DU: higher odds of reporting of respiratory disease than ESCC but SIGN. level not tested
Cardenas V.M. (3) 2020 USA	None	A state-level, population-based public health surveillance system that monitors key maternal behaviors	Prospective design: EC exposure during the 3 months before pregnancy and/or during the last 3 months of pregnancy	1594 pregnant women User: Daily and non-daily use in last 30 days 372 ESCC 100 DU 18 EC only	6.6% of all 80% of EC	Low risk of selection bias Risk of recall and social desirability-ty bias Weighted data Adjusted for 4 confounders	Risk of small-for-gestational-age (SGA)	Estimated adjusted RR for SGA ESCC: 1.7 (95% confidence interval [CI]: 1.1, 2.7), DU: 1.8 (95% CI: 1.0, 3.4) Women who were DU and continued using EC but stopped smoking cigarettes had an increased risk for SGA compared with NU, 3.2 (95% CI: 1.5, 6.6).	DU: higher odds of giving birth to a small-for-gestational-age child than ESCC, but SIGN. level not tested
Carroll D.M. (4) 2018 USA	None	Clinical cross-sectional study	No follow-up	94 persons of American Indian descent Mean age 38 DU definition: smoked ≥ 5 CC in the past 3 months, smoked in the past 24 hours, used an EC every day in the past 3 months,	33% of sample 54% of EC	High risk of selection bias Adjusted for urine creatinine only Measurement bias	NNAL carcinogen metabolite in urine CO (cardiovascular toxicant)	NNAL (pg/mg) EC: 6.1 ESCC: 261.4 DU: 228.0 (ESCC vs. DU: p = 0.35) CO (ppm) EC: 2.4 ESCC: 14.7 DU: 16.8 (ESCC vs. DU: p = 0.54)	DU same level of carcinogen biomarker and cardiovascular toxicant as ESCC

				used an EC in the past 24 hours, and had not used any other tobacco products in the past 3 months. 34 ESCC 31 DU 29 EC only					
Chen D. TH. (5) 2021 UK	None	Cross-sectional study Data from wave 1 (May 2020) of University College London Centre for Longitudinal Studies COVID-19 study. Online survey.	No follow-up	N= 13,077 adults (20-63 y/o) Self-reported non-smoker, current or occasionally ESCC, EC or DU. 287 DU 1198 ESCC 489 EC only	2.2 % of all 37% of EC	Low risk of selection bias Risk of recall bias and of desirability bias Adjusted for 6 confounders Weighted data	Self-reported experience of covid-19 symptoms, adherent of social-distancing, confirmed/suspected covid-19 diagnosis, received covid-19 test.	NU= ref. Experiencing Covid-19 symptoms: ESCC: aOR= 1.21 (0.87, 1.69) p= 0.26 EC: aOR= 1.08 (0.61, 1.89) p= 0.8 DU: aOR= 1.41 (0.79, 2.54) p= 0.25 Confirmed/suspected covid-19 diagnosis: ESCC: aOR= 1.1 (0.89, 1.36) p= 0.66 EC: aOR= 1.22 (0.90, 1.65) p= 0.97 DU: aOR=2.15 (1.15, 4.05) p= 0.02 Received covid-19 test: ESCC: aOR= 1.05 (0.75,1.48) p= 0.75 EC: aOR= 0.85 (0.48, 1.50) p= 0.16 DU: aOR= 1.97 (0.62, 6.32) p= 0.25	DU had higher odds of covid-19 symptoms and higher odds of confirmed/suspected covid-19 diagnosis than ESCC but SIGN. level not tested
Cho J. H. (6) 2016 South Korea	None	Cross-sectional analysis on data from the Korea Youth Risk Behaviors Web-based survey (2014)	Past 12 months	N= 35,904 adolescents (10^{th} – 12^{th} grade in high school) Current (past 30 days), former and never users of EC and ESCC. 2,513 EC 31,313 Never -EC 26,490 never- ES 4,694 ESCC DU?	5.6 % of all	Low risk of selection bias Adjusted for 7 confounders Not stated that it is weighted/not weighted?	Self-reported asthma diagnosis	Never user: (ref.) FormerEC+ESCC: AOR= 1.16 (0.42, 3.19) FormerEC-CurrentESCC: AOR= 0.91 (0.34, 2.40) CurrentEC-FormerESCC: AOR= 0.60 (0.21, 1.71) DU: AOR= 0.46 0.20, 1.07) Du higher odds of asthma compared to ESCC-neverEC and ESCC-formerEC (05% CI). Only SIGN. in DU in unadjusted model: ESCC-neverEC: ref. ESCC-formerEC: OR= 0.92 (0.57, 1.51) DU: OR= 1.45 (1.00, 2.11), p< 0.05 ESCC-neverEC: ref. ESCC-formerEC: aOR= 0.91 (0.54, 1.54) DU: aOR=1.30 (0.86, 1.96)	DU higher odds of reporting asthma than ESCC but not SIGN. in adjusted analyses
Choi D-W (7) 2018 South Korea	None	National survey Cross sectional data		N= 8,809 adults Current use: not specified 142 DU 1359 ESCC 1654 Ex-ESCC 5654 NU	1.6% of all (no info on EC)	Low risk of selection bias Adjusted for 12 confounders Took former tobacco consumption into account	Diabetes (HbA1c)	DU: β: 0.1116; SE: 0.0343 (p=0.001) ESCC: β: 0.0752; SE:0.0245 (p=0.002) Ex-ESCC: β: 0.0261; SE: 0.0234 (p=0.26) NU: ref	DU SIGN. worse than NU DU worse than ESCC but not SIGN.

						Weighted data			
Chung S. J. (8) 2020 South Korea	None	Cross-sectional analysis on data from the Korea youth Risk Behavior Survey (2018)	Past 12 months	N= 60,040 adolescents (13-18 y/o) Current (past 30 days), former and never use of EC, CC and HTP (HTP not included here) 1456 EC 3722 ESCC 531 DU and never user of heated tobacco	2.7 % of all 36% of EC	Low risk of selection bias Adjusted for 8 confounders Weighted data	Self-reported asthma and allergic rhinitis diagnosis	DU had higher odds for current allergic rhinitis than ESCC compared to ESCC but SIGN. not tested NUs: ref. ESCC-only: aOR= 1.3 (1.1, 1.6), p= 0.02 DU: aOR= 1.6 (1.2, 2.2), p= 0.002 DU had lower odds for current asthma than ESCC in adjusted analysis but SIGN. not tested. Never users: ref . ESCC-only: OR= 1.6 (1.1-2.2), p=0.005 DU: OR= 1.2 (0.8-2.0),p=0.39	DU had higher odds for current allergic rhinitis but lower odds of current asthma than ESCC, but SIGN. not tested
Clemens M.M. (9) 2019 USA	None	A state-level, population-based public health surveillance system that monitors key maternal behaviors (Important: subsample of (3))	Prospective design: EC exposure during the 3 months before pregnancy and/or during the last 3 months of pregnancy	248 pregnant women 76 singleton livebirths from 81 women Past 30 day use 27 ESCC 11 DU 38 NU	6.6% of all	Low risk of selection bias Risk of social desirability bias Weighted data Adjusted for 4 confounders Confirmed smoking status	Carcinogen metabolites (TSNAs, NNAL, and NNK) in hair samples Risk of small-for-gestational-age (SGA)	DU: levels of TSNAs similar to ESCC RR for SGA, confirmed smoking status by hair nicotine level (only 58 women) NU: ref. DU RR= 8.3; 1.0–69.1 (p=0.05) ESCC: RR= 7.8; 1.0–59.0 (p=0.05)	DU same level of carcinogen biomarkers as ESCC
Dinkeloo E. (10) 2019 USA	None	Online survey Cross sectional data	Use of product in the last 30 days	2,854 men, active duty soldiers, mean age 25 years current DU: EC use and tobacco cigarette use within the last 30 days and smoking 100 CC in their lifetime 2298 NU 355 ESCC 63 EC 138 DU	4% of all 69% of EC were DU	Low risk of selection bias Risk of social desirability bias Adjusted for 2 confounders	Physical activity (Exposure-Specific APFT Performance): 2-mile run, push-p test and sit-up test	NU averaged the most total physical training, followed by EC, ESCC, and then DU. DU had significantly ($p<0.05$) lower scores than ESCC and NU on all 3 fitness events (2 mile run time, push-up and sit-up performance)	DU: SIGN. worse fitness than ESCC
Fetterman J. (11) 2020	None	Clinical study	-	N= 467 healthy adults 21-45Y	11 % of all/sample, 59% of EC	High risk of selection bias	Cardiovascular health Augmentation index (arterial stiffness)	Many measures of vascular health did not	DU

USA		Cross-sectional data collected in one visit Noninvasive vascular function testing		Current users Dual use: lifetime usage of ≥100 CC and EC usage of at least 5 days per week 94 NU 285 ESCC 36 EC only 52 DU		Adjusted for 4 confounders		differ between NU, EC, DU and ESCC, including measures of large and small vessel vasodilator response In multivariable adjusted models: Augmentation index values (P=1.0) DU: 134.9±4.0 ESCC: 129.8±1.5 The augmentation index was similar between ESCC, EC and DU	same arterial stiffness as ESCC
Flacco M. E. (12) 2019 Italy	Yes △	Cohort study 4th follow-up of study described by Manzoli 2015	48 ± 3 months	1355 adults enrolled at baseline N= 915 Current users of products at least 6 months at baseline 228 EC only 471 ESCC 216 DU	59% of EC	High risk of recall and selection bias 63% validated by hospital records Adjusted for 13 confounders Took former tobacco consumption into account	Changes in self-reported health Possibly smoking-related disease: (PSRD) (COPD, myocardial infarction and/or angina, congestive heart failure, transitory cerebrovascular ischemia or stroke, any cancer)	Multivariate analyses: (OR, 95% CI) of PSRD observed among baseline-users: No significant differences across groups ESCC ref (0) EC: aOR: 1.01 (0.52-1.98), p=0.9 DU: aOR: 1.57 (0.84-2.96), p=0.16 No significant differences across groups when restricted to non-switchers. Self-reported health score (diff. baseline) ESCC: ref (0) EC: -0.34 (-0.65, -0.04), p= 0.028 DU: 0.45 (-0.13, 1.04), p= 0.13	DU same self-reported health and same rate of smoking related disease after 4 years as ESCC
Flacco M. E. (13) 2020 Italy	Yes ▲	Cohort study 5th follow-up of study described by Manzoli 2015	72 ± 3 months	1355 adults enrolled at baseline N= 912 Current users of products at least 6 months at baseline 228 EC 469 ESCC 215 DU	Baseline: 15.9 % of all Follow-up: 5.2 %	High risk of recall and selection bias 62.8 % validated by hospital records Analyses A adjusted for 5 confounders ; analyses B adjusted for 13 confounders Took former tobacco consumption into account	Changes in self-reported health Possibly smoking-related disease: (PSRD) (COPD, myocardial infarction and/or angina, congestive heart failure, transitory cerebrovascular ischemia or stroke, any cancer)	Multivariate analyses A: (OR, 05% CI) of PSRD: Observed among baseline-users: No significant differences across groups ESCC: ref. EC: aOR= 1.17 (0.64, 2.13) p= 0.6 DU: aOR= 1.48 (0.81, 2.70) p= 0.2 No significant differences across groups when restricted to non-switchers. Multivariate analyses B: Self-reported health score (diff. baseline) ESCC: ref. EC: -0.19 (-0.42, 0.05) p= 0.12 DU: 0.16 (-0.08, 0.39) p= 0.19 No significant differences across groups when restricted to non-switchers.	DU had higher odds of possibly smoking related disease after 6 years than ESCC but not SIGN.
Gaiha S. M. (14) 2020 USA	None	National online survey Cross-sectional data	-	N= 4,351 Adolescents and young adults 13-24 years Current (past 30 days) use 2,168 NU 2,183 EC-ever	?	Low risk of selection bias Recall bias Weighted data Adjusted for 5 confounders	Self-reported COVID-19 related symptoms, testing and diagnosis	Multivariate adjusted analyses: COVID-19 diagnosis in past 30 days users of product; aOR (95CI%) ESCC: 1.53 (0.29, 8.14) EC: 1.91 (0.77, 4.73) DU: 6.84 (2.40, 19.55) NU: ref Current COVID-19 symptoms in past 30 days users of product aOR (95CI%) ESCC: 1.15 (0.58, 2.27) EC: 1.43 (0.84, 2.43)	DU higher risk of COVID-19 symptoms and diagnosis than NU (and probably ESCC (SIGN. not tested)

								DU: 4.69 (3.07, 7.16) NU: ref	
Goniewicz M.(15) 2018 USA	Yes	Nationally representative, longitudinal cohort study (PATH) 2013-2014 Cross-sectional analyses	-	N=5,105 adults (18+) Current every day or some day use ESCC: 2411 EC: 247 DU:792 (only 20% used EC daily) NU: 1655 (n lower for VOC metabolite analyses)	15.5 % of all 77% of EC	Low risk of selection bias creatinine level corrected weighted data Measurement bias Adjusted for 7 confounders	50 biomarkers of toxicity (TSNAs, metals, PAHs & VOCs) in urine	DU had higher geo mean in 46/50 biomarkers. The higher concentrations of biomarkers were statistically significant compared to ESCC in 28/50 biomarkers: 5/8 urinary nicotine metabolites 3/4 TSNAs 2/8 heavy metals 5/7 PAHs 13/20 VOCs Mean concentrations of lead and cadmium did not differ between DU and ESCC	DU: SIGN. higher concentration of most biomarkers of toxicity/carcinogenicity than ESCC
Harlow A. (16) 2020 USA	None	Prospective preconception cohort study Online survey (PRESTO study)	Bimonthly follow-up questionnaires until self-reported pregnancy, up to 12 months	N= 4,586 women trying to conceive 21-45 years 3427 completed, 1115 lost to f-up Current and use Baseline: ever use, follow-up: use in the previous 4 weeks. NU: 3,432 ? ESCC Former EC:609 Current EC:172 DU: 34	0.7% of all 17% of EC	Low risk of selection bias High risk of social desirability bias Adjusted for 12 confounders Took former tobacco consumption into account	Fecundability (menstrual cycle and achieved pregnancy)	Adjusted fecundability ratio (FR 95%CI)) compared to noncurrent users (never and former EC and/or ESCC) EC: 0.91 (0.70, 1.18) ESCC: 1.01 (0.85, 1.20) DU: 0.83 (0.54, 1.29) (only 25 pregnancies, low power)	DU lower fecundability ratio than ESCC but not SIGN. (low power)
Hedman L. (17) 2018 Sweden	Yes	Cross-sectional analyses on data from two population-based surveys Obstructive Lung Disease in Northern Sweden (OLIN) and West Sweden Asthma Study (WSAS) same validated questionnaire	Past year	N= 30,272 adults Adults age 20-75 Current use: ESCC: Do you smoke? EC daily or occasional use EC: 529 ESCC: 3694 FESCC: 7305 DU: 350	1.1 % of all 67% of EC	Low risk of selection bias Recall bias Adjusted for 4 confounders	Self-reported respiratory symptoms: long-standing cough (past year), sputum production, chronic productive cough (3 months – 2 years), any wheeze (12 months), recurrent wheeze	All symptoms were most common in DU (p<0.01). Adjusted analyses, aOR (95%CI) for having any respiratory symptom: NU: ref DU: 4.03; (3.23-5.02) ESCC: 2.55; (2.36-2.77) FESCC: 1.27; (1.19-1.36)	DU had SIGN. more self-reported respiratory symptoms than NU Worse than ESCC (SIGN. not tested)

Jain R. (18) 2019 USA	None	Cross-sectional analysis on data from the population-based survey NHANES (2013-2016)	-	1139 US residents aged ≥12 years Current use of products during the last 5 days ESCC: 891 EC only: 52 DU: 46 TP: 105	4 % of all 47% of EC	Low risk of selection bias Weighted analyses Adjusted analyzes, 5 confounders Measurement bias	Levels of metals in blood (cadmium, lead and mercury)	DU and EC did not have lower levels of blood cadmium, lead, and mercury than ESCC or TP. Adjusted geometric means (AGM)of cadmium: DU: 0.64 (0.44-0.93) ESCC: 0.78 (0.72-0.84) EC: 0.7 (0.49-1.01) Adjusted geometric means (AGM)of lead: DU: 1 (0.78-1.29) ESCC: 1.19 (1.11-1.28) EC: 1.17 (0.9-1.52) Adjusted geometric means (AGM)of mercury: DU: 0.66 (0.45-0.97) ESCC: 0.68 (0.61-0.76) EC: 0.83 (0.48-1.43)	DU same levels of metals in blood as ESCC and EC
Keith R. (19) 2020 USA	None	Cross-sectional analysis on data from a cohort CITU (2014-2016)	-	371 healthy adults mean age 32 years Current (past 30 days) use NU: 87 EC only: 17 ESCC: 237 DU: 30	8 % of all 64% of EC	Low risk of selection bias Measurement bias Adjusted for 3 confounders	Toxicity Volatile organic compound (VOC) metabolites in urine	ESCC and DU had SIGN. elevated levels of all VOC metabolites except MU, BPMA, and BMA DU and ESCC had similar levels of all VOC metabolites except PGA, PHEMA, and 3MHA + 4MHA, which were all significantly higher in ESCC than DU DU: lower levels of metabolites of styrene and xylene than ESCC	DU and ESCC had similar levels of most VOC metabolites
Kim C. (20) 2020 South Korea	None	Cross-sectional analysis on data from the population-based survey KNHANES (2013-2017) Professional physiological measures and a survey	-	N= 7,505 adult men (19+) Mean age 37 years DU: 100 CC in lifetime; EC use in the past month DU: 337 ESCC: 4,079 EC only: 62 NU: 3,027	5.1 % of all 84% of EC DU: SIGN. higher poly-use of new tobacco products	Low risk of selection bias Recall bias Adjusted for 14 confounders Measurement bias Weighted data	Cardiovascular risk factors Risk factors: Elevated waist circumference (WC), blood pressure (BP), triglycerides (T) and fasting glucose (FG), reduced HDL-cholesterol (HDL-C) and diagnosis of metabolic syndrome (MetS)	Fully adjusted model: DU SIGN. higher association compared to ESCC and NU. aPOR (95%CI) Elevated WC DU vs. ESCC: 1.96 (1.19, 3.23), p= 0.008 DU vs. NU: 2.26 (1.31, 3.91), p=0.003 Elevated triglycerides DU vs. ESCC: 1.44 (0.99, 2.10), p= 0.058 DU vs. NU: 2.81 (1.90, 4.14), p<0.001 Reduced HDL-cholesterol DU vs. ESCC: 1.9 (1.31, 2.76), p= 0.001 DU vs. NU: 2.48 (1.66, 3.71), p<0.001 Diagnosis of MetS DU vs. ESCC: 1.57 (1.03, 2.40), p= 0.038 DU vs. NU: 2.79 (1.72, 4.53), p< 0.001 Elevated BP: DU vs. ESCC: 0.68 (0.47–0.98), p=0.037 DU vs. NU: 0.62 (0.41–0.94), p=0.023 Elevated fasting glucose DU vs. ESCC: 1.19 (0.78–1.82), p=0.425 DU vs. NU: 1.38 (0.89–2.16), p=0.153	DU SIGN. worse cardiovascular risk factors than ESCC Except for fasting glucose

Kim T. (21) 2020 South Korea	None	Cross-sectional analysis on data from the 6th Korea National Health and Nutrition Examination Survey (2013-2015)	No follow-up	N= 14,738 adults (≥19 y/o) DU: 100 cigarettes and smoke currently + EC in the past month 325 EC 271 DU	1.8 % of all 85 % of EC	Low risk of selection bias Recall bias Adjusted for 6 confounders Measurement Bias Weighted data	Metabolic syndrome, abdominal obesity, high triglyceride, high fasting glucose, low HDL-cholesterol, High blood pressure	DU significant higher association with abdominal obesity compared to ES and ESCC_everEC (aOR 95% CI), p< 0.001: ESCC: ref. ESCC_everEC: OR= 1.28 (1.04, 1.58) DU: 1.71 (1.25, 2.34) No significant differences between groups in other outcomes.	DU: SIGN. higher odds of abdominal obesity than ESCC Other outcomes: no SIGN. difference but tendency to higher odds in DU (except blood pressure)
Kim T. (22) 2021 South Korea	None	Cross-sectional analysis on data from the nationally representative population-based survey KNHANES (2016-2017) Professional physiological measures (urine and blood sample) and a survey		N= 10,692, adults (>19 y/o). DU: 100 cigarettes and smoke currently + EC in the past month 9,905 NU 178 EC users total 173 DU	97.4 % of EC	Low risk of selection bias Recall bias Selection bias Adjusted for 10 confounders Measurement bias Weighted data	Levels of serum uric acid and hyperuricemia	DU SIGN. higher prevalence of hyperuricemia among all, men, and women who smoke (p< 0.001) ESCC: 14.2 % (0.9) ESCC_ECever: 19.2 % (2.1) DU: 26.6 % (3.6) Fully adjusted model: DU SIGN. higher association between EC use and serum uric acid levels among all, men, and women who smoke (N2,361) All (p= 0.001) ESCC: 5.29 (5.18, 5.39) ESCC_ECever: 5.44 (5.29, 5.59) DU: 5.62 (5.41, 5.83) DU SIGN. higher association between EC use and hyperuricemia among all and men who smoke. All (p= 0.006), aOR (95%CI) ESCC: (ref.) ESCC_ECever: 1.17 (0.83, 1.65) DU: 1.96 (1.29, 2.99)	DU SIGN. higher levels of uric acid and risk of hyperuricemia than ESCC
Leavens E. (23) 2020 USA	None	Cross-sectional analysis on data from The Minnesota Homeless Study 2015 and 2018 Interview-survey. Participants received a $10 gift card.	-	Homeless adults in Minnesota N(2015)= 3627 N(2018)= 4148 Current (past 30 days) use In 2018: DU: 539 EC: 607 ESCC: 2482	13 % of all 89% of EC	High risk of selection bias Recall bias Adjusted for 2 confounders	Self-reported chronic health conditions	DU SIGN. higher rates of asthma and cancer compared to NU and ESCC (Percent and 95%CI) Asthma DU: 28.0 % (24.2, 31.8) ESCC: 21.0 % (19.4, 22.6) NU: 14.7 % (12.7, 16.8) Diff in rates: DU vs. ESCC: -0.07 % (-0.11, -0.3), p< 0.01 DU vs. NU: -0.13 % (-0.18, -0.9), p< 0.001 Cancer DU: 5.2 % (3.0, 7.5) ESCC: 2.7 % (2.0, 3.3) NU: 1.6 % (0.8, 2.3) Diff in rates: DU vs. ESCC: -0.02 % (-0.05, 0.00), p< 0.05 DU vs. NU: -0.04 % (-0.06, -0.01), p< 0.001	DU SIGN. higher rates of asthma and cancer compared to ESCC

Lee A. (24) 2019 South Korea	None	Cross-sectional data from the Korea Youth Risk Behavior Survey (2018)	-	N= 58,336 adolescents (12-18 y/o) Ever use of EC, CC and HTP (HTP not included here) 8129 ESCC 4144 EC	57.1 % of EC users	Low risk of selection bias Recall bias Adjusted for 6 confounders Weighted data	Self-reported asthma, allergic rhinitis and atopic dermatitis	ESCC significant higher odds of asthma than DU (not signf.) compared to never users (95% CI). ESCC: aOR= 1.30 (1.08, 1.56) DU: aOR= 1.14 (0.84, 1.54) DU higher odds of allergic rhinitis than ESCC compared to never users. Not significant. ESCC: aOR= 1.02 (0.94, 1.10) DU: aOR= 1.10 (0.99, 1.21) DI significant higher odds of atopic dermatitis than ESCC compared to never users. ESCC: aOR= 1.20 (1.07, 1.33) DU: aOR= 1.24 (1.06, 1.46)	DU har lower odds of asthma than ESCC, but comparable odds of allergic rhinitis and atopic dermatitis. SIGN. not tested
Li D. (25) 2020 USA	Yes	Cross-sectional analysis on data from population-based PATH study wave 2 (2014-2015)	-	N= 28,171 adults (18+) smoked at least 100 cigarettes in their lifetime, and currently smoke every day or some days EC: 641 only ESCC: 8525 DU: 1106 NU: 17899	3.9 % of all 63% of EC	Low risk of selection bias Risk of recall bias Confounding taken into account (11 variables) Weighted data	Respiratory symptoms Self-perceived physical and mental health	DU reported higher percentage of mental health compared to ESCC, SIGN. not tested DU: 7.46 % (6.01, 9.26) ESCC: 5.01 (4.54 to 5.53) No SIGN. differences were found between DU and ESCC in risk of wheezing and related respiratory symptoms (aOR=1.06, 95% CI: 0.91 to 1.24).	DU same odds of respiratory symptoms as ESCC
Mainous A. (26) 2020 USA	None	Cross-sectional analysis on data from nationally representative survey, NHANES 2015-2016	-	Adults 20+ years Unweighted N= 4,659. Weighted N= 206,172,949 DU: 100 CC in lifetime; EC in the past month NS, EC, ESCC or DU.	Not specified	Low risk of selection bias Weighted data Adjusted for 7 confounders Measurement bias	Biomarker of inflammation and predictor of cardiovascular disease (CRP)	DU had the highest prevalence of elevated hs-CRP (>3 mg/l) (45,6 %) DU had SIGN. higher odds of elevated hs-CRP compared with ESCC in adjusted analyses DU: aOR= 2.13 (1.35, 3.37) ESCC: aOR= 1.38 (1.07, 1.78) DU had the highest level of serum cotinine.	DU SIGN. higher probability of elevated CRP than ESCC
Manzoli L. (27) 2015 Italy	None stated, the first 2 years of study were unfunded Please see study by Flacco (12)	Cohort study Questionnaire at baseline, and follow-up Recruited by general practitioners and e-	12 months	1355 adults at baseline 30-75 years old 959 with 1-year data Current (past 6 months) use 236 EC 491 ESCC	17.1 % of all 50% of EC	High risk of selection bias Risk of recall bias Adjusted for 13 confounders Took former tobacco	Self-reported health	Self-reported health at 1 year, mean (SD): EC: 8.0 (1.3) ESCC: 7.8 (1.3) DU: 7.7 (1.2) Difference in the self-reported health score from 12 months to baseline: aOR (95%CI) ESCC: ref =0 DU: 0.14 (-0.13; 0.40) EC: 0.31 (0.04; 0.59)	DU same self-reported health as ESCC

		cigarette shops, via internet and social networks		232 DU		consumption into account		DU had similar quitting rate, no difference in self-related health, non-significant reduction in cigarettes smoked pr. day.	
Manzoli L. (28) Same study as (12) (13) and (27) 2017 Italy	None stated, the first 2 years of study were unfunded Please see study by Flacco (12)	Cohort study Questionnaire at baseline and 12 and 24 months follow-up CO validation in 25 % of study population	24 months	1355 adults at baseline 30-75 years old 959 with 2-year data Current (past 6 months) use 229 EC only 480 ESCC 223 DU	16.5 % of total population 49% of EC	High risk of selection bias Risk of recall bias Adjusted for 13 confounders Took former tobacco consumption into account	Self-reported health	Self-rated health and adverse events were similar between all groups. Improvement in self-reported health in baseline DU and ESCC who switched to EC (p< 0.05). DU at baseline remained SIGN. more likely to report a serious adverse event than ESCC (OR 2.40; 95% CI 1.09 to 5.26; p=0.029). DU experienced highest % in adverse effects (6.3 %, p< 0.005) No significant difference in the proportion of participants that achieved complete abstinence and reduced tobacco consumption by 50 % or more, or by ≥5 cigarettes pr. day in all groups (p> 0.05). DU (52,5 %) and ESCC (13,7 %) reduced cigarette consumption with ≥50 % (p< 0.001)	DU: same self-rated health and adverse events as ESCC
McDonell BP (29) 2020 Ireland	None	Pregnancy Risk Assessment Monitoring Prospective cohort study	From first hospital visit till birth	322 pregnant women current self-reported smoking and vaping status 218 EC only 195 DU 99 ESCC	47% of EC	Low risk of selection bias Social desirability bias Adjusted for 4 confounders	Infant birthweight, gestation at delivery, incidence of low birthweight	Mean gestation at delivery and mean Apgar scores were similar in all three groups Mean birthweight and birth centile of EC was similar to that of NU and SIGN. greater than that of ESCC Birth weigth EC: 3470 ±555 g (ref) DU: 3140±628 g, p< 0.001 ESCC: 3166± 502 g, p< 0.001 NU: 3471 ±504 g, p=0.97 Neonatal intensive care unit admission: EC: 15 (6.9%) ref DU: 15 (7.6%) ESCC: 6 (6%) NU: 5 (4.6%) Incidence of birthweight <10th centile EC: 24 (11%) ref DU: 60 (30.7%) ESCC: 28 (28%) NU: 14 (12.9%)	Mean birthweight and birth centile of EC was similar to that of NU and SIGN. greater than that of ESCC DU: same birthweight as ESCC DU: more frequent admission to neonatal intensive care unit and higher incidence of birthweight <10th centile than ESCC but SIGN. level not tested
McRobbie H. (30) 2015 UK	Yes	Experimental prospective study Smokers should use EC ad libitum	4 weeks	N=44 smokers wanting to stop, all ESCC at baseline Current use 33 at follow-up:	51.5 % of EC in sample	High risk of selection bias Measurement bias	Measured cardiovascular toxicity (CO), and toxicity (urinary 3-HPMA, a major metabolite of acrolein)	Changes in CO from baseline to 4 weeks: DU: -52 % (p= 0.001) EC: -80 % (p< 0.001) Changes in 3-HPMA from baseline to 4 weeks DU: -60 % (p< 0.001) EC: -79 % (p< 0.001)	DU had SIGN. reductions in toxicity after switching from ESCC in experimental setting

				16 EC 17 DU DU: Reduction from 21 CPD to very little (seven had smoked one to five cigarettes in the last week and 10 had smoked more than 5)				Changes in cotinine DU: -44 % (p= 0.010) EC: -17 % (p= 0.486)	
Merianos A. (31) 2021 USA	None	Secondary data analysis of the school based 2017 Youth Risk Behavior Survey	-	11,296 high school students Use in the past 30 days 566 EC only 157 ESCC 235 DU	2% of all 29% of EC	Low risk of selection bias Adjusted for 8 covariates Weighted data	Self-reported hours of sleep on an average school night Insufficient sleep was defined as <8 h/night and <7 h/night	Insufficient sleep <8 h/night ESCC: 1 ref EC: 3.20 aOR (95%CI = 1.65–6.22) DU: 3.26 aOR (95%CI = 1.51–7.03) to Insufficient sleep <7 h/night ESCC: 1 ref DU; 1.89 times more likely (95%CI = 1.01–3.51)	DU were SIGN. more likely to report insufficient sleep compared with ESCC
Miller C. R. (32) 2021 USA	Yes	Cross-sectional analysis on data from PATHS wave 3 (2015-2016)	-	N= 19,147 adults (18-54 y/o) Dual use: had smoked at least 100 CC in a lifetime, and currently smoked and vaped every day or some days 1100 EC all 5654 ESCC 581 DU	3 % of all 53% of EC	Low risk of selection bias Recall bias Adjusted for 12 confounders Weighted data	Self-reported diagnosis of hypertension in the last 12 months	DU had highest prevalence of self-reported hypertension in weighted analysis: NS: 14.6%, EC-former ESCC: 22.5%, EC: 7.6%, former ESCC: 20.9%, ESCC: 22.4% and DU: 23.8% DU had significant higher odds for hypertension than former ESCC and ESCC compared to NS (95 % CI): Former ESCC: aOR= 1.28 (1.05, 1.57) ESCC: aOR= 1.36 (1.15, 1.62) DU: 1.77 (1.32, 2.39) DU had the highest odds for hypertension than any other group compared to ESCC and former ESCC, but results were not significant.	DU had higher odds for hypertension than ESCC, but SIGN. difference not reached (0.99 for lower 95%CI)
Orimoloye O. (33) 2019 USA	None	Cross-sectional analysis on data from population-based survey NHANES (2013-2014 & 2015-2016)	-	N= 3415 adults (18+) EC: last 5 days use ESCC: smoked within the last year 2636 NU 711 ESCC 30 EC 38 DU	1 % of all 56% of EC	Low risk of selection bias Analyses adjusted for 6 confounders Measurement bias Weighted data	Insulin resistance (measured by HOMA-IR and GTT levels)	No statistically significant association between insulin resistance and product use	DU same risk of insulin resistance as ESCC, EC and NU
Osei A. (34) 2019 USA	None	Cross-sectional analysis on data from the nationally representativ	-	N=449,092 adults (18+) Current use Dual use: had smoked at least 100 CC in	2.9 % of all 49% of EC	Low risk of selection bias Risk of recall bias Weighted data	Self-reported cardiovascular disease (CVD); told by doctor (Has a doctor, nurse, or other health professional ever told you that you had a stroke, myocardial infarction or coronary heart disease?)	DU had higher odds of CVD compared with ESCC and EC and the odds increased with daily use Risk of cardiovascular disease, adjusted OR (95%) ESCC: ref DU (all): 1.36 (1.18, 1.56) DU_occasional: 1.30 (1.12, 1.52)	DU had SIGN. higher risk of CVD than ESCC

		e, cross-sectional telephone survey BRFSS 2016-2017		a lifetime, and currently smoked and vaped every day or some days 390,303 NU 15,863 EC 58,789 ESCC 12,908 DU		Adjusted for 9 confounders		DU_daily: 1.59 (1.20, 2.08) Risk of premature cardiovascular disease, adjusted OR (95%) ESCC: ref DU (all): 1.45 (1.20, 1.74) DU_occasional: 1.36 (1.11, 1.66) DU_daily: 1.84 (1.32-2.56)	
Osei A. (35) 2020 USA	Yes	Cross-sectional analysis on data from the nationally representative, cross-sectional telephone survey BRFSS 2016-2017	-	N= 705,159 adults (18+) Current use 25,175 EC 64,792 ESCC 432,462 NU 14,036 DU	2.0 % of all 36% of EC	Low risk of selection bias Risk of recall bias Weighted data Adjusted for 5 confounders	Self-reported COPD, told by doctor (Has a doctor, nurse, or other health professional ever told you that you have chronic obstructive pulmonary disease or COPD, emphysema, or chronic bronchitis?)	DU had SIGN. higher odds of COPD compared with ESCC and EC Risk of COPD, adjusted OR (95%) ESCC: ref DU: 1.66 (1.50, 1.84) DU_occasional: 1.67 (1.50, 1.86) DU_daily: 1.64 (1.34, 2.00) DU compared to NU had the highest odds for COPD compared to any other group DU: OR= 6.89 (6.29, 7.55)	DU had SIGN. higher odds of COPD than ESCC
Parekh T. (36) 2019 USA	None	Cross-sectional analysis on data from the nationally representative, cross-sectional telephone survey BRFSS 2016-2017	-	N= 161.529 young adults (18-44) Current use 133,077 NU 13,318 ESCC 7,641 EC 7,493 DU	5 % of all 50% of EC	Low risk of selection bias Risk of recall bias Weighted data Adjusted for 13 confounders	Self-reported stroke	DU had higher risk of stroke than any other group Risk of stroke, adjusted OR (95%) NU ref. EC: 0.69 (0.3-1.4) (p= 0.69) ESCC: 1.59 (1.1-2.2) (p< 0.01) DU: 2.91 (1.6-5.3) (p<0.01) Risk of stroke, adjusted OR (95%) ESCC: ref DU: 1.83 (1.1-3.2) (p< 0.05)	DU SIGN. higher risk of stroke than ESCC
Parekh T. (37) 2020 USA	None	Cross-sectional analysis on data from the nationally representative, cross-sectional telephone survey BRFSS 2016-2017	-	N=161.965 young adult women (18-44) Current use 3125 DU 76161 NU 2572 EC 6583 ESCC (no EC use prev.)	3 % of all 55% of EC	Low risk of selection bias Risk of recall bias Weighted data Adjusted for 9 confounders	Self-reported COPD and asthma (Ever told that you had asthma?) (Ever told you have COPD, emphysema, or chronic bronchitis?)	DU had highest odds for self-reported asthma and COPD Risk of asthma, adjusted OR (95%) NU: ref EC: 1.74 (1.29, 2.35) ESCC: 1.49 (1.25, 1.77) DU: 2.11 (1.72, 2.59) Risk of COPD, adjusted OR (95%) NU: ref EC: 1.37 (0.71, 2.63) ESCC: 3.28 (2.62, 4.12) DU: 5.07 (3.91, 6.56)	DU SIGN. higher risk of asthma and COPD compared with NU; higher risk than ESCC, but SIGN. not tested

Piper M (38) 2018 USA	None	Cross-sectional analysis Baseline data from a 2-year cohort	-	422 adults (18+) DU: EC use once a week for 3 months and smoked daily 3 months 66 ESCC 256 DU Changes in DU criteria 6 months in	61 % of sample	Low risk of selection bias Adjusted for 4 confounders , including psychiatric history Measurement bias	Toxicity NNAL and CO	CO levels (p=0.67) ESCC: 16,7 DU: 16,3 NNAL levels (p= 0.001) ESCC: 453.31 DU: 340.99 Effects were consistent when baseline demographic variables that differed between the two groups were included as covariates DU smoked less cigarettes, were less likely to smoke within 30 minutes after waking up and had higher FTCD scores but were also more likely to have a psychiatric history. Similar cotinine levels in ESCC and DU	ESCC had SIGN. higher levels of NNAL but same levels of CO as DU
Prokopowicz A. (39) 2019 Poland	Yes ▲	Cross-sectional study Questionnaire and blood sample	-	156 young volunteer adults (19-39 years old) not occupationally exposed to Cadmium (Cd) and Lead (Pb) DU: CC for at least 2 years and EC for at least 6 months 51 NU 48 EC 29 DU 28 ESCC	38% of EC	High risk of selection bias Analyses adjusted for 2 confounders Measurement bias	Harmful metals Cadmium (Cd) and Lead (Pb) in blood	Geometric mean blood Cd concentrations (adjusted for age+sex) NU: 0.31 (0.26, 0.36) EC: 0.44 (0.37, 0.52) DU: 1.38 (1.11, 1.72), not SIGN. from ESCC ESCC: 1.44 (1.16, 1.78) Geometric mean blood Pb concentrations (adjusted for sex) NU: 11.9 (10.6, 13.3) EC: 14.2 (12.5, 16.0) DU: 13.9 (11.9, 16.2), not SIGN. from ESCC ESCC: 15.9 (13.6, 18.6)	Levels of harmful metals (cadmium and lead) not SIGN. different between DU and ESCC
Prokopowicz A. (40) 2020 Poland	Yes ▲	Cross-sectional study Questionnaire and urine sample	-	88 young volunteer adults (19-39 years old) DU: CC for at least 2 years and EC for at least 6 months 25 EC 25 ESCC 25 NU 13 DU	50% of EC sample	High risk of selection bias Adjusted analyses for 3-5 confounders Measurement bias	11 toxic metals in urine	Various tests showed no significant difference between the groups. After controlling for age, BMI and sex, a SIGN. higher level was observed only for urinary antimony (Sb; possibly carcinogenic to humans) in DU compared to NU	DU had SIGN. higher urinary level of a toxic metal, antimony than NU
Riehm K. E. (41) 2019 USA	Yes ▽	Cross-sectional analysis on data from a nationally representative cohort, PATH Wave 1+2.	Past year (12 months)	9.588 adolescents 12-17years old Past 12 month use (any) 294 ESCC 474 DU 588 EC 8232 NU	5 % of all 45% of EC	Low risk of selection bias Recall bias Weighted data Adjusted for many confounders	Sleep-related complaints	Statistically SIGN. association between sleep-related complaints and EC + DU in all 4 models. Final, full adjusted model (among others for lifetime-depression and life-time sleeping problems), aOR 95% CI EC: 1.29 (1.05, 1.59) DU: 1.57 (1.24,1.99) ESCC: 1.30 (0.98,1.71) Post hoc analysis indicates that odds for sleep-related complaints were not higher in DU than EC.	DU higher risk of sleep-related complaints than ESCC but not SIGN. DU higher risk of sleep-related complaints than NU

Rostron B. L. (42) 2019 USA	None	Cross-sectional analysis on data from a nationally representative cohort PATH Wave 1 (2013-2014)	-	2.710 adults Dual use: currently used CC every day and EC every day or some days 1952 ESCC 648 DU 110 ESCC+ ST (smokeless tobacco)	24 %	Low risk of selection bias Weighted data Adjusted for 4 confounders	Toxicity Biomarkers measured in urine and blood samples	DU had higher levels of TNE2, NNAL, 1-HOP, HPMA and MHB3 compared to ESCC ESCC+ST had higher levels of NNAL and NNN compared to ESCC	DU have higher levels of some harmful (toxic and carcinogenic) biomarkers compared to ESCC
Sanou A. Z. (43) 2020 USA	None	Register study with retrospective data collection from a cohort followed in the US Defense Medical Surveillance System which includes inpatient and outpatient medical encounter data and the annual Health Assessment	Incidence in last 9 months	802.621 adult military members Current (past 30 days) use 37,915 EC 91,135 ESCC 22,010 DU 651,561 NU	3% of all 37% of EC	Low risk of selection bias Risk of social desirability bias Analyses adjusted for 4 confounders	Incident cases of acute respiratory infections (ARI) Register data, ICD-9 and 10 codes, in- or out patients	Highest incidence rate of ARI for DU compared to ESCC, EC and NU. Adjusted incidence rate ratios (95% CI) for ARI NU: ref EC: 1.02, 0.99–1.04, p= 0.123 ESCC: 1.01, 0.99–1.03, p=0.304 DU: 1.04, 1.01–1.07, p=0.021	DU had SIGN. higher risk of acute respiratory infections than NU, higher than ESCC but difference between DU and ESCC not tested
Shahab L.(44) 2017 UK	Yes	Cross-sectional study with self-selected sample	-	181 adults with long-term use of a nicotine product Current (past 6 months) use 37 ESCC 36 ESCC-NRT 36 NRT 36 DU 36 EC	20% of sample	High risk of selection bias Measurement bias Adjusted for 3 confounders Took former tobacco consumption into account	Carcinogen and toxin exposure Biomarkers measured in urine and saliva samples, VOCs and TSNAs	DU higher nicotine levels than any other group TSNA levels: Compared with ESCC there were no large differences in NNAL levels for DU VOC level: ESCC+NRT, DU og ESCC had very similar urinary VOC metabolites levels DU had higher VOC metabolites PMA, MU and PHEMA levels than any other group DU: PMA (carcinogenic) SIGN. higher than in ESCC Geometric mean (95% CI) DU 1.43 (1.11-1.83) ESCC: 0.64 (0.48-0.84) ESCC+NRT: 0.44 (0.30-0.63)	DU and ESCC had similar levels of toxic and carcinogenic substances, but DU had SIGN. higher level of one carcinogenic substance, benzene than ESCC

Smith D. (45) 2020 Poland, UK and USA	Yes	Secondary analysis on data from international cross-sectional study with self-selected sample in three countries Participants from UK, Shahab 2017, also included in this study	-	456 adults with long-term use of EC or CC use US=166 UK=129 PL=161 Current (past 6 months) use 124 EC 95 DU 127 ESCC	US: 17% UK: 28% PL: 19% of sample	High risk of selection bias Measurement bias Adjusted for 3 confounders and for multiple comparisons	Carcinogen and toxin exposure Biomarkers measured in urine and saliva samples, VOCs, TSNAs and minor tobacco alkaloids	DU: comparable levels of nicotine as ESCC DU: no statistically SIGN. differences in minor tobacco alkaloids or most measured VOCs SIGN. lower levels of acrylonitrile (CYMA) and three TSNAs in DU compared with ESCC. DU in UK showed higher levels of several biomarkers of harm compared with US and Polish DU (difference in product use) Characteristics: DU smoked fewer CPD than CS. No differences in number of puffs on e-cigarette per day between EC and DU. Nicotine intake: EC had higher levels of several nicotine metabolites compared with CS and DU.	DU and ESCC had similar levels of toxic and carcinogenic substances, but ESCC had SIGN. higher level of three TSNAs and acrylonitrile than DU
Vindhyal M. (46) 2020 USA	None	Cross-sectional study nationally representative survey Data from NHIS (2014, 2016, 2017, 2018)	-	16.855 adults Dual use: every or some days CC and EC 2,848 NU 7,291 TP 401 EC 2,240 DU 1,139 Former TP, now EC 2,936 Former TP	13% of all 40% of EC	Low risk of selection bias Risk of recall bias Weighted data Adjusted for 3 confounders	Self-reported disease – told by doctor/health professional	DU had highest odds of myocardial infarction than any other group, aOR (95%CI) NU: ref TP: 4.52 (2.49-8.21) EC: 4.09 (1.29-12.98) DU: 5.44 (2.90-10.22) F-TP now EC: 3.71 (1.89-7.28) DU had highest odds of stroke than any other group, aOR (95%CI) NU: ref TP: 2.15 (1.38-3.35) EC: 1.22 (0.36-4.18) DU: 2.32 (1.44-3.74) F-TP, now EC: 1.92 (1.12-3.29) For coronary heart disease DU has almost the same odds as former ESCC (OR=2.27)	DU had higher odds of self-reported (told by doctor) myocardial infarction and stroke than EC and ESCC, but SIGN. level not tested
Wang J. B. (47) 2018 USA	Yes	Cross-sectional study using available baseline data (2013-2017) from the ongoing internet-based Health eHeart survey	Retrospective symptoms past month; cardio-pulmonary conditions "ever told by doctor"	39.747 adults DU: 100 CC; EC in the past month 573 EC 1,693 ESCC 514 DU	1.3% of all 47%	Low risk of selection bias Risk of recall bias Adjusted for 8 confounders	Health outcomes including cardiopulmonary symptoms and conditions	DU exhibited worse median general health scores SF-12 (p= 0.002) and breathing scores (p= 0.001) in the past month compared to ESCC No SIGN. difference in medical 19 cardiopulmonary conditions between DU and ESCC; only having a history of an arrhythmia was found to be SIGN. higher in DU (17.8%) than in ESCC (14.2%), after adjusting for covariates (p = 0.02)	DU exhibited worse median general health scores and breathing scores and had SIGN. higher prevalence of history of an arrhythmia than ESCC
Wang X. (48) 2020 USA	None	Data from Pregnancy Risk Assessment Monitoring System	3 months before pregnancy and 3 months before birth	N= 31,973 women N(weighted)= 1,918,031 Use during the 3 months before	265 before pregnancy (3 %) 265 Late pregnancy (0,8 %)	Low risk of selection bias Social desirability bias	Preterm birth or small-for-gestational-age (SGA)	OR* associated with preterm birth and SGA, adjusted for pre-pregnancy product use (model 2 adjusted for use of EC/ESCC before pregnancy) Preterm birth ESCC: aOR= 1.6 (1.2, 2.0) EC: aOR= 1.2 (0.5, 2.7) DU: aOR= 1.3 (0.8, 2.3)	DU had lower odds of preterm birth than ESCC, but SIGN. not tested

		(PRAMS) from 2016. High participant rate: 83 % of all U.S. births.		their pregnancy, and during the last 3 months of pregnancy Mothers that had singleton births in the U.S. 5029 ESCC 976 DU		Adjusted for 11 confounders Weighted data		SGA ESCC: aOR= 2.4 (1.8, 2.9) EC: aOR= 2.4 (1.0, 5.7) DU: aOR= 2.3 (1.3, 4.1) *no p-value	DU and ESCC had same risk of small-for-gestational-age
Wills T. A. (49) 2019 USA	None	Cross-sectional analysis on 2016 Behavioral Risk Factor Surveillance Survey on Hawaii (BRFSS)	-	N= 8,087 adults (18+) Smoked/vaped every day or some day 235 EC 934 ESCC	?	Low risk of selection bias Weighted data Adjusted for 7 confounders	Self-reported diagnosis of asthma and COPD (told by doctor/nurse)	Asthma No SIGN. difference between ESCC and DU, p= 0.94 None: ref. DU: aOR= 1.26 (1.04, 1.53), p= 0.02 ESCC: aOR= 1.27 (1.10, 1.47), p= 0.001 COPD Absolute risk from multivariate model for COPD was highest for dual users in all age groups DU significant higher odds than ESCC and EC compared to NU (95% CI): NU: ref. DU: aOR= 3.92 (2.82, 5.44), p< 0.0001 ESCC: 2.98 (2.34, 3.78), p< 0.0001 EC: 2.58 (1.36, 4.89), p= 0.004 Higher aOR for DU compared to ESCC and EC, but not significant: DU vs. EC:1.52 (0.81, 2.87), p= 0.20 DU vs. ESCC: 1.32 (0.98, 1.77), p= 0.70	DU and ESCC same odds of asthma. DU higher odds of COPD than ESCC but not SIGN.
Wills T. A. (50) 2020 USA	None	Cross-sectional analysis on 2017 Youth Risk Behavior Survey	Past 30 days	N= 14,765 adolescents Ever, never and current use of EC, CC, and marijuana (marijuana not included here) Past 30 days use: 1,659 EC 1,269 ESCC	?	Low risk of selection bias Risk of recall bias Adjusted for 5 covariates Weighted data	Self-reported asthma diagnosis	DU SIGN. higher odds of asthma than NU (ESCC not SIGN. higher odds). Higher odds in DU than ESCC but not SIGN. p=0.10 Nonuser: ref. EC: aOR= 1.29 (1.07, 1.55), p= 0.01 ESCC: aOR= 1.23 (0.92, 1.64), p= 0.17 DU: aOR= 1.62 (1.32, 1.99), p< 0.0001 A sensitivity analysis tested in a sample with complete data: NU: ref Current DU vs. ESCC: aOR 1.35 (1.03-1.76) p= 0.03). (an increment in absolute risk attributable to EC above and beyond that for smoking)	DU higher odds of asthma and past 30-day use than ESCC, but not SIGN. Complete data, current users: DU had higher risk of asthma than ESCC
Xie Z. (51) 2020 USA	None	Cross-sectional using data from nationally	-	887,182 with smoking and vaping status DU: have smoked at	1.8 % of all 64% of EC users	Low risk of selection bias Recall bias Weighted data	Self-reported COPD diagnosis (told by doctor)	Association between vaping and self-reported COPD diagnosis: aOR, 95% CI NU: ref DU: 4.39 (3.98, 4.85) ESCC: ref	DU had SIGN. higher risk of self-reported (told by doctor) COPD than ESCC

		representative survey BRFSS survey (2016 and 2017).		least 100 CC in life, now smoke every day or some days, and currently vaping every day or some days. 15,986 DU 115,189 ESCC 8876 EC only		Analyses adjusted for 9 confounders		DU: 1.16 (1.05, 1.27) Association in different age-groups: DU did not show significantly higher association with self-reported COPD diagnosis in 18–34 age group compared to ESCC DU: COPD diagnosis became significantly higher in 35–64 and over 65 age groups, with aOR = 1.15 (1.02 to 1.30) and aOR = 1.57 (1.22 to 2.00), respectively compared to ESCC aOR (95% CI) for COPD in 65+ years old: NU: ref DU: 8.38 (6.57, 10.68) ESCC: 5.35 (4.87, 5.89) EC: 2.48 (0.81, 7.53) FESCC: 3.21 (2.98, 3.45)	
Ye D. (52) 2020 USA	None	Cross-sectional, pilot experimental study; saliva sample + questionnaire		N=48 Smoking and vaping status not defined in detail 12 ESCC 12 DU 12 EC 12 NU	25 % of sample	High risk of selection bias Measurement bias	Systemic inflammation, oxidative stress, angiogenesis and tissue injury/repair in saliva and gingival crevicular fluid (GCF)	Smoking/vaping produces differential effects on oral health PGE2: SIGN. higher in ESCC vs. NU, EC and DU. SIGN. higher EN-RAGE (DU vs. NU), MPO (DU vs. EC), Uteroglobin (DU vs. EC). Most GCF mediators were higher for DU than ESCC, but not statistically significant DU had higher OR in all age groups compared to NU, increased with increasing age. Compared with ESCC significantly higher association from age-group 35	DU had non-SIGN. higher levels of most biomarkers than ESCC No SIGN. difference between ESCC and DU in biomarkers of systemic inflammation

Conflict of interest: pharmaceutical industry
Conflict of interest from anonymous contributors
Conflict of interest with the tobacco or e-cigarette industry
Prospective design

EC= e-cigarettes
ECU= e-cigarette users
DU= dual use/users of conventional cigarettes and e-cigarettes
ESCC= exclusive smokers/smoking of conventional cigarettes
TPU= users of combustible tobacco products (ES, cigarillos, cigars, pipe, water pipe)
NU= Non-user of conventional cigarettes and e-cigarettes
1-HOP= 1-hydroxypyrene (PAH)
3-HPMA =Urinary 3-hydroxypropyl mercapturic acid, a major metabolite of acrolein

CO= carbon monoxide HPHC = harmful and potentially harmful constituents
COPD = chronic obstructive pulmonary disease
CRP = human c-reactive protein
CYMA: a metabolite of acrylonitrile (VOC)
TSNA = Tobacco-specific *N*-nitrosamines
PAH = polycyclic aromatic hydrocarbons
GTT = glucose tolerance test
HbA1c = glycosylated haemoglobin
HOMA-IR = homeostatic model assessment of insulin resistance
HPMA: N-acetyl-S-3-hydroxypropylcysteine, a metabolite of acrolein (VOC)
MHB3, a metabolite of 1,3-butadiene (VOC)
MU = *trans,trans*-Muconic acid (VOC, benzene)
NNAL = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, the principal metabolite of the lung carcinogen NNK (TSNA)
NNN = N0-nitrosonornicotine (TSNA)
NRT=nicotine replacement therapy
PHEMA= N-Acetyl-S-(1 and 2-phenyl-2-hydroxyethyl)-L-cysteine (VOC, styrine)
PMA= benzene
SIGN. = significant/significance
VOC= Volatile organic compounds

Conflict of interest:

- Flacco: The sixth year was partially supported by British American Tobacco. Two years of follow-up were funded by a research grant from the University of Catania and through crowdfunding (Kickstarter project titled "E-cigarette long-term efficacy and safety: a study to complete"). Besides 7 authors (MEF, RS, MRG, GL, MFi, PV, CM) and 7 anonymous contributors, who donated a total of €565 and €80, respectively, all other contributors were private citizens who had no role in any phase of the study.
- Goniewicz: M.L.G receives fees for serving on an advisory board from Johnson & Johnson and grant support from Pfizer.
- Hedman: LH reported grants from the Swedish Heart-Lung Foundation, the Swedish Research Council, a regional agreement between Umea University and Vasterbotten County Council (ALF), the Swedish Asthma-Allergy Foundation, VISARE NORR Fund: Northern County Councils' Regional Federation, and Norrbotten County Council during the conduct of the study. HB reported grants from the Swedish Heart-Lung Foundation, VBG Group's Herman Krefting Foundation for Asthma and Allergy Research, a regional agreement between Umea University and Vasterbotten County Council (ALF), Norrbotten County Council, and VISARE NORR Fund: Northern County Councils' Regional Federation during the conduct of the study; and personal fees from Boehringer Ingelheim outside the submitted work. AL reported personal fees from AstraZeneca, Boehringer Ingelheim, Novartis, and ActiveCare outside the submitted work. ER reported grants from the Swedish Heart-Lung Foundation, Norrbotten County Council, and Umea University during the conduct of the study; and grants from FORMAS, AstraZeneca, and GlaxoSmithKline outside the submitted work. LE reported grants from VBG Group's Herman Krefting Foundation for Asthma and Allergy Research during the conduct of the study; and grants from VBG Group's Herman Krefting Foundation for Asthma and Allergy Research outside the submitted work.
- Li: MLG received a research grant from Pfizer and served as a member of advisory board to Johnson & Johnson, manufacturers of smoking cessation medications.
- McRobbie: H. McRobbie is Clinical Director at The Dragon Institute The Dragon Institute; reports receiving commercial research grant from Pfizer; and has received speakers bureau honoraria from Johnson&Johnson and Pfizer. M.L. Goniewicz reports receiving commercial research grant from Pfizer. P. Hajek has received speakers bureau honoraria from and is a consultant/advisory board member for the manufacturers of stop-smoking medications.
- Miller: M.L.G. has received a research grant from Pfizer, Inc. and served as a member of the scientific advisory board to Johnson & Johnson.
- Osei 2019: declared funding from public health and NGO funds, such as American Heart Association. No personal fees declared.
- Osei 2020: DeFilippis has unrelated research funding from Astra Zeneca and is a consultant on an unrelated topic for Radiometer America, Inc. No
- Polosa: in some publication Polosa declares no COI. He has founded the Center of Excellence for the Acceleration of Harm Reduction (CoEHAR), an interdepartmental Research Centre within the University of Catania. This has received significant funding from a tobacco-industry front group, the Foundation for a Smoke-Free World (Philip Morris). He is also a Special Scientific Advisor to the International Network of Nicotine Consumer Organizations (INNCO). The INNCO was formed in 2016 and represents organisations promoting Next Generation Products such as e-cigarettes, heated tobacco products and snus. In November 2018 INNCO was granted $100,300 from the Foundation for a Smoke-Free World (Philip Morris).

- Prokopowicz 2019: AP, MS–C, PO, and AS are employees of the Institute of Occupational Medicine and Environmental Health. One of the institute's objectives is outsourcing for the industrial sector, including manufacturers of e-cigarettes. AS accepted personal fees from the eSmoking Institute in Poznan, Poland, and nonfinancial support from Chic Group LTD, a manufacturer of electronic cigarettes in Poland, outside of the submitted work. LK works as an expert for the Polish National Committee for Standardization and for the European Committee for the standardization of requirements and test methods for e-liquids and emissions.
- Prokopowisz 2020: same as 2019.
- Kosmider: employees of the Institute of Occupational Medicine and Environmental Health. Leon Kosmider also works as an expert for the Polish National Committee for Standardization and for the European Committee for Standardization (CEN) in the field of requirements and test methods for e–liquids and emissions.
- Pulvers: Benowitz is a consultant to pharmaceutical companies that market smoking cessation medications and has been an expert witness in litigation against tobacco companies. The other authors have no conflicts of interest.
- Riehm: APS received an honorarium from Springer Nature Switzerland AG for Guest Editing a Special Issue of Current Sleep Medicine Reports.
- Rubinstein: Dr Benowitz is a consultant to several pharmaceutical companies that market medications to aid smoking cessation and has served as a paid expert witness in litigation against tobacco companies. Drs Ramo and Rubinstein have consulted for Carrot Inc, which makes a tobacco cessation device.
- Shahab: Dr. Shahab reports grants from Cancer Research UK during the conduct of the study and grants from Pfizer (unrestricted research funding to study smoking cessation) and personal fees from Atlantis Health Care outside of the submitted work. Dr. Goniewicz reports grants from Pfizer (2011 GRAND [Global Research Awards for Nicotine Dependence] recipient) and personal fees from Johnson & Johnson (as a member of the advisory board) outside the submitted work. Dr. Brown reports grants (unrestricted research funding to study smoking cessation) from Pfizer outside the submitted work. Dr. West reports grants, personal fees, and nonfinancial support (that is, research grants, consultancy, travel, and hospitality) from Pfizer, Johnson & Johnson, and GlaxoSmithKline outside the submitted work
- Smith: M.L.G. received a research grant from Pfizer and served as a member of an advisory board to Johnson & Johnson, pharmaceutical companies that both market smoking cessation medications. L.S. has received honoraria for talks, an unrestricted research grant and travel expenses to attend meetings and workshops by pharmaceutical companies that make smoking cessation products (Pfizer, Johnson & Johnson), has acted as a paid reviewer for grant awarding bodies and as a paid consultant for healthcare companies.
- Soule: E.S. is named on a patent application for a smartphone app that determines electronic cigarette device and liquid characteristics.
- Wang J.B.: The study was partially supported by 24K Data (http://24Kdata.com). There are no patents, products in development or marketed products to declare.
- Wiernik: GA has received speaker and consulting fees from Lundbeck and Pfizer, outside the submitted work. FL has received speaker and consulting fees from AstraZeneca, Eutherapie-Servier, Janssen, Lundbeck, Otsuka Pharmaceuticals France and Roche, outside the submitted work. CL reports grants, personal fees and non-financial support from Lundbeck, personal fees from Servier, Daiichi-Sankyo and Janssen, non-financial support from Otsuka Pharmaceuticals, outside the submitted work.

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Appendix S1 **JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES**

Author_____McRobbie H_____ Year___2015_____

		Yes	No	Unclear	Not applicable
1.	Were the two groups similar and recruited from the same population?	X	☐	☐	☐
2.	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	X	☐	☐	☐
3.	Was the exposure measured in a valid and reliable way?	☐	X	☐	☐
4.	Were confounding factors identified?	☐	X	☐	☐
5.	Were strategies to deal with confounding factors stated?	☐	X	☐	☐
6.	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	X	☐	☐	☐
7.	Were the outcomes measured in a valid and reliable way?	X	☐	☐	☐
8.	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	X	☐	☐	☐
9.	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	☐	X	☐	☐
10.	Were strategies to address incomplete follow up utilized?	☐	X	☐	☐
11.	Was appropriate statistical analysis used?	X	☐	☐	☐

NOT ADJUSTED FOR FORMER TOBACCO CONSUMPTION

JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES

Author_ _ _ _ _ _ _ _ _ _ _ _ _Bhatta DN_ _ _ _ _ _ _ _ _ _ _ _ _Year___2020_____

		Yes	No	Unclear	Not applicable
1.	Were the two groups similar and recruited from the same population?	X	☐	☐	☐
2.	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	X	☐	☐	☐
3.	Was the exposure measured in a valid and reliable way?	☐	X	☐	☐
4.	Were confounding factors identified?	X	☐	☐	☐
5.	Were strategies to deal with confounding factors stated?	X	☐	☐	☐
6.	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	X	☐	☐	☐
7.	Were the outcomes measured in a valid and reliable way?	X	☐	☐	☐
8.	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	X	☐	☐	☐
9.	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	X	☐	☐	☐
10.	Were strategies to address incomplete follow up utilized?	X	☐	☐	☐
11.	Was appropriate statistical analysis used?	X	☐	☐	☐

NOT ADJUSTED FOR FORMER TOBACCO CONSUMPTION

JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES

Author_____Sanou AZ_____Year___2020_____

		Yes	No	Unclear	Not applicable
1.	Were the two groups similar and recruited from the same population?	X	☐	☐	☐
2.	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	X	☐	☐	☐
3.	Was the exposure measured in a valid and reliable way?	☐	X	☐	☐
4.	Were confounding factors identified?	X	☐	☐	☐
5.	Were strategies to deal with confounding factors stated?	X	☐	☐	☐
6.	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	X	☐	☐	☐
7.	Were the outcomes measured in a valid and reliable way?	X	☐	☐	☐
8.	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	X	☐	☐	☐
9.	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	☐	☐	X	☐
10.	Were strategies to address incomplete follow up utilized?	☐	☐	X	☐
11.	Was appropriate statistical analysis used?	X	☐	☐	☐

NOT ADJUSTED FOR FORMER TOBACCO CONSUMPTION

JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES

Author_ _ _ _ _ _ _ _ _ _Cardenas VM _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _Year____2020_____

		Yes	No	Unclear	Not applicable
1.	Were the two groups similar and recruited from the same population?	X	☐	☐	☐
2.	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	X	☐	☐	☐
3.	Was the exposure measured in a valid and reliable way?	☐	X	☐	☐
4.	Were confounding factors identified?	X	☐	☐	☐
5.	Were strategies to deal with confounding factors stated?	X	☐	☐	☐
6.	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☐	☐	☐	X
7.	Were the outcomes measured in a valid and reliable way?	X	☐	☐	☐
8.	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	X	☐	☐	☐
9.	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	X	☐	☐	☐
10.	Were strategies to address incomplete follow up utilized?	☐	☐	☐	X
11.	Was appropriate statistical analysis used?	X	☐	☐	☐

NOT ADJUSTED FOR FORMER TOBACCO CONSUMPTION

JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES

Author_ _ _ _ _ _ _ _ _Clemens MM_ _ _ _ _ _ _ _ _ _ _ _ _ _ _Year___2019_____

		Yes	No	Unclear	Not applicable
1.	Were the two groups similar and recruited from the same population?	X	☐	☐	☐
2.	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	X	☐	☐	☐
3.	Was the exposure measured in a valid and reliable way?	☐	X	☐	☐
4.	Were confounding factors identified?	X	☐	☐	☐
5.	Were strategies to deal with confounding factors stated?	X	☐	☐	☐
6.	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☐	☐	☐	X
7.	Were the outcomes measured in a valid and reliable way?	X	☐	☐	☐
8.	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	X	☐	☐	☐
9.	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	X	☐	☐	☐
10.	Were strategies to address incomplete follow up utilized?	☐	☐	☐	X
11.	Was appropriate statistical analysis used?	X	☐	☐	☐

NOT ADJUSTED FOR FORMER TOBACCO CONSUMPTION

JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES

Author_ _ _ _ _ _ _ _ _Flacco ME_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _Year__2020_____

		Yes	No	Unclear	Not applicable
1.	Were the two groups similar and recruited from the same population?	X	☐	☐	☐
2.	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	X	☐	☐	☐
3.	Was the exposure measured in a valid and reliable way?	☐	X	☐	☐
4.	Were confounding factors identified?	X	☐	☐	☐
5.	Were strategies to deal with confounding factors stated?	X	☐	☐	☐
6.	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	X	☐	☐	☐
7.	Were the outcomes measured in a valid and reliable way?	X	☐	☐	☐
8.	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	X	☐	☐	☐
9.	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	☐	X	☐	☐
10.	Were strategies to address incomplete follow up utilized?	X	☐	☐	☐
11.	Was appropriate statistical analysis used?	X	☐	☐	☐

JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES

Author_ _ _ _ _ _ _ Harlow A _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ Year_____2020____

		Yes	No	Unclear	Not applicable
1.	Were the two groups similar and recruited from the same population?	X	☐	☐	☐
2.	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	X	☐	☐	☐
3.	Was the exposure measured in a valid and reliable way?	☐	X	☐	☐
4.	Were confounding factors identified?	X	☐	☐	☐
5.	Were strategies to deal with confounding factors stated?	X	☐	☐	☐
6.	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☐	☐	☐	X
7.	Were the outcomes measured in a valid and reliable way?	X	☐	☐	☐
8.	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	X	☐	☐	☐
9.	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	X	☐	☐	☐
10.	Were strategies to address incomplete follow up utilized?	☐	☐	X	☐
11.	Was appropriate statistical analysis used?	X	☐	☐	☐

JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES

Author_ _ _ _ _ _ _ _ _ _ _ _ _ _ _Manzoli L_ _ _ _ _ _ _ _ _ _ Year__2015_____

		Yes	No	Unclear	Not applicable
1.	Were the two groups similar and recruited from the same population?	X	☐	☐	☐
2.	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	X	☐	☐	☐
3.	Was the exposure measured in a valid and reliable way?	☐	X	☐	☐
4.	Were confounding factors identified?	X	☐	☐	☐
5.	Were strategies to deal with confounding factors stated?	X	☐	☐	☐
6.	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	X	☐	☐	☐
7.	Were the outcomes measured in a valid and reliable way?	X	☐	☐	☐
8.	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	X	☐	☐	☐
9.	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	☐	X	☐	☐
10.	Were strategies to address incomplete follow up utilized?	☐	X	☐	☐
11.	Was appropriate statistical analysis used?	X	☐	☐	☐

JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES

Author_ _ _ _ _ _ _ _ _ _ _ _ _ _ _Manzoli L _ _ _ _ _ _ _ _ _ Year____2017_____

		Yes	No	Unclear	Not applicable
1.	Were the two groups similar and recruited from the same population?	X	☐	☐	☐
2.	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	X	☐	☐	☐
3.	Was the exposure measured in a valid and reliable way?	☐	X	☐	☐
4.	Were confounding factors identified?	X	☐	☐	☐
5.	Were strategies to deal with confounding factors stated?	X	☐	☐	☐
6.	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	X	☐	☐	☐
7.	Were the outcomes measured in a valid and reliable way?	X	☐	☐	☐
8.	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	X	☐	☐	☐
9.	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	☐	X	☐	☐
10.	Were strategies to address incomplete follow up utilized?	☐	X	☐	☐
11.	Was appropriate statistical analysis used?	X	☐	☐	☐

JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES

Author_ _ _ _ _ _ _ _ _ _McDonnell BP_ _ _ _ _ _ _ _ _ _ _ _Year___2020_____	Yes	No	Unclear	Not applicable
1. Were the two groups similar and recruited from the same population?	X	☐	☐	☐
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	X	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☐	☐	X	☐
4. Were confounding factors identified?	X	☐	☐	☐
5. Were strategies to deal with confounding factors stated?	X	☐	☐	☐
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☐	☐	☐	X
7. Were the outcomes measured in a valid and reliable way?	X	☐	☐	☐
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	X	☐	☐	☐
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	X	☐	☐	☐
10. Were strategies to address incomplete follow up utilized?	☐	☐	☐	X
11. Was appropriate statistical analysis used?	X	☐	☐	☐

NOT ADJUSTED FOR FORMER TOBACCO CONSUMPTION

JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES

Author_ _ _ _ _ _ _ _ _ _ _Riehm KE_ _ _ _ _ _ _ _ _ _ _ _ _ Year___2019_____

		Yes	No	Unclear	Not applicable
1.	Were the two groups similar and recruited from the same population?	X	☐	☐	☐
2.	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	X	☐	☐	☐
3.	Was the exposure measured in a valid and reliable way?	☐	X	☐	☐
4.	Were confounding factors identified?	X	☐	☐	☐
5.	Were strategies to deal with confounding factors stated?	X	☐	☐	☐
6.	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☐	☐	☐	X
7.	Were the outcomes measured in a valid and reliable way?	X	☐	☐	☐
8.	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	X	☐	☐	☐
9.	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	X	☐	☐	☐
10.	Were strategies to address incomplete follow up utilized?	☐	☐	☐	X
11.	Was appropriate statistical analysis used?	X	☐	☐	☐

NOT ADJUSTED FOR FORMER TOBACCO CONSUMPTION

JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES

Author_ _ _ _ _ _ _ _ _ _ _ _Wang X_ _ _ _ _ _ _ _ _ _ _ _ _Year___2020_____

		Yes	No	Unclear	Not applicable
1.	Were the two groups similar and recruited from the same population?	X	☐	☐	☐
2.	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	X	☐	☐	☐
3.	Was the exposure measured in a valid and reliable way?	☐	X	☐	☐
4.	Were confounding factors identified?	X	☐	☐	☐
5.	Were strategies to deal with confounding factors stated?	X	☐	☐	☐
6.	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☐	☐	☐	X
7.	Were the outcomes measured in a valid and reliable way?	X	☐	☐	☐
8.	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	X	☐	☐	☐
9.	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	X	☐	☐	☐
10.	Were strategies to address incomplete follow up utilized?	☐	☐	☐	X
11.	Was appropriate statistical analysis used?	X	☐	☐	☐

NOT ADJUSTED FOR FORMER TOBACCO CONSUMPTION

Appendix S2. Effect measures, data items, study design, characteristics of studies, definition of use and prevalence of use

Effect measures

Effect measures varied depending on the outcome. Most papers on symptoms or disease risk presented unadjusted and adjusted odds ratios with a 95% confidence interval (CI). We present adjusted odds ratios if available (aCI). Papers on toxic effects typically presented geometric means and 95% CI and/or ranges and interquartile intervals.

Data items

Papers were included if any outcome data comparing DU with ESCC were presented, even if significance levels between ESCC and DU were not shown. We extracted the same predefined information from all papers (Appendix 3). If data on any variable were missing, we searched in supplementary material and/or in study protocols.

Study design

One study was a switch-of-product experimental studies [1]. The majority of studies reported results of cross-sectional analyses, mostly using self-reported data from large population-based surveys. Thirteen papers/10 studies reported results from studies with a prospective design [1-13].

Almost all population-based studies had weighted data for non-response, thereby diminishing the risk of selection bias. One study adjusted for only one confounder [14], while most adjusted for several confounders, and some for up to 13 [3, 8, 9, 15]. The experimental human studies that recruited volunteers in newspapers [1], print or radio, in EC shops, social media, general practice, etc. [3, 4, 8, 9, 16], or where the recruitment method was not defined [17] were assessed to have a high risk of selection bias. Studies with pregnant women/women trying to conceive [5, 6] and military personnel [7, 11, 18] were supposed to have a high risk of social desirability bias (underreporting of EC/CC use). Studies investigating symptoms/disease in the past were at risk of recall bias.

Characteristics of studies (Appendix S3)

Fifty-two studies were included: three from the UK [1, 19, 20], one from Ireland [2], one from Sweden [21], two from Poland [17], [22], four from Italy [3, 4, 8, 9], seven from South Korea [23-29], one study used data from three countries (Poland, the UK and the USA) [30], and the remaining were from the USA. Seven studies reported on health outcome in adolescents [13, 23, 25, 29, 31-33], with the age for inclusion ranging from 12 [34] to 20 years [19]; the rest included adults/young adults.

Definitions of use

There was great variation both in duration and in frequency of use of products for details. The definitions of ESCC, EC users and DUs were based on self-reports and varied a lot across studies. There was variation both in duration and in frequency of use of products. Many studies included persons with current use, defined as use in the past 30 days (DUs = past 30 days use of both CCs and of ECs) [6, 11, 18, 23, 25, 32, 33, 35-37], some included current use as in past 6 months [3, 8, 9, 20] [30] or use in past 12 months [13]. A study including adolescents defined users as ever users [29]. Several studies defined smokers and EC users differently, and some had complex definitions (Appendix 3 for details).

Between 36% [38] and 97% [28] of EC users also smoked CCs, as reported in large population-based studies including adults. Among adolescents, smoking was reported in between 29% [32] and 66% [31] of EC users. At the population level, most of the nationally representative surveys reported DU in 1–3% of the general population.

Definition of exclusive smokers and of dual users

A study including pregnant women measured use during the 3 months before their pregnancy, and during the last 3 months of pregnancy [12]. Several studies defined current use as daily and some-day use of both products [5] [39] [7] [40] [41], while some did not provide any detailed definition of current users [19] [24] [2] [16] [42]. Two studies included long-term users defined as CC use for at least 2 years and EC use for at least 6 months [17] [22]. Some included persons with use of the product during the last five days [34] [43]. In several studies smokers and EC users were defined differently, e.g. smokers were defined as those who gave an affirmative answer to the question “Do you smoke?” while EC users were those who used EC sometimes or daily [21], or smokers had smoked

every day and vapers had used EC every or some days [44], or they had used EC once a week for 3 months and smoked daily for 3 months [45]. Some studies used complex definitions of dual users such as: smoked ≥ 5 cigarettes per day (CPD) in the past 3 months, smoked in the past 24 hours, used an EC every day in the past 3 months, used an EC in the past 24 hours, and had not used any other tobacco products in the past 3 months [14], smoked more than 100 CC in their lifetime and now smoke every day or some days/currently [46] [47] [48] [49] and have used EC for the past month [26] [27] [50] [51], or those who with a lifetime usage of ≥100 cigarettes and EC and CC usage of at least 5 days per week [52].

Prevalence of dual use in the population

In South Korea large population based studies including adults found that 84% [26], 85% [27] and 97% [28] of EC users also smoked CC. In Sweden 67% of EC users in the adult general population were also smokers [21] whereas a population-based study from the UK found that only 37% of adult EC users [19] also smoked. In the population-based surveys from the USA the lowest reported prevalence of dual use in adults was 36% [38] and the highest was 77% [39]. The largest of the studies from USA, based on 2016 and 2017 Behavioral Risk Factor Surveillance System national survey data on almost one million adult participants reported that 64% had a dual use [49]. Among adolescents, smoking was reported in 29% [32], 45% [13] and 66% [31] of EC users in the USA and in 36% [25] of EC users in South Korea.

At population level most of the included nationally representative surveys reported DU in 1-3% of the general population; e.g. 1.1% in Sweden [21], 1.8% in South Korea [27], 2.2% in UK [19] and 1.8% [49], 2.9% [48] and 3% [47] in the USA. Population-based studies with the lowest rate of dual users, 0.7% [7] and 0.8% [12], were studies in pregnant women. Large population-based studies including adolescents reported DU in between 1.4% [31] (USA) and 5.6% [23] (South Korea) of the included youth. The highest rate of DU in a nationally representative survey was reported in the National Health Interview Survey (2014, 2016, 2017 and 2018 data) where 13.3% used CC and EC every day or some days [40].

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