REVIEWPAPER

Comparison of carcinogen biomarkers in electronic cigarette users versus conventional cigarette users in the development of urothelial cancer: a systematic review and meta-analyses

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Introduction Despite the increasing use of electronic cigarettes globally, limited understanding persists regarding their effects on urothelial cancer. This study aimed to conduct a systematic review and meta-analyses comparing carcinogen exposure associated with urothelial cancer development in electronic and conventional cigarette users.

Material and methods The study was conducted through a systematic search of multiple databases adhering to PRISMA guidelines. Eligible articles were evaluated for quality using established scoring systems, and data were synthesized using a random effect model. Heterogeneity was assessed, and sensitivity analysis was conducted. Included carcinogen substances were identified using the Collaborative on Health and the Environment Toxicant and Disease Database, including their potential association with urothelial cancer.

Results The search identified 1,221 records, of which 14 observational studies involving 14,065 participants met the inclusion criteria. A total of 28 carcinogenic or potentially carcinogenic substances were detected in the urine of electronic cigarette users and compared with conventional cigarette users. These included compounds strongly associated with urothelial cancer (aromatic hydrocarbons and 2-naphthylamine), compounds with a limited association (tobacco-specific nitrosamines and metals), and compounds strongly associated with cancer in general (volatile organic compounds). The meta-analysis showed that only 2-hydroxyfluorene was significantly lower in electronic cigarette users compared with conventional cigarette users (SMD −0.53; 95% CI: from −0.60 to −0.46; p <0.00001). Other biomarkers – including cotinine, 1-hydroxypyrene, 2-naphthol, hydroxyfluorenes, NNAL, AAMA, and MHBMA – showed comparable concentrations between the two groups.

Conclusions Although several carcinogenic biomarkers appear at lower concentrations than in conventional cigarette users, multiple urothelial cancer–associated carcinogens remain detectable in the urine of electronic cigarette users, suggesting potential long-term carcinogenic risk.

Key Words: electronic cigarettes ‹› carcinogens ‹› traditional cigarettes ‹› urinary biomarker ‹› urothelial cancer

INTRODUCTION

Bladder cancer ranks as the 10th most prevalent cancer worldwide, with GLOBOCAN 2020 reporting 573,000 new cases and 213,000 deaths [1]. The disease is marked by high recurrence rates, affecting 50-80% of cases, and potential progression in 10–45% of instances [2, 3]. Given these challenges, identifying key risk factors is crucial. Current literature highlights various factors such as genetics, age, gender, diet, smoking, infections, obesity, and occupational/environmental exposure [4, 5] Notably, smoking has been extensively studied in relation to bladder cancer and is a key target for disease prevention [4]. However, with the emergence of electronic cigarettes or vaping products – a popular substitute with a 900% increase in use within four years of introduction [6] – it was initially believed that these substance may be a safer alternative for smokers or even a gateway to tobacco use cessation [7, 8].

Despite initial perceptions of safety, numerous studies have refuted this notion. Both pre-clinical and clinical investigations concerning bladder cancer (BC) have demonstrated that electronic cigarettes can instigate cancer-related damage to bladder tissues in mice [9]. Bjurlin et al.'s findings support these observations, highlighting biological effects akin to those seen in animal models. Early evidence from *in vitro* and *in vivo* mouse studies suggests that e-cigarette smoke induces DNA damage and impedes DNA repair in various cell types, including urothelial cells [10]. Furthermore, e-cigarette aerosols have been linked to urothelial hyperplasia – a potential precursor in the adenoma–carcinoma sequence – especially in cases of flat and/or papillary urothelial hyperplasia with heightened mitotic activity [10, 11]. Notably, electronic cigarette liquids have been found to contain multiple carcinogens found in tobacco smoke [12]. These findings are concerning, especially considering the reported increase in electronic cigarette usage, with 3.2% of adults and 3.6 million school-aged children (in junior and high school) reportedly using them in the United States alone [13]. Conventional smoking is also closely associated with the incidence of BC, with a 5-year prevalence in 2022 of 490,902 cases. Europe had the highest prevalence (154.4 per 100,000), followed by Asia (131.1 per 100,000), North America (66.8 per 100,000), Latin America and the Caribbean (21.5 per 100,000), Africa (19.6 per 100,000), and Oceania (3.6% 3.6 per 100,000). Smoking was also considered the most important modifiable factor for BC, accounting for 37% of the global bladder cancer burden, with risk increasing linearly with smoking intensity and pack-years. Smoking cessation after diagnosis is not associated with a low risk of progression; however, smoking cessation is beneficial, even though the risk remains elevated in comparison to never smokers. Addressing this issue necessitates comprehensive investigations to provide a rationale for effective policy planning with respect to the widespread use of conventional and e-cigarettes [13].

Despite growing evidence, there remains a lack of comprehensive understanding regarding the impact of electronic cigarette usage on urothelial cancer, preventing definitive conclusions. Studies to date have suffered from small sample sizes, limited statistical power, and conflicting findings [8, 10, 11, 13–15]. To address these challenges, this study aimed to undertake a systematic review of available literature and conduct meta-analyses comparing the development of urothelial cancer – whether in the bladder or upper urinary tract – between e-cigarette and conventional cigarette users.

MATERIAL AND METHODS

Data search strategy

A comprehensive literature search was conducted using electronic databases, including EBSCOhost, SCOPUS, Cochrane Library, and PubMed, up to March 2024. The search used the following keywords across all databases: ((Electronic OR Electric) OR Vape) AND Cigarette AND (((Urothelial OR "Bladder Cancer") OR "Upper urinary tract*") OR UTUC). No restrictions were placed on language or publication date. Additionally, handsearching was performed on references listed in relevant studies and literature. The search methodology adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.

Selection criteria

The articles underwent screening of titles and abstracts by two independent reviewers to identify potentially eligible studies. These studies were then assessed for eligibility through full-text reading and further deliberation by the two reviewers. Any uncertainties regarding the eligibility of studies were resolved through discussion and verification of the source data, with consultation of a third reviewer if necessary. Inclusion criteria for eligible studies encompassed observational studies (including cross-sectional, cohort, or case-control designs)

and clinical trials that investigated compounds referenced in the Collaborative on Health and the Environment, Toxicant and Disease Database [16, 17] (Table 1) and reported risk estimates, including standardized mean differences (SMDs), standard deviations (SDs), relative risks (RRs), odds ratios (ORs), or hazard ratios (HRs), along with corresponding 95% confidence intervals (CIs). Reviews and studies lacking available full texts were excluded from this study.

Data extraction

Two authors independently extracted data using a predefined form, which included the following variables: first author's name, publication year, patient settings, study design, compounds being studied and their units, characteristics of the exposed and comparison groups, sample size, concentration reported as mean with corresponding SD or percentage (%) with 95% CIs, and any adjusted variables if applicable. In cases of disagreement, consensus was reached through discussion between the two authors or consultation with a third party.

Quality assessment

The methodological quality and risk of bias of all included studies were assessed using the Newcastle-Ottawa Scale for observational studies. The Newcastle-Ottawa Scale generates a total score ranging from 0 to 9, evaluating three components: selection of study groups, comparability, and ascertainment of exposure of interest. Studies scoring below 5 are deemed low quality, while those scoring between 5 and 9 are considered high quality. Consensus was sought for resolution in cases of disagreement.

Statistical analysis

The gathered data were used to compute concentration values in form of percentages or mean concentrations and their corresponding standard deviations (SDs) or 95% CIs. A pooled analysis was conducted to determine the SMD difference of each identified compound using the random-effects model, which considers both within-study and between-study variations, providing summary SMD estimates and SD. Heterogeneity was assessed using the I2 statistic, with values of approximately 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. A p-value <0.1 indicated significant heterogeneity. Publication bias was evaluated using a funnel plot. Additionally, pooled analysis was conducted on adjusted effect sizes from studies providing such data. Similar methods were employed to assess heterogeneity and publication bias. Meta-analyses were carried out using RevMan 5.4 (Cochrane, Copenhagen).

RESULTS

Literature searches yielded a total of 1,221 publications (Figure 1). Duplicates were excluded, and the remaining 834 publications were screened for their titles and abstracts. About 36 publications were assessed for eligibility through full-text reading, and 14 articles [18–31] were found to be eligible, meeting inclusion and exclusion criteria, and thus were included in the systematic review and meta-analyses.

All 14 included studies [18–28] were observational studies with a total of 14,065 participants, with the quality score ranging from 5 to 8. Based on the compounds reported in the Collaborative on Health and the Environment Toxicant and Disease Database, a total of 28 substances suspected of being carcinogenic were investigated in e-cigarettes and were directly compared with conventional cigarettes. The substances were present in the urine samples of e-cigarettes patients, albeit mostly in a considerably lower concentration compared to conventional cigarettes. According to the toxicant database, aromatic hydrocarbons such as 1-hydroxypyrene (1-OHP), 2-naphthol,

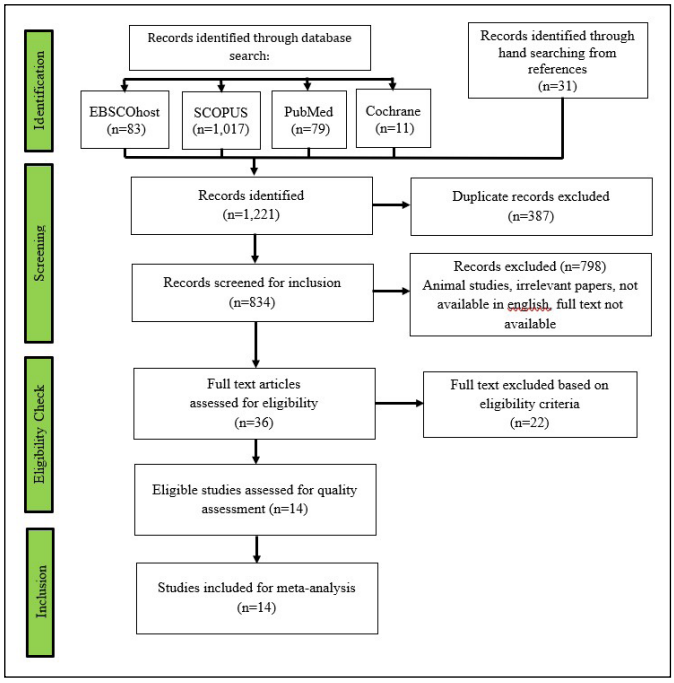

Figure 1. *Literature search protocol based on PRISMA guidelines [32].*

Table 1. *Toxicants, carcinogens, and biomarkers detected in e-cigarette users and their potential association with urothelial cancer [16, 17]*

Chemical class	Parent compound (abbreviation)	Biomarker	IARC Group classification on assessment of carcinogenic risks to humans	Association with urothelial cancer (evidence strength)
Tobacco-specific nitrosamines				
	1 N-nitrosonornicotine (NNN)	N0-nitrosonornicotine (NNN)	1	Limited
	2 4-(Methylnitrosamino)-1-(3- pyridyl)-1-butanone (NNK)	4-(Methylnitrosamino)-1-(3-pyridyl)-1- butanone (NNAL)	1	Limited
	3 N0-nitrosoanatabine (NAT)	Free plus N-glucuronidated (total) N0-nitrosoanatabine (NAT-T)	1	Limited
	4 N0-nitrosoanabasine (NAB)	Free plus N-glucuronidated (total) N0-nitrosoanabasine (NAB-T)	1	Limited
Nicotine				
	5 Nicotine	Cotinine 3-Hydroxycotinine Nicotine cotinine N-oxide Nicotine N-oxide Norcotinine Nornicotine Nicotine equivalents (Neq)	Not listed	Not associated
Polycyclic aromatic hydrocarbons				
	Pyrene	1-Hydroxypyrene (1-OHP)	3	Strong
	6 Naphthalene	1-Hydroxynaphthalene	2B	Strong
		2-Hydroxynaphthalene	2B	
		2-Naphthol	2B	
	7 Fluorene	1-Hydroxyfluorene	3	
		2-Hydroxyfluorene	3	Strong
		3-Hydroxyfluorene	3	
	8 Phenanthrene	1-Hydroxyphenanthrene	3	Strong
		P2,3-Hydroxyphenanthrene	3	
		3-, 4-Hydroxyphenanthrenes	3	
Volatile organic compounds				
	9 Acetaldehyde	Acetate	2B	Not associated
	10 Acrolein	3-Hydroxypropylmercapturic acid (3-HPMA)	3	Not associated
		N-acetyl-S-(2-carboxyethyl)-L-cysteine (CEMA)		
	11 Acrylamide	2-Carbamoylethylmercapturic acid (AAMA)	2A	Strong, cancer not otherwise specified
		2-Carbamoylethylmercapturic acid (AAMA)		
		N-acetyl-S-(2-hydroxy-3-propionamide)- L-cysteine (GAMA)		
	12 Acrylonitrile	2-Cyanoethylmercapturic acid (CNEMA)	2B	Not associated
		N-acetyl-S-(2-cyanoethyl)-L-cysteine (CYMA)		
	13 Benzene	Phenylmercapturic acid (PMA) (or S-phenylmercapturic acid [SPMA])	1	Not associated
		Trans,trans-muconic acid (MU)		
	14 1-Bromopropane	N-acetyl-S-propyl-L-cysteine (BPMA)	2B	Not associated
	15 1,3-Butadiene	4-Hydroxy-2-buten-1-yl-mercapturic acid (MHBMA)	1	Strong, cancer not otherwise specified

Table 1. *Continued*

Chemical class	Parent compound (abbreviation)	Biomarker	IARC Group classification on assessment of carcinogenic risks to humans	Association with urothelial cancer (evidence strength)
		N-acetyl-S-[1-(hydroxymethyl)--2-propen- 1-yl)-L-cysteine (MHBMA1)		
		N-acetyl-S-(2-hydroxy-3-buten--1-yl)-L- cysteine (MHBMA2)		
		N-acetyl-S-(4-hydroxy-2-buten--1-yl)-L- cysteine (MHBMA3)		
		N-acetyl-S-(3,4-dihydroxybutyl)-L-cysteine (DHBMA)		
	16 Carbon disulfide	2-Thioxothiazolidine-4-carboxylic acid (TTCA)	Not listed	Not associated
	Crotonaldehyde	3-Hydroxy-1-methyl-propylmercapturic acid (HMPMA)	3	Not associated
	17 Cyanide	2-Aminothiazoline-4-carboxylic acid (ATCA)	Not listed	Not associated
	18 N,N-Dimethylformamide	N-acetyl-S-(N-methylcarbamoyl)-L-cysteine (AAMC)	2A	Not associated
	19 Ethylbenzene, styrene	Phenylglyoxylic acid (PGA)	2B	Not associated
	20 Ethylene oxide, with a possible contribution from acrylonitrile and vinyl chloride	2-Hydroxyethylmercapturic acid (HEMA)	1	Not associated
	21 Formaldehyde	Formate	1	Not associated
	22 N-nitrosodimethylamine		2A	Not associated
	23 Propylene oxide	2-Hydroxypropylmercapturic acid (2-HPMA)	2B	Not associated
	24 Styrene	N-acetyl-S-(2,5-dimethylbenzene)--L- cysteine (PHEMA)	2A	Not associated
		Mandelic acid (MA)		
	25 O-toluidine	N-acetyl-S-benzyl-L-cysteine (BMA)	1	Strong
	26 Trichloroethylene	N-acetyl-S-(1,2-dichloroethenyl)-L-cysteine (1,2DCVMA)	1	Not associated
		N-acetyl-S-(2,2-dichloroethenyl)-L-cysteine (2,2DCVMA)		
	27 Xylene	2-Methyl hippuric acid (2MHA)	3	Not associated
		3-Methyl hippuric acid + 4-methyl hippuric acid (3MHA + 4MHA)		
Flame retardants				
	28 Triphenyl phosphate (TPhP)	Diphenyl phosphate (DPhP)	Not listed	Not associated
	29 Tris(1,3-dichloro-2-propyl) phosphate (TDCPP)	Bis(1,3-dichloro-2-propyl) phosphate (BDCPP)	Not listed	Not associated
	30 Tris(1-chloro-2-propyl) phosphate (TCPP)	Bis(1-chloro-2-propyl) phosphate (BCPP)	Not listed	Not associated
	31 Tris(2-chloroethyl) phosphate (TCEP)	Bis(2-cholroethyl) phosphate (BCEP)	Not listed	Not associated
	32 Tri-p-cresyl phosphate (TpCP)	Di-p-cresyl phosphate (DpCP)	Not listed	Not associated
	33 Tri-o-cresyl phosphate (ToCP)	Di-o-cresyl phosphate (DoCP)	Not listed	Not associated
	34 Tributyl phosphate (TBUP)	Dibutyl phosphate (DBUP)	Not listed	Not associated
	35 Tribenzyl phosphate (TBzP)	Dibenzyl phosphate (DBzP)	Not listed	Not associated
	36 2-Ethylhexyl-2,3,4,5- tetrabromobenzoate (TBB)	2,3,4,5-Tetrabromobenzoic acid (TBBA)	Not listed	Not associated

Table 1. *Continued*

Chemical class	Parent compound (abbreviation)	Biomarker	IARC Group classification on assessment of carcinogenic risks to humans	Association with urothelial cancer (evidence strength)
Others				
	37 2-Naphthylamine	2-Naphthylamine	1	Strong
	38 Hydrogen cyanide	Thiocyanate	Not listed	Not associated
Metals				
	Lead	Urinary lead	2B	Limited
	Cadmium	Urinary cadmium	1	Not associated
	Nickel	Urinary nickel	2B	Not associated
	Chromium	Urinary chromium	3	Limited

IARC – International Agency for Research on Cancer. a Group 1: carcinogenic to humans; group 2A: probably carcinogenic to humans; group 2B: possibly carcinogenic to humans; group 3: not classifiable as to its carcinogenicity to humans; and group 4: probably not carcinogenic to humans

2-hydroxyfluorene, 3-hydroxyfluorene, P2,3-hydroxyphenanthrene, and 3-,4-hydroxyphenanthrenes, alongside 2-naphthylamine, were found to be strongly associated with urothelial cancer; tobacco-specific nitrosamines (NNN and NNAL) and metals (lead and chromium) were found to have limited associations with urothelial cancer; while volatile organic compounds, specifically AAMA, MHBMA and DHBMA, were found to have strong associations with cancer in general (non-specific). Further details of the studies, including the results for each compound and their comparison between e-cigarettes and conventional cigarettes, are presented in Table 2.

Meta-analyses of toxicant and carcinogenic substances

Among the investigated substances, several pooled analyses were performed. Among the nicotine derivatives, nicotine equivalents and cotinine were investigated by four and five studies, respectively (Figure 2). Pooled analysis for nicotine equivalents showed a standardized mean difference (SMD) of –1.96 (95% CI: –5.79 to 1.87), with no significant difference between e-cigarettes and conventional cigarettes (p=0.31). Cotinine also showed no statistically significant difference (p = 0.87), with an SMD of –0.07 (–0.95 to 0.81). Tobacco-specific nitrosamines (NNAL) also showed no statistically significant difference between e-cigarette and conventional cigarette users (p = 0.07), with an SMD of –1.18 (–2.47 to 0.11). Although not found to be associated with urothelial cancer in past research, the toxicants are an integral part of e-cigarette liquids and have been linked to inflammation, potentially contributing to carcinogenic risk through a pathway not yet discovered.

Pooled analyses on polycyclic aromatic hydrocarbons, which were strongly associated with urothelial cancer, showed a lower concentration only for the 2-hydroxyfluorene compound, with an SMD of –0.53 = (95% CI: –0.60 to –0.46) in favor of e-cigarettes (Figure 3). 1-Hydroxypyrene (1-OHP) showed an SMD of –1.22 (95% CI: –3.12 to 0.68), without statistical significance (p = 0.21). 2-Naphtol, with an SMD of –8.82 (–23.09 to 5.46), was also not statistically significant, with a p-value of 0.23. 3-Hydroxyfluorene was also found to be statistically nonsignificant, with an SMD of –12.18 (–28.74 to 4.38) and a p-value of 0.15.

Pooled analyses of volatile organic compounds that were strongly associated with urothelial cancer were conducted for AAMA, MHBMA, and DHBMA (Figure 4). All were present in urine of e-cigarette users; however no statistical significance was observed in comparison to conventional cigarettes, with SMDs of –3.08 (–9.33 to 3.16), –1.41 (–3.22 to 0.40), and –1.51 (–3.74 to 0.73), respectively.

DISCUSSION

Electronic cigarettes, marketed as a substitute for conventional cigarettes, have emerged as a significant health concern due to their potential association with malignancy, particularly urothelial cancer [7, 13], and further exacerbated by their widespread usage [8, 12] Although current understanding of the precise mechanisms underlying development of malignancy remains limited, potential risks are thought to stem from the constituents of e-cigarettes present in the e-liquid, including nicotine, flavorings, and other chemicals dissolved in carrier solvents. When vaporized and heated, these components may form toxic carcinogenic compounds akin to those found in conventional

Table 2. *Summary and systematic review of included studies investigating the compounds of electronic cigarettes in comparison with conventional cigarettes along with the quality assessment for risk of bias*

Author	Year	Study design	Participant number	Compounds of interest	Electronic cigarette smoker characteristics	Comparison/ Control	Results	Quality Score
Kotandeniya et al. [18]	2015	Non-randomized cohort	27 electronic cigarettes (EC), 38 controls	NNN (pmol/ml) and NNAL (pmol/ml)	Electric Cigarette (EC) only	Conventional cigarette (CC)	**NNN and NNAL** were greater in CC (0.060 ±0.035 and 2.41 ±1.41) compared to EC (not further described; p <0.001).	6
Cravo et al. [19]	2016	Randomized cohort	306 EC, 102 controls	Neq (mg), 3-HPMA (ug), S-PMA (ng), NNAL (ng)	Previously CC. Given EC for 12 weeks	CC	**NeQ:** EC 7.4 (6–8.7) vs CC 9.5 (7.2–12) **3-HPMA:** EC 1290 (1002–) vs CC 1806 (1382–2220) **S-PMA:** EC 2480 (1710–3247) vs CC 3691 (2641–1732) **NNAL:** EC 170 (124–215) vs CC 250 (176–324)	8
Goney et al. [20]	2016	Non-randomized cohort	24 controls, 32 EC	Cotinine	Never smoker. EC	CC	**Cotinine:** EC: 1755 ±1848 ng/g, CC: 1720 ±1335 ng/g	7
Goniewicz et al. [21]	2016	Non-randomized cohort	20 controls, 20 EC (same patients, different timepoints)	1-Hydroxyfluorene (ng/g), 3-, 4-Hydroxyphenanthrenes (ng/g), 2-Hydroxyfluorene (ng/g), 1-Hydroxypyrene (ng/g), 3-Hydroxyfluorene (ng/g), 2-Hydroxyphenanthrene (ng/g), 1-Hydroxyphenanthrene (ng/g), 2-Naphthol (µg/g), HEMA (ng/g), MHBMA (ng/g), HPMMA (µg/g), 3HPMA (µg/g), SPMA (ng/g), AAMA (µg/g), CNEMA (µg/g), 2HPMA (µg/g), NNAL (ng/g), Cotinine (µg/g), NeQ	Previously CC, but cessation for 6 months. Given EC for two weeks	CC	**Cotinine:** 2287 ±1381 (1344–2941) in CC, and 1927 ±1728 (792–2590) in EC. **NNAL:** 225 ±165 (89–340) in CC and 80 ±69 (32–120) in EC **2HPMA:** 45 ±24 (23–55) CC and 21 ±15 (12–23) EC **SPMA:** 792 ±674 (249–1203) in CC, and 188 ±481 (33–161) in EC **1-OHP:** 778 ±338 (556–1000) in CC and 746 ±627 (430–733) in EC **NeQ:** 50 ±27 (35–66) in cc, and 43 ±40 (27–59) in EC 1-Hydroxyfluorene: EC 592 ±833 (48–1074) and CC 1414 ±864 (674–2052) **3-,4-Hydroxyphenanthrenes:** EC 1314 ± 669 (808–1720) and CC 1410 ± 1262 (759–1429) **2-Hydroxyfluorene:** EC 842 ± 495 (543–1078) and CC 1029 ±463 (609–1401) **3-Hydroxyfluorene:** EC 451 ±349 (211–768) **and CC** 679 ±312 (407–878) **2-Hydroxyphenanthrene:** EC 655 ±333 (339–933) and CC 968 ±800 (522–1026) **1-Hydroxyphenanthrene:** EC 584 ±415 (346–716) and CC 488 ±211 (316–678) **2-Naphthol: EC** 19 ±14 (8–30) and CC 24 ±13 (12–34) **MHBMA (ng/g):** EC 305 ±887 (0–140) and CC 1912 ±1283 (830–2860) **AAMA (µg/g):** EC 110 ±97 (50–132) and CC 254 ±148 (119–395)	5
Shahab et al. [22]	2017	Non-randomized cohort	37 controls, 36 EC	Neq (µmol/g), Cotinine (µg/g), NNAL (ng/g), 3HPMA (µg/g),	EC only, with previous history of CC	CC	**NeQ:** EC 126.9 (82.1, 196.2) and CC 104.2 (64.3, 168.9) **Cotinine:** EC 75.1 (45.3, 124.4) and CC 46.8 (26.3,83.3) **NNAL:** EC 2.5 (1.5, 4.2) and CC 57.1 (33.1, 98.4) **3-HPMA:** EC 33.3 (20.9–53.1) and 107.1 (71.8–159.7) **AAMA:** EC 42.9 (31.1–59.2) and CC 80.2 (57.9–111.1) **MHBMA: EC** 11.0 (7.5–16.1) and CC 101.9 (64.6–160.7)	5
Wagener et al. [23]	2017	Cross-sectional	10 controls, 20 EC (9 2nd generation, 11 3rd genera-tion)	Cotinine (µg/g), NNAL (ng/g)	EC only	CC only	**Cotinine: EC** 430.5 ±225.4 EC and CC 331.1 ±179.3 **NNAL: EC** 0.21 ±0.47 and CC 1.47 ±0.82	6

Table 2. *Continued*

Author	Year	Study design	Participant number	Compounds of interest	Electronic cigarette smoker characteristics	Comparison/ Control	Results	Quality Score
Goniewicz et al. [24]	2018	Non-randomized cohort	2411 controls, 247 EC	Nicotine: NeQ (µmol/g), Cotinine (µg/g), 2-Naphthol (µg/g), 1-OHP (ng/g), 3HPMA (µg/g), AAMA (µg/g), cadmium, lead	EC only	CC	**NeQ:** EC 2.000 (1.100–3.500) and CC 27.90 (23.80–32.70) **NNAL:** EC 4.887 (3.817–6.257) and CC 203.5 (181.7–227.9) **1-OHP:** EC 0.161 (0.143–0.181) and CC 0.303 (0.287–0.321) **3-HPMA:** EC 108.0 (95.93–121.6) and CC (255.1–289.0) **2-Naphthol:** EC 5.287 (4.693–5.956) and CC 13.91 (13.21–14.65) **AAMA:** EC 56.05 (51.07–61.50) and CC 136.4 (129.3–143.8)	6
Pulvers et al. [25]	2018	Non-randomized cohort	40 controls, 6 EC (same patients, different timepoints)	Cotinine (µg/g), NNAL (ng/g), 2-HPMA, 3-HPMA (µg/g), AAMA (ng/mg), HPMMA (ng/mg)	EC only, with previous history of CC	CC	**Cotinine:** EC 266.40 (123.6, 386.4) and CC 574.79 (99.53, 1417.02) **NNAL: EC** 3.50 (2.0, 20.3) and CC 102.75 (7.75, 291.17) **2-HPMA:** EC 37.35 (21.6, 51.3) and CC 68.39 (32.35, 29.45) **3-HPMA:** EC 390.35 (370.4, 513.8) and CC 818.90 (556.66, 818.90) **AAMA:** EC 168.88 (94.41, 326.97) and CC 192.28 (100.93, 294.92) **HPMMA:** EC 390.35 (370.4, 513.8) and CC 818.90 (556.66, 818.90)	6
Wei et al. [26]	2018	Non-randomized cohort	298 controls, 14 EC	Triphenyl phosphate (TPhP) (ng/g), Tris(1,3-dichloro-2-propyl) phosphate (TDCPP) (ng/g), Tris(2-chloroethyl) phosphate (TCEP) (ng/g), Tributyl phosphate (TBUP) (ng/g)	EC only	CC only	**TPhP:** EC 0.74 (0.49, 1.12) and CC 0.72 (0.61, 0.85) **TDCPP:** EC 0.71 (0.29, 1.68) and CC 0.65 (0.54, 0.77) **TCEP:** EC 0.67 (0.44, 1.04) and CC 0.39 (0.31, 0.49) **TBUP:** EC 0.20 (0.11, 0.36) and CC 0.17 (0.14, 0.21)	7
Czoli et al. [27]	2019	Non-randomized cohort	24 controls, 24 EC	1-OHP (%), NNAL (%)	Previously CC, but cessation for 6 months. Given EC for a week	CC	**1-OHP:** MD 1.78 (1.29–2.47) % p = 0.001, **NNAL:** MD 1.52 (1.17–1.96) %	7
Wang et al. [28]	2019	Cross-sectional	5767 controls, 860 EC	1-Hydroxynaphthalene (ng/g), 2-Hydroxynaphthalene (ng/g), 2-Hydroxyfluorene (ng/g), 3-Hydroxyfluorene (ng/g), 1-Hydroxyphenanthrene (ng/g), Σ2,3-Hydroxyphenanthrene (ng/g), 1-OHP (ng/g)	EC only (every-day use)	CC only (every-day use)	**1-Hydroxynaphthalene:** EC 1.53 (1.24–1.90) EC and CC 13.2 (12.3–14.2) **2-Hydroxynaphthalene1:** EC 4.88 (4.15–5.74) and CC 14.5 (13.9–15.2) **2-Hydroxyfluorene:** EC 197 (167–233) and CC 1147 (1098–1199) **3-Hydroxyfluorene:** EC 76.5 (63.5–92) and CC 665 (636–696) **1-Hydroxyphenanthrene:** EC 102 (90.3–116) and CC 183 (176–190) **Σ2,3-Hydroxyphenanthrene:** EC 118 (102–136) and CC 315 (301–330) **1-OHP:** EC 150 (135–166) and CC 333 (321–346)	6

Table 2. *Continued*

Author	Year	Study design	Participant number	Compounds of interest	Electronic cigarette smoker characteristics	Comparison/ Control	Results	Quality Score
Chung et al. [29]	2020	Case-control	276 controls, 138 patients with UC	N-acetyl-S-(3,4-dihydroxy-butyl)-L-cysteine (DHBMA), N-acetyl-S-(4-hydroxy-2- buten--1-yl)-L-cysteine-3 (MHBMA-3), trans,trans-muconic acid (t,t-MA), S-phenylmercapturic acid (SPMA), N-acetyl-S-(2-carbamoylethyl) -L-cysteine (AAMA), N-acetyl-S-(2--carbamoyl-2- hydroxyethyl)-L-cysteine (GAMA)	EC, CC, and never smoker with UC	EC, CC and never smoker without UC	**AAMA:** CC and EC with UC vs CC and EC without UC 1.88 (1.14–3.10) **GAMA:** CC and EC with UC vs CC and EC without UC 1.33 (0.77–2.29) **DHBMA:** CC and EC with UC vs CC and EC without UC 1.23 (0.71–2.13) **MHBMA-3:** CC and EC with UC vs CC and EC without UC 0.65 (0.39–1.09) **t,t-MA:** CC and EC with UC vs CC and EC without UC 1.93 (1.13–3.29) **SPMA:** CC and EC with UC vs CC and EC without UC 2.19 (1.23–3.89)	7
Dai et al. [30]	2021	Non-randomized cohort	2356 CC, 855 EC	TNE2 (nicotine equivalent), cotinine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), N'-nitrosonornicotine (NNN), cadmium, lead, 2-naphthol, 1-hydroxypyrene, 3-hydroxyfluorene, N-acetyl-S-(2-carbamoylethyl)-L--cysteine (AAMA), N-acetyl-S-(2--carboxyethyl)- L-cysteine (CEMA), N-acetyl-S-(2-cyanoethyl)-L-cysteine (CYMA)	EC	CC	**TNE2:** CC 35.19 (32.1–38-58) and EC 7.46 (3.35–16.62) **Cotinine:** CC 2264.7 (2069.2–2478.7) and EC 469.5 (200.2–1101) **NNAL:** CC 243.1 (225.1–262.5) and EC 152.6 (78.8–295.2) **NNN:** CC 12.5 (11.4–13.8) and EC 4.4 (3.4–5.7) **Cadmium:** CC 0.33 (0.3–0.9) and EC 0.25 (0.21–0.3) **Lead:** CC 0.49 (0.47–0.51) and EC 0.4 (0.4–0.5) **2-NAP:** CC 15.3 (14.6–16) and EC 5.6 (4.8–6.6) **3-FLU:** CC 0.65 (0.62–0.69) and EC 0.09 (0.07–0.11) **1-PYR:** CC 0.3 (0.3–0.3) and EC 0.2 (0.1–0.2) **AAMA:** CC 140.5 (134.2–147.1) and EC 57.1 (47.9–68.1) **CEMA:** CC 292 (276.2–308.6) and EC 100 (85.2–117.4) **CYMA:** CC 143.4 (133.3–154.3) and EC 3.2 (2.4–4.5)	7
Gallart-Mateu et al. [31]	2023	Non-randomized cohort	63 EC, 14 CC	N-acetyl-S-(2-cyanoethyl)-L-cysteine (CEMA), N-acetyl-S-(3,4-dihydroxybutyl)-L-cysteine (DHBMA), N-acetyl-S-[1-(hydroxymethyl)-2-propen-1-yl)-L-cysteine (MHBMA), N-acetyl-S-(3-hydroxypropyl)-L--cysteine (3HPMA), 2R-N-acetyl--S-(4-hydroxybutan-2-yl)-L-cysteine (HMPMA), and N-acetyl-S-(3--carboxy-2-propyl)-L-cysteine (CMEMA), cotinine	EC	CC	**Cotinine:** CC 2482.5 (276–5463) and EC 3430 (36–17,820) **3HPMA:** CC 1852 (735–4995) and EC 761.5 (172–3037) **CEMA:** CC 169 (41–370) **HMPMA:** CC 2960.5 (881–5650) and EC 368.5 (<LOQ–5388) **MHBMA:** CC 252 (76–1829) and EC 110 (31–396) **CMEMA:** CC 863 (116–6102) and EC 1459.5 (213–10,989) **DHBMA:** CC 444 (53–855) and EC 373 (58–961)	6

cigarettes [12, 16, 17]. These compounds include nitrosamines, polycyclic aromatic hydrocarbons (such as pyrene, naphthalene, fluorene, and phenanthrene), volatile organic compounds (such as acetaldehyde, acrylamide, acrolein, benzene, and O-toluidine), and metals [12]. Numerous studies have investigated the carcinogenic properties and potency of each of these substances in relation to development of urothelial cancer [16, 17]. Therefore, this study represents the first attempt to compare urinary concentrations of carcinogenic toxins and compounds associated with development of urothelial cancer between users of electronic cigarettes and traditional cigarettes.

Our study identified 28 substances suspected of being carcinogenic agents present in the urine samples of e-cigarettes users, which were compared directly to the concentrations of conventional cigarettes users. According to the Collaborative on Health and the Environment Toxicant and Disease Database [16, 17], these include strongly urothelial cancer-associated substances such as aromatic hydrocarbons (1-hydroxypyrene, 2-naphthol, 2-hydroxyfluorene, 3-hydroxyfluorene, P2,3-hydroxyphenanthrene, and 3-,4-hydroxyphenanthrenes) and 2-naphthylamine, limited urothelial cancer-associated substances such as tobacco-specific nitrosamines (NNN and NNAL) and metals (lead and chromium), and strongly can-

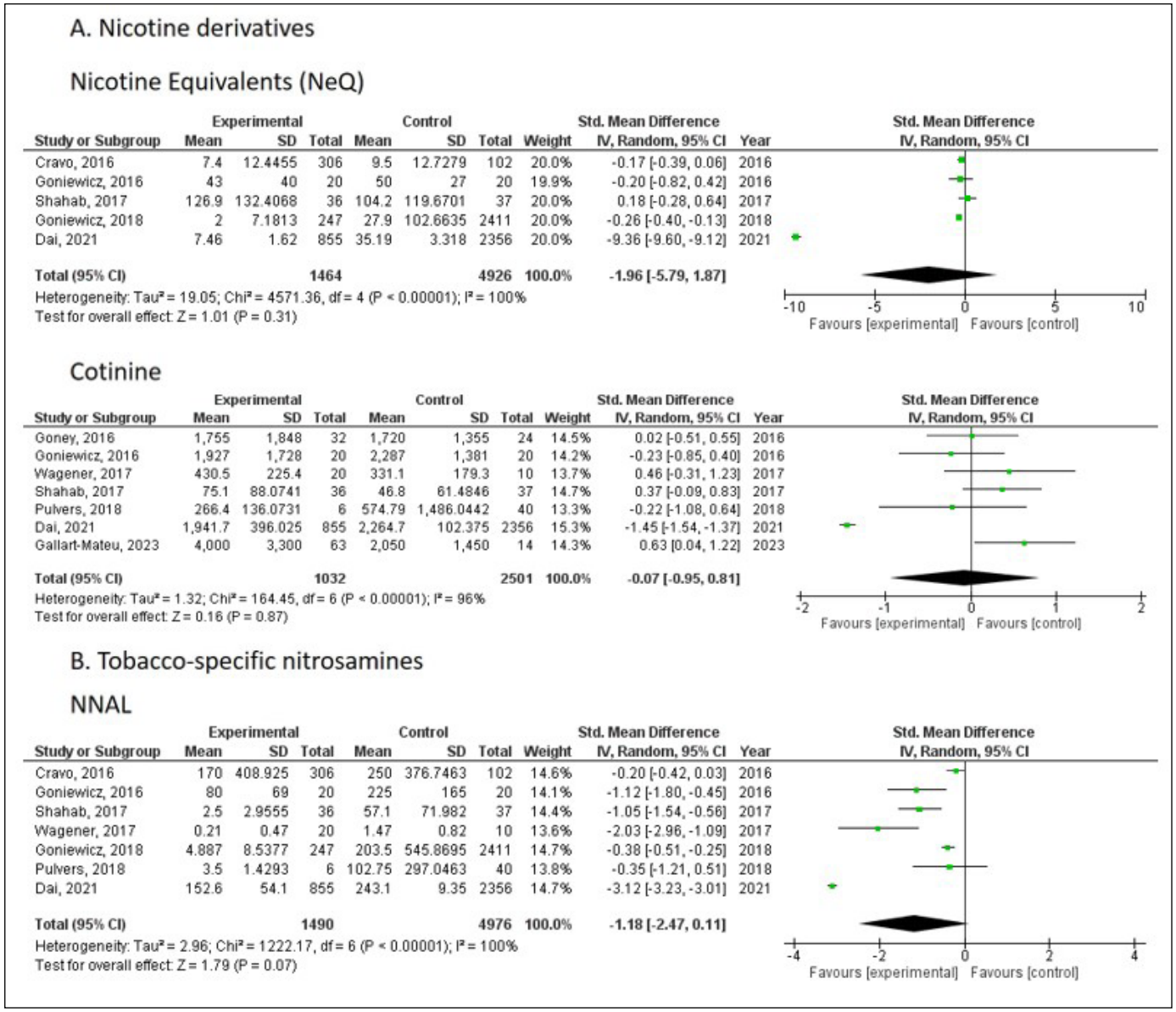

Figure 2. *Meta-analyses comparing electronic cigarettes and conventional cigarettes for urine toxicant and carcinogen concentrations:* **A)** *nicotine derivatives including nicotine equivalents and cotinine;* **B)** *tobacco-specific nitrosamines (NNAL).*

cer-associated substances such as volatile organic compounds (AAMA, DHBMA and MHBMA). Similarly, the systematic review by Bjurlin et al. [12] demonstrated the presence of all of the aforementioned compounds in the urine of e-cigarette users, along with 45 other toxicants or carcinogenic metabolites. The authors highlighted higher concentrations of these substances compared with non-smokers, although without conducting any direct pooled comparisons [12]. The systematic review by Bjurlin et al. [12], however, did not reference concentration levels of the conventional smokers [12]. To our surprise, although these substances were present in the urine of e-cigarettes users, our study showed that concentrations of these urothelial carcinogens may be significantly lower than among conventional cigarettes users. A few compounds suggested to be strongly associated with urothelial cancer – such as 1-hydroxypyrene, 2-naphtol, 2- and 3-hydroxyfluorene, NNAL, AAMA, and MHBMA – showed no difference in favor of e-cigarettes compared to conventional cigarettes, except for 2-hydroxyfluorene ($p < 0.00001$). These findings raise the question of whether e-cigarettes were the same as conventional cigarettes with similar concentrations of carcinogenic compounds associated with urothelial cancer [6].

While it may be tempting to conclude that e-cigarettes are safe to consume due to lower concentrations

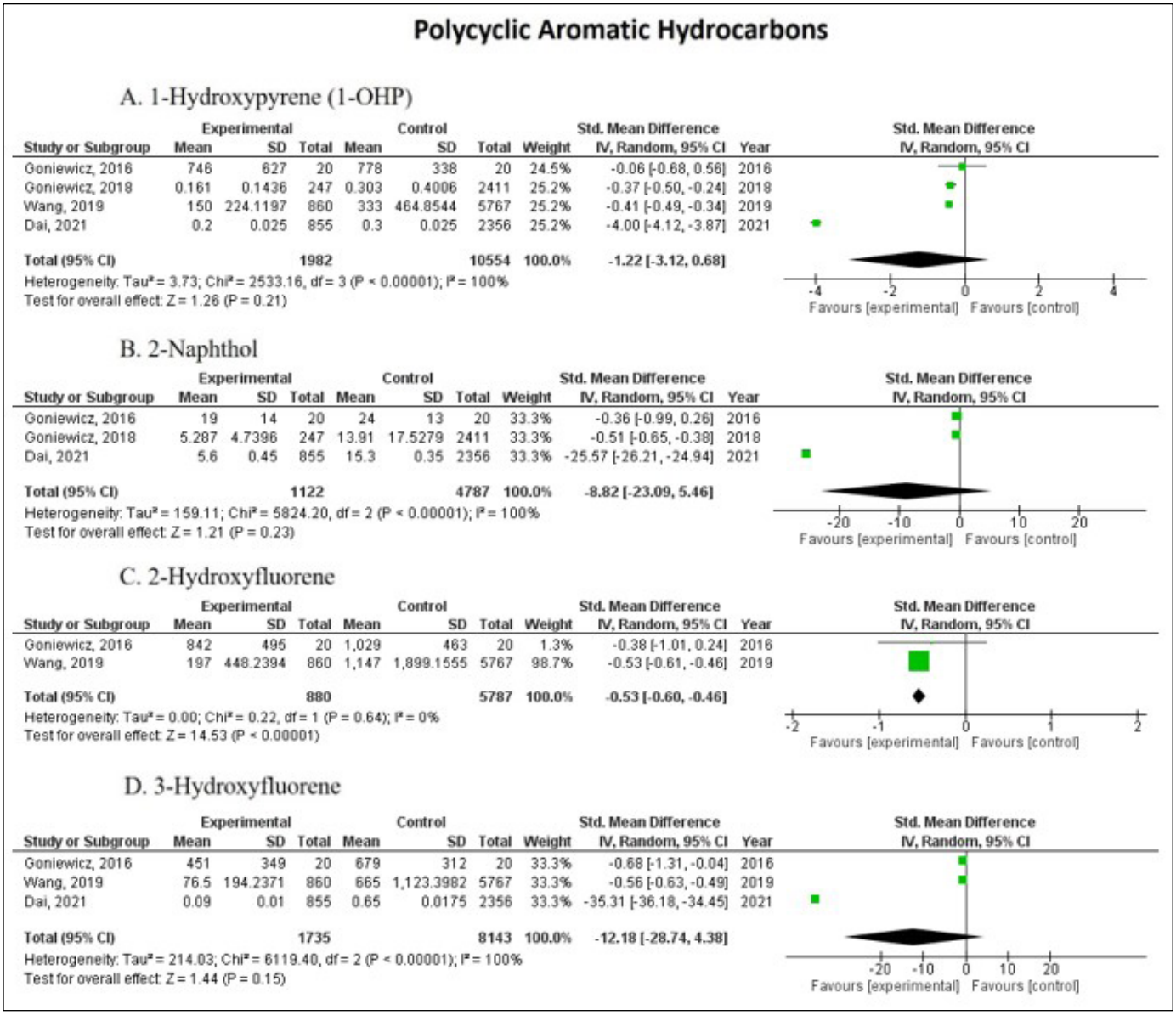

Figure 3. *Meta-analyses comparing electronic cigarettes and conventional cigarettes for urinary polycyclic aromatic hydrocarbons:* **A)** *1-hydroxypyrene;* **B)** *2-naphtol;* **C)** *2-hydroxyfluorene;* **D)** *3-hydroxyfluorene.*

of some carcinogenic substances, it is important to consider the broader implications [6]. Contradicting our findings, numerous studies have reported significantly reduced levels of these harmful and carcinogenic materials in e-cigarettes compared to conventional cigarettes [33–35]. However, a critical oversight in these investigations is the fact that e-cigarettes contain as much nicotine as, if not more than, conventional cigarettes [36, 37]. Our study supported this point by revealing statistically comparable levels of almost all harmful substance between e-cigarettes and conventional cigarettes. Notably, nicotine itself has been shown to induce sarcomas and leiomyomas in animal models [38]. Therefore, it is important to prioritize the measurement of the harmful and carcinogenic effects of e-cigarette aerosols (ECAs), rather than solely focusing on the carcinogenic components present in conventional cigarettes [11]. A recent study by Tang et al. reported that long-term exposure to ECAs induces bladder urothelial hyperplasia in mice, suggesting mechanisms involving the induction of specific DNA adducts and a reduction in DNA repair proteins and activity [9]. Additionally, nicotine and its derivatives have been implicated in similar DNA damage and repair inhibition in human cells [10]. Furthermore, nicotine derivatives in e-cigarettes can undergo nitrosation in both mouse and human cells, leading to the formation of nitrosamines and potentially exacerbating carcinogenic effects [39, 40]. These findings collectively suggest that ECA exposure is carcinogenic in mice and underscore the need for comprehensive assessment of the health risks associated with e-cigarette use.

Establishing a direct causative interaction between e-cigarettes and urothelial cancer poses challenges due to the very recent introduction of e-cigarettes.

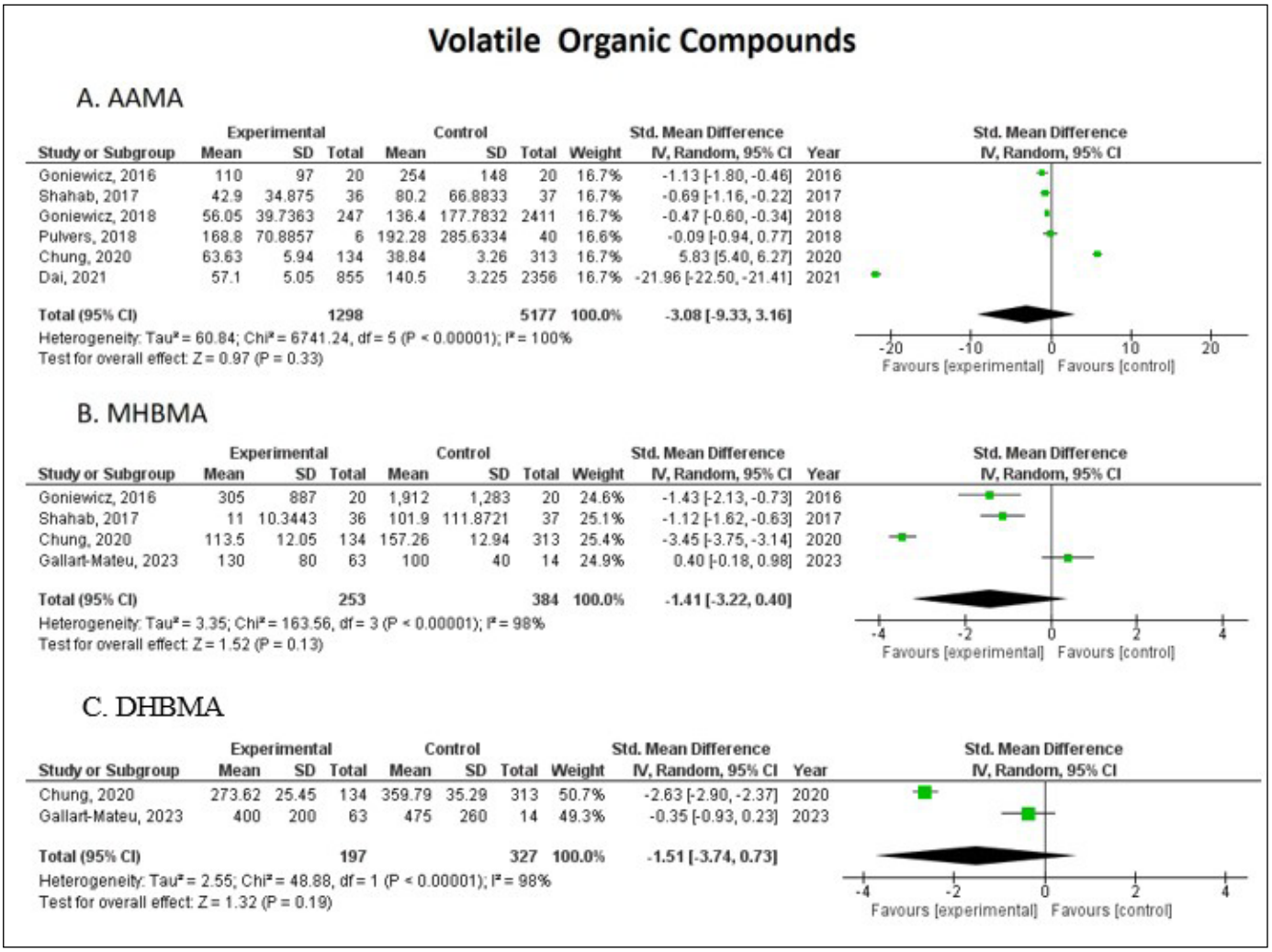

Figure 4. *Meta-analyses comparing electronic cigarettes and conventional cigarettes for urinary volatile organic compounds:* **A)** *AAMA;* **B)** *MHBMA.*

Since the average latency period from carcinogen introduction to cancer development is about 30 years, decades of data collection and research are needed to confirm the association [41, 42]. Considering that carcinogen concentrations and progression to cancer may have a dose-dependent relationship, current evidence is not yet sufficient, as downstream consequences may only be visible after a long period (decades) of e-cigarette usage [42]. Further large-scale observational studies are necessary, also considering other risk factors that may act as potential confounders, to determine whether e-cigarettes may be an independent risk factor for the development of urothelial cancer.

There are several limitations of our study, mainly due to the heterogeneity of included participants in selected studies. Due to e-cigarettes being novel, most people use them as a substitute for conventional smoking, meaning they had years of previous history of conventional smoking before turning to e-cigarettes or using both simultaneously. This causes a problem in identifying whether the carcinogenic substances originated from e-cigarettes or previously smoked conventional cigarettes. The different methods of examining the compounds and measuring units also add to the heterogeneity of the study. It should also be noted that different e-cigarettes (models and generations) have different components and solvents, making broad generalizations inappropriate. We tried to correct the heterogeneity by measuring risk of bias and employing a random effect model, as well as calculating the standardized mean difference as opposed to calculating the conventional mean difference. Lastly, few studies have specifically examined the effects of e-cigarettes on the development of urothelial cancer, which raises the question: "Are electronic cigarettes theoretically better than conventional smoking with respect to the risk of developing urothelial cancer?"

CONCLUSIONS

Despite lower concentrations of several markers compared to conventional cigarettes, multiple carcinogenic substances strongly associated with urothelial cancer development are present in the urine of e-cigarette users, suggesting a potential for carcinogenesis. Further large-scale observational studies investigating direct causation are necessary, considering other potential confounding risk factors, to determine whether e-cigarettes independently contribute to the development of urothelial cancer or confer a similar risk to conventional cigarettes.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ETHICS APPROVAL STATEMENT

The ethical approval was not required.

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