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Journal
Toxicology Reports, 17

ISSN
22147500

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Publication Date
2026-12-01

DOI
10.1016/j.toxrep.2026.102303

Toxicology Reports 17 (2026) 102303

Contents lists available at ScienceDirect

Toxicology Reports

journal homepage: www.elsevier.com/locate/toxrep

Comparison of effects of charcoal versus electric heating of waterpipe tobacco on carbon monoxide levels; cardiovascular measures; benzene, pyrene, and nicotine uptake; and subjective reactions☆

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ARTICLE INFO

Keywords:
Waterpipe
Hookah
Charcoal
Carbon monoxide

ABSTRACT

Toxicants are released from charcoal burned to heat waterpipe tobacco (WPT) and from WPT itself. This natural home setting trial tested a strategy to reduce harm of WPT use by comparing the effects of charcoal versus electric heating of WPT on outcome measures of toxicity. Fifty WPT smokers and 25 non-smokers (controls) participated. Within-subjects measures were collected in charcoal heated and in electric heated WPT smoking sessions. Pre-to-post differences in levels of ambient carbon monoxide (CO), exhaled CO, and heart rate were significantly lower when WPT was electrically heated; there were no differences for urinary biomarkers of nicotine, benzene and pyrene uptake. Comparing levels of controls to post smoking levels of urinary biomarkers of exposure to WPT indicated that electric heating of WPT versus charcoal heating did not significantly reduce exposure to the addictive drug nicotine or the toxicant pyrene, but did significantly reduce exposure to the carcinogenic compound benzene. Furthermore, we found visual evidence of charred WPT from electric sessions, suggesting excessively heated WPT. Participants reported smoking electric-heated WPT was less appealing; harsher and hurt their throat; but healthier and cleaner. To prevent negative subjective reactions from smokers and potential adverse health effects, electric heating devices should be regulated to prevent overheating and excessive thermal degradation of WPT. The findings also inform a harm reduction strategy, particularly for children living in homes of WPT smokers: smokers who use burning charcoal to heat WPT should avoid smoking indoors, as ambient CO levels proved significantly higher indoors than outdoors.

1. Introduction

Strategies to reduce harm of tobacco use among smokers unable or unwilling to quit have been focused on cigarettes [1]. Attention is needed for other forms of tobacco, such as waterpipe tobacco (WPT). WPT smoking has been associated with increased risk for cancers, cardiovascular diseases, and pulmonary diseases [2–6]. The use of a waterpipe (aka hookah) to smoke WPT has become increasingly popular worldwide, particularly among youth and young adults in several eastern Mediterranean, eastern European, and western countries, including the United States (U.S.) [7–9].

Burning charcoal to heat WPT is a traditional tobacco use method, producing smoke from the burning charcoal and from the WPT. The waterpipe consists of a head (bowl) containing WPT and charcoal, a stem (body) which is a vertical tube that passes into a partially filled water jar at the base, a flexible hose, and a mouthpiece (**e**Fig. 1. Waterpipe diagram and photo); smoke passes through the water before reaching the user. Charcoal accounts for most of the carbon monoxide

☆ Registered at clinicaltrials.gov, ID# NCT03253653, release date 8.18.2017

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https://doi.org/10.1016/j.toxrep.2026.102303
Received 1 February 2026; Received in revised form 21 June 2026; Accepted 24 June 2026
Available online 25 June 2026

Fig. 1. An example from one participant of 2 typical residue waterpipe tobacco (WPT) samples, and 2 typical waterpipe rubber connectors, after completion of a charcoal session and an electric session.

(CO) and polycyclic aromatic hydrocarbons (PAHs) in the smoke generated during WPT smoking [10–13].

Acute CO poisoning is one of the most immediate serious injuries post WPT smoking, and has been reported internationally as case studies [10,14–16]. In the U.S., data from the National Poison Database System (2011–2017), showed that WPT smoking was associated with acute CO poisoning that involved admission to emergency medical departments [17–19]. Exposure to CO, a highly toxic gas, is dangerously unsafe, particularly that WPT smokers are unlikely alerted by the CO's odorless and tasteless characteristics [20]. Inhaled CO binds with the iron in blood hemoglobin to produce carboxyhemoglobin (COHb), displacing oxygen from heme-binding sites [21]. Human toxicity results from the direct interference of CO with cellular processes, thus compromising the capacity of the blood to carry oxygen to the body's cells, leading to hypoxia [15,16].

Besides CO, WPT smokers are exposed to other toxicants exacerbated by charcoal, that were found to be higher in mainstream WPT smoke than in cigarettes', such as benzene (271 μg vs 20–70 μg) and pyrene (12,950 μg vs 44.8 μg), respectively [11,13,22–25]. Benzene, a volatile organic compound (VOC), is a proven human carcinogen that causes lymphohematopoietic cancers, including acute myelogenous leukemia [26,27]. Pyrene occurs as part of a mixture of PAHs, many of which (e.g. benzo[*a*]pyrene) are considered carcinogenic to humans [28]. Similar to CO exposure, benzene and pyrene uptake were found to be higher in WPT smokers compared to cigarette smokers [29–33].

Exposure of WPT smokers to charcoal-related toxicants underscores the importance of identifying WPT harm reduction strategies, such as substituting charcoal with electric-heating devices [11,34–37]. In a laboratory setting, using a human-derived puffing regimen, a study found a significant decrease in mainstream CO and pyrene yields (8.2 and 2.1 times lower, respectively) when WPT was machine smoked via a waterpipe fitted with a commercial electric head compared to charcoal [35]. Another laboratory study devised and used an electric heating element, finding that about 90% of the CO and greater than 95% of the benzo(a)pyrene in the smoke was attributed to charcoal [11]. A third laboratory study, using two types of commercial electric heads and one electric coal, found a 90% reduction in CO and 80% reduction in total PAH emissions [38].

In a laboratory chamber study, the boost in both exhaled breath CO and exhaled benzene was significantly lower when WPT was smoked using a charcoal-like electric heater compared to burning charcoal (0.1 vs 51.7 ppmv for CO and -0.1 vs 8.5 ppmv for benzene) [36]. Similarly, in a smoking chamber in a clinical research center, exhaled breath CO boost was 9.5-fold significantly lower after smoking WPT heated with a charcoal-like electric heater compared to charcoal (2.5 vs 23.6 parts per million, respectively) [34].

There is limited knowledge on the impact of replacing charcoal with WPT electric heaters on the uptake of toxins in WPT smoke. To our knowledge this is the first natural home setting clinical trial in the U.S. that investigated potential differential effects of using charcoal versus electric heating of WPT via an electric head on: cardiovascular measures; subjective reactions when using electrically heated WPT; and ambient air CO, exhaled breath CO, and urinary metabolites of nicotine, benzene, and pyrene in WPT smokers. This study also explored potential differential effects on outcome measures of smoking WPT inside the home versus outside, for both charcoal and electric heated sessions.

2. Materials and methods

2.1. Participant recruitment, screening, and consent

Between December 2017 and September 2018, we recruited a convenience sample of 50 WPT smokers (25 men, 25 women) and 25 non-smokers (controls) (12 men and 13 women) from San Diego County, California, U.S. via bulletin board flyers (e.g., community colleges, universities, cafés), electronic flyers on social media (e.g. Instagram, Facebook, Snapchat, Reddit, Twitter), and participant enlistment of others by word of mouth.

Trained research assistants (RAs) qualified participants via phone-screening based on inclusion/exclusion criteria. At an office visit we explained study activities, obtained signed informed consent forms, collected smoking history and demographics via self-administered questionnaire, provided training on giving a proper exhaled CO measure, took physiological measures (height, weight, exhaled breath CO), and scheduled 2 home visits for WPT smokers and one home visit for non-smokers.

WPT smoker inclusion criteria were: exclusive WPT smoker; ≥ 21 years old; smoked WPT at least once each week but less than daily or smoked WPT at least once a month but less than weekly; smoked ≥ 1WPT head/smoking session; no use of nicotine products (e.g. Nicorette) or tobacco products (besides WPT) in the past 30 days; no WPT home smoking restrictions. Non-smoker inclusion criteria were: ≥ 21 years old; not living with a smoker; not using any tobacco or nicotine replacement products; not allowing tobacco smoking at home during the study; passing the exhaled CO screening test.

Exclusion criteria for all participants were: major physical/psychiatric illnesses that might interfere with providing informed consent or completing an interview; history of chronic health problems (e.g. asthma); regular prescription medication use (other than vitamins or birth control); pregnancy.

We phone-screened 101 WPT smoker respondents; 54 were eligible and were enrolled; 4 withdrew before the home visit (due to travel/change of mind). We phone-screened 51 non-smoker respondents; 31

were eligible and were enrolled; 5 were excluded because of high blood pressure; on medication; potential exposure to tobacco smoke based on exhaled breath CO ≥ 3.6 parts per million (ppm) cut-off level [39]; 1 non-smoker dropped out before the home visit (due to school/work schedule) (**eFigure 2.** CONSORT Flowchart).

2.2. Study design

This natural home setting clinical trial used a repeated measures design. For WPT smokers, RAs collected data during an office visit and two home visits; Home visit 1 – Charcoal Session: charcoal was used, and Home visit 2 – Electric Head Session: a commercial ceramic electric head (*Hookah-Shisha Heater, Ren Headstream*, China [40]) was used (**eFigure 3.** WPT electric heater).

Over two weeks, 50 WPT smokers smoked, in their home, one WPT head during each of the 2 separate WPT smoking sessions, with a 7-day washout period before each session. During the washout periods, prescheduled phone texts reminded WPT smokers about smoking abstinence, avoiding secondhand smoke (SHS), collecting urine samples, and confirming scheduled home visits. WPT smokers received $175 in cash at study completion: $75 for the 1st home visit, and $100 for the 2nd home visit.

RAs also collected data from 25 non-smokers during an office visit and one home visit. During 7 days before the home visit, prescheduled phone texts reminded non-smokers about avoiding SHS, collecting urine samples, and confirming scheduled home visit. Non-smokers received $75 in cash at completion of study activities. San Diego State University's Institutional Review Board approved the study.

2.3. WPT smoking sessions

During the 2 home visits, the RAs provided the WPT smokers with a single-hose medium-size waterpipe with glass water jar [height = 22 in. (55.8 cm); *Khalil Mamoon Safari* brand, Egypt; **e**Fig. 1] and a disposable plastic hose (length = 50 in. (125 cm); *Fancy Hose, Zebra Smoke* brand, Amazon.com). Following a standardized protocol, RAs placed a standardized volume (2 cups = 470 mL) of room temperature commercial drinking water (*Nestlé® Pure Life™ Purified Bottled Water* brand, U.S.) in the waterpipe jar, covering the metal stem with an inch (2.5 cm) of water. RAs weighed (using an analytical balance) and loaded one head of flavored WPT (10 g; *Exotic Double Apple* flavor, *Starbuzz* brand, U.S.) in the clay head for session 1 and in the electric head for session 2, covering it with a manufacturer pre-perforated sheet of aluminum foil (*Zebra Smoke* brand, Amazon.com) (**eFigure 4.** Pictorial protocol for preparing the clay head and the electric head). The WPT was purchased between December 2017 and August 2018 from two WPT supply stores in San Diego, California, and stored at room temperature. Each smoker smoked WPT from the same batch for both sessions.

For the charcoal session, using a portable lighter, RAs lit a single quick-light charcoal (40 mm; *Three Kings* brand, Holland), placing it on the foil-covered waterpipe head (no additional charcoal was added). For the electric session, RAs assembled the electric head, plugged it to the adapter, turned the adjustable temperature dial (heat setting range = 0–9) to level 3, and waited 3 min for the electric head to heat up, after which participants started to smoke. Smokers were turning the dial between levels 3 and 5 based on their preference of the amount of generated smoke; none of the smokers turned the dial above 5, because the tobacco started to char. Parameters for using the electric head were based on 1) findings from our pilot tests with two WPT smokers, who each did several trials of using the electric head in their home; and 2) instructions provided by the manufacturer of the electric head [40].

Smokers smoked at the same preferred location at home during the 2 sessions; smoked as they typically do during the evening hours between 5:00 pm and 8:00 pm, with no other smokers present; ended smoking when desired; were informed that the waterpipe would be available for 45 min per smoking session. At the conclusion of each home visit, RAs returned the waterpipe device and WPT use waste (in sealed containers/Ziploc bags) to our center, took pictures of examples of the residual WPT (remaining WPT after completion of a smoking session) and the waterpipe rubber connectors (connecting the waterpipe head to the waterpipe stem). They disposed of all WPT waste in our laboratory biohazard trash (residual WPT, connectors, disposable hose, aluminum foil, gloves, etc.). RAs thoroughly cleaned waterpipe devices with soap and water between sessions and between participants. Each participant had a new disposable hose and rubber connector/session.

2.4. Measures

2.4.1. Demographics and WPT smoking behaviors

During the office visit, participants completed a self-administered questionnaire that asked about demographics (age, gender, education, race/ethnicity), and WPT smoking behaviors.

2.4.2. Physiological measures

During the office visit, height (Ht.) and weight (Wt.) were taken to calculate Body Mass Index [BMI = Wt. (kg) / Ht. (m)^2]. An exhaled breath CO measurement was taken using a CO breath analysis monitor (Micro+pro™ Smokerlyzer® Covita, Bedfont, U.S., sensitivity = 1 ppm; device use validated by a Federal Drug Administration study [41]). Participants were asked to inhale deeply, hold breath for 15 s, and then exhale (blow) slowly into the mouthpiece, aiming to empty the lungs completely.

2.4.3. Smoking Duration and Residual WPT

During each home visit, RAs recorded length of smoking time, from first to last puff to calculate smoking duration, and weighed the residual WPT.

2.4.4. Ambient Air CO concentrations

Using a CO monitor (Micro+pro™ Smokerlyzer® Covita, Bedfont, U.S.; sensitivity: 1 ppm; "Ambient air test/mode" selected), we took 2 consecutive ambient air CO measurements, 5 min apart, at the beginning of the home visit before smoking, up to 8 consecutive measurements every 5 min throughout the smoking session, and 2 consecutive measurements, 5 min apart, after the last puff. In non-smokers' homes, 2 consecutive measurements, 5 min apart, were taken and averaged. Ambient air CO measurements were collected in the participant's breathing zone (∼ 3–4 feet).

2.4.5. Exhaled breath CO

Using a CO breath analysis monitor (Micro+pro™ Smokerlyzer® Covita, Bedfont, U.S., sensitivity = 1 ppm), 2 exhaled breath CO measurements were taken 2 min before lighting the charcoal or turning the heat on the electric head, after 15 min of smoking, and within 2 min after the last puff. For non-smokers, we averaged their 2 exhaled breath CO measurements.

2.4.6. Cardiovascular measures

Before and after each WPT smoking session, using an upper arm blood pressure monitor (*Omron 3 Series* brand, U.S.), we took and averaged 2 blood pressure and heart rate measurements of smokers in a seated resting position 5 min apart [42]. For non-smokers, we averaged 2 blood pressure and heart rate measurements taken 5 min apart.

2.4.7. Subjective reactions measures

After the electric session, participants were provided a self-administered questionnaire that asked about subjective reactions when using electrically heated WPT compared to charcoal heated WPT. All recruited smokers had smoked the traditional charcoal heated WPT, and had never experienced smoking WPT using an electric heater. Thus, to enable participants to make an informed comparison, it was essential to wait until after both sessions had been completed before providing the questionnaire.

2.5. Urinary Metabolites of WPT Smoking

WPT smokers provided first-void morning urine samples on the day of each smoking session and on the day after; non-smokers provided first-void morning urine samples on 2 consecutive days. Participants stored urine samples in their refrigerator's freezer section until pickup by RAs within 12 h and transfer (frozen) to our research center laboratory. Urine samples were aliquoted and stored in a freezer (-20°C), then sent frozen in dry ice to two laboratories. The San Diego State University Environmental Health Laboratory analyzed urinary creatinine using isotope-dilution liquid chromatography/tandem mass spectrometry (LC-MS/MS) with the sample preparation methods and multiple-reaction-monitoring transitions [43], and an adapted chromatographic separation [44]; urinary cotinine was analyzed by isotope-dilution LC-MS/MS with a limit of detection (LOD) of 0.03 ng/mL [45]. The Masonic Cancer Center, University of Minnesota laboratory analyzed urinary SPMA (S-phenyl-mercapturic acid, a metabolite of benzyne) and 1-HOP (1-Hydroxypyrene, a metabolite of pyrene) by LC-APCI-MS/MS-SRM with LODs of 0.12 pmol/mL and 0.10 pmol/mL, respectively [46,47].

2.6. Statistical analyses

Data were double entered and analyzed using SPSS v28 and Stata v15 to compute statistics for the two WPT smoking sessions (charcoal vs electric head). For cardiovascular measures (systolic and diastolic blood pressure, heart rate) we used means, standard deviations (SDs), and *t*-tests. Carbon monoxide (CO) measures (ambient air CO, exhaled breath CO), and assays of creatinine-corrected urinary biomarkers of WPT smoking (cotinine, SPMA, 1-HOP) were too skewed to be normalized by log transformation; we used medians, interquartile ranges, and nonparametric tests. Geometric means (GM) and 95% confidence intervals (CI) are presented for all measures.

Dependent *t*-tests or Wilcoxon signed-rank tests identified within-group differences in measures before and after each WPT smoking session. Independent *t*-tests or Mann–Whitney *U* tests identified between-group differences in pre-to-post WPT smoking changes in measures for charcoal vs electric sessions, and for smokers vs non-smokers.

Independent *t*-tests or chi-square tests, as applicable, identified differences of demographic measures by smoking status. For urinary biomarkers, we excluded instances of laboratory assay interference and replaced values less than the limit of detection (LOD) with half of the LOD. All statistical tests were two-tailed with an alpha level of 0.05; 'pmol/mg creatinine' is referred to as 'pmol/mg'.

3. Results

3.1. Demographics and WPT Use (Table 1)

WPT smokers (mean age = 25.3 years), were 50% males, identifying as White (22%); Hispanic (32%); Black (10%); Middle Eastern/Arab, Chaldean, Persian, or Kurdish (26%); or multi-ethnic (10%). Most WPT smokers had a college degree (50%) or some college (36%). More than a third (40%) resided in apartments or townhouses while 60% resided in houses. WPT smokers smoked 'At least once each week but less than daily' (62%) or 'At least once a month but less than weekly' (38%), and were borderline overweight (mean BMI = 27.5 kg/m^2) [48]. WPT smokers and non-smokers did not differ significantly by age, gender, education, home setting, BMI, or exhaled breath CO concentrations when screened for study inclusion.

3.2. Awareness of WPT electric heating devices

Before enrolling in this study, none of our participants had ever

Table 1
Characteristics of waterpipe tobacco (WPT) smokers and non-smokers.

	WPT smokers (n = 50)		**Non-smokers** (n = 25)		
	n	(%)	n	(%)	p[a]
Age (years)					
Mean ± standard deviation (SD)	25.3	±3.13	25.5	±4.56	0.668
Median (Minimum-Maximum)	25.0	(21–35)	23.5	(21–37)	
Gender					
Male	25	(50)	12	(48.0)	0.870
Female	25	(50)	13	(52.0)	
Race/ethnicity					
White, Caucasian, European	11	(22)	5	(20)	**0.005**
Mexican, Hispanic, or Latino	16	(32)	8	(32)	
Black or African American	5	(10)	1	(4)	
Middle Eastern[b]	13	(26)	0	(0)	
Asian/Multi-ethnic[c]	5	(10)	11	(44)	
Highest level of education completed					
High school	7	(14)	1	(4.2)	0.219
College, no degree	18	(36)	8	(33.3)	
College degree	25	(50)	15	(62.5)	
Type of natural home setting					
House	30	(60)	12	(48)	0.324
Apartment/ Townhouse	19	(40)	13	(52)	
Live with a tobacco smoker					
Yes	17	(34)	0	(0)	**< 0.001**
No	33	(66)	25	(100)	
WPT smoking frequency					
At least once each week but less than daily	31	(62)	N/A		
At least once a month but less than weekly	19	(38)			
Type of WPT currently smoke					
Only flavored	47	(92)	N/A		
Flavored and unflavored	3	(8)			
Location of WPT smoking session					
Indoor area	28	(56)	N/A		
Outdoor area	22	(44)			
Aware of electric head use					
Yes	10	(20)	N/A		
No	40	(80)			
Ever used electric head to heat WPT					
Yes	0	(0)	N/A		
No	50	(100)			
Body Mass Index (BMI)[d]					
Mean ± SD	27.5	±4.42	26.3	±5.65	0.351
Median (Minimum-Maximum)	27.1	(19.6–39.9)	25.4	(18.0–38.5)	
Exhaled Carbon Monoxide (ppm)[e]					
Mean ± SD	5.8	±21.94	1.6	±1.32	0.519
Median (Minimum-Maximum)	2.0	(0.0–156.0)	2.0	(0.0–4.0)	

[a] p = p-value for WPT smokers vs. non-smokers test of equality, derived from Chi-Square test or Mann-Whitney U tests, as applicable; two-tailed alpha level $p < 0.05$; significant levels are bolded

[b] Participants were Middle Eastern/Arab, Chaldean, Persian, or Kurdish

[c] Asian/Multi-ethnic: WPT Smokers were German/Mexican (n = 1), Lebanese/Black/White (n = 1), and Mexican/Caucasian (n = 3); Non-smokers were

Native Hawaiian or Pacific Islander (n = 8), Filipino (n = 2), and Mexican/Filipino (n = 1)

[d] Body Mass Index = weight in kilograms / (height in meters) [2]

[e] Exclusion criteria for non-smokers; we used eCO (exhaled carbon monoxide) cut-off-point: mean ± SD = 3.61 ± 2.15 ppm [40]

smoked electrically heated WPT, and the majority (80%) were not aware of its availability. The 10 participants who were aware of it learned of it as follows: a friend (2), from the study (2), heard of it but never used it (1), internet and forums (1), smoke shops (1), tobacco store (1), Youtube (1), and "do not know" (1).

3.3. *Smoking duration and residual WPT (Table 2)*

The duration of WPT smoking session was significantly shorter for the electric session than for the charcoal session (Table 2). The mean elapsed smoking time was 4.8 min less in the electric session (28.3 vs 33.1 min, respectively). Less residual WPT remained in the bowl after the electric session than after the charcoal session (5.5 g versus 7.0 g, respectively).

We observed that the residual WPT was more charred and the waterpipe rubber connector was more burnt, following the electric sessions, than following the charcoal sessions. **Figure 1** provides an example from one participant of 2 typical residue WPT samples, and 2 typical waterpipe rubber connectors, after completion of a charcoal session and of an electric session.

3.4. *Cardiovascular measures (Table 2)*

Systolic blood pressure levels did not change significantly pre-to-post smoking for either the charcoal session or the electric session. Diastolic blood pressure levels increased significantly after both WPT heating methods; however, the pre-to-post session change in diastolic blood pressure levels did not differ significantly between charcoal and electric sessions.

Heart rate increased significantly after the charcoal session, though not after the electric session; the difference in the increase between these two changes was statistically significant. The pre-to-post increase in arithmetic mean heart rate was 5.06 beats per minute for the charcoal session compared to 0.67 beats per minute for the electric session.

3.5. *Carbon monoxide measures*

Pre-to-post change in ambient air CO level was significantly higher after the charcoal session but not after the electric session (Table 2). The pre-to-post change in GM level was 3.5 times higher after the charcoal session vs 1.2 times higher after the electric session (Table 2). GM ambient air CO levels at 5-minute intervals during the charcoal session and the electric session are shown in (Fig. 2).

The pre-to-post change in GM exhaled breath CO levels was 47 times higher after the charcoal session, compared to 1.3 times higher after the electric session. After 15 min of smoking, GM exhaled breath CO levels were 28 times higher in the charcoal session than in the electric session—81 vs 2.9 ppm, respectively (Fig. 3).

3.6. *Cardiovascular and carbon monoxide measures: WPT smokers vs non-smokers (Table 2)*

The GM systolic blood pressure levels of WPT smokers after neither the charcoal session nor the electric session were significantly different from non-smokers' systolic levels. Post-session GM diastolic blood pressure levels in WPT smokers were significantly higher than in non-smokers after the charcoal session but not after the electric session.

After the charcoal session, GM ambient air CO and exhaled breath CO levels for WPT smokers were significantly higher than for nonsmokers, for example, GM exhaled breath CO levels were 38.2 imes higher in WPT smokers compared to non-smokers.

After the electric session, GM ambient air CO levels for WPT smokers were lower by 0.3 ppm compared to non-smokers' homes, and GM exhaled breath CO levels were only 1.3 times higher in WPT smokers compared to non-smokers.

3.7. *Biomarkers of WPT Use (Table 3)*

3.7.1. *Urinary cotinine*

Urinary cotinine levels increased pre-to-post session by a factor of 26.1 for the charcoal session, and by a factor of 21.6 for the electric session. The pre-to-post session change in GM urinary cotinine levels did not differ significantly between charcoal session and electric session. Compared to non-smoker levels, the post-session GM cotinine level for WPT smokers was 1745 times higher for the charcoal session and 1320 times higher for the electric session.

3.7.2. *Urinary SPMA*

Urinary SPMA levels did not significantly increase from pre-session to post-session for either charcoal heating or electric heating, and the degree of pre-to-post-session change in SPMA level did not significantly differ between the two sessions. Post-charcoal-session urinary SPMA levels were significantly higher than levels in non-smokers; however, post-electric-session urinary SPMA levels were not significantly different from levels in non-smokers. Compared to non-smokers, GM urinary SPMA levels were 6.6 times higher after the charcoal session versus 1.7 times higher after the electric session.

3.7.3. *Urinary 1-HOP*

The pre-to-post change in urinary 1-HOP levels did not differ significantly between charcoal and electric sessions. At post-session, 1-HOP levels for the charcoal and electric sessions were significantly higher than levels in non-smokers; GM urinary 1-HOP levels after both charcoal and electric sessions were twice as high as non-smoker levels.

3.8. *Location of Smoking at Home – Indoors vs Outdoors*

We categorized participants' descriptions of the places where their smoking session took place to create a binary (indoor/outdoor) variable. Indoor locations (n = 28) included living room (18), bedroom (3), kitchen (3), dining room (2), and garage (2); outdoor locations (n = 22) included patio/backyard (20), and front driveway (2). For both charcoal and electric sessions, we tested 3 CO measures, 3 cardiovascular measures, and 3 biomarkers for difference by smoking location (indoor vs outdoor) in pre-to-post change. The only significant difference we found was for ambient air CO during the charcoal session. At the end of 30 min of smoking in that session, the GM ambient air CO level among indoor smokers (3.96 ppm) was 7.8 times as high as the level among outdoor smokers (0.51 ppm) (Fig. 4).

3.9. *Subjective Reactions*

eTables 1–3 present participants' reactions to questions about their experience with electric heating of the WPT compared to charcoal.

4. Discussion

Findings substantiate and extend evidence from previous studies showing substantially reduced potential risk to health from exposure to CO when WPT is electrically vs charcoal heated [11,34,36,38]. Pre-to-post change in levels of ambient air CO, exhaled breath CO, and heart rate were significantly higher for charcoal vs electrically heated WPT—consistent with two previous human studies [34,36].

Table 2
Physiological measures in waterpipe tobacco (WPT) smokers (n = 50), by WPT heating source (Charcoal *vs* Electric Head), and in non-smokers (n = 25).

	WPT heated by Charcoal		WPT heated by Electric Head		Non-Smokers		Charcoal vs Electric Head		Charcoal vs Non-Smokers		Electric head vs Non-Smokers	
	M ± SD,[a]	GM (95% CI)[b]	M ± SD,[a]	GM (95% CI)[b]	M ± SD,[a]	GM (95% CI)[b]	M Δ[c]	p[d]	M Δ[c]	p[d]	M Δ[c]	p[d]
Time Smoked (minutes)	33.1 ± 9.45,	31.9 (30–34)	28.3 ± 5.07,	27.9 (27–29)			−4.74	**< 0.001**				
Residual WPT (grams)[e]	7.01 ± 0.94,	6.9 (6.7–7.2)	5.52 ± 1.19,	5.4 (5.1–5.7)			−1.49	**< 0.001**				
Blood Pressure (mmHg)[f]												
Pre-Smoking Systolic	122.2 ± 11.5,	122 (119–125)	119.3 ± 14.1,	119 (115–123)	118.2 ± 16.44,	117 (111–124)	−2.92	0.052	−4.00	0.283	−1.08	0.780
Post-Smoking Systolic	122.3 ± 13.3,	122 (118–125)	120.4 ± 12.4,	120 (116–123)	118.2 ± 16.44,	117 (111–124)	−1.87	0.215	−4.08	0.288	−2.21	0.557
Mean Δ[g]	0.08		1.13									
t-test p[h]	0.944		0.327									
Charcoal vs Electric Head p[i]								0.549				
Pre-Smoking Diastolic	78.1 ± 9.26,	78 (75–80)	76.0 ± 8.26,	76 (73–78)	75.7 ± 7.23,	75 (73–78)	−2.10	0.075	−2.38	0.227	−2.77	0.882
Post-Smoking Diastolic	79.5 ± 8.25,	79 (77–81)	78.3 ± 8.51,	78 (75–80)	75.7 ± 7.23,	75 (73–78)	−1.17	0.305	−3.82	**0.045**	−2.65	0.165
Mean Δ[g]	1.44		2.37									
t-test p[h]	**0.041**		**0.002**									
Charcoal vs Electric Head p[i]								0.361				
Heart Rate (beats/minute)												
Pre-Smoking	75.5 ± 10.4,	75 (72–78)	77.5 ± 11.6,	77 (73–80)	76.6 ± 11.8,	76 (71–81)	1.98	0.096	1.10	0.695	−0.88	0. 761
Post-Smoking	80.5 ± 12.3,	80 (76–83)	78.1 ± 11.5,	77 (74–80)	76.6 ± 11.8,	76 (71–81)	−2.42	0.103	−3.97	0.182	−1.54	0.592
Mean Δ[g]	5.06		0.67									
t-test p[h]	**< 0.001**		0.521									
Charcoal vs Electric Head p[i]								**0.001**				
	Median (q1-q3)[j]	GM (95% CI)[b]	Median (q1-q3)[j]	GM (95% CI)[b]	Median (q1-q3)[j]	GM (95% CI)[b]	Ratio[k]	p[l]	Ratio[k]	p[l]	Ratio[k]	p[l]
Ambient Air CO[m] (ppm)[n]												
Pre-Smoking	0 (0–0)	0.82 (0.45–1.5)	0 (0–0),	0.87 (.39–1.9)	0 (0–1),	1.4 (0.95–2.0)	0.94	0.773	0.59	**0.001**	0.63	**0.003**
Post-Smoking	1 (0–4)	2.9 (2.0–4.3)	0 (0–0),	1.06 (.65–1.7)	0 (0–1),	1.4 (0.95–2.0)	2.8	**< 0.001**	2.14	**0.012**	0.77	**0.007**
GM ratio,[o] GM Δ[p]		3.6, 2.1		1.2, 0.19								
Signed-rank test p[q]		**< 0.001**		0.938								
Charcoal vs Electric Head p[i]								**< 0.001**				
Exhaled Breath CO[r] (ppm)												
Pre-Smoking	0 (0–1)	2.3 (1.5–3.4)	0 (0–2),	0.46 (0.21–0.74)	3 (0–4),	2.8 (2.1–3.6)	0.8	0,156	0.82	**0.002**	0.38	**< 0.001**
Post-Smoking	100 (73–177)	107 (84–136)	0 (0–2),	0.58 (0.28–0.96)	3 (0–4),	2.8 (2.1–3.6)	30.8	**< 0.001**	39.57	**< 0.001**	1.25	**0.006**
GM ratio,[o] GM Δ[p]		47.1, 104.7		1.3, 0.8								
Signed-rank test p[q]		**< 0.001**		0.065								
Charcoal vs Electric Head p[i]								**< 0.001**				

Note. All values are rounded up; number of decimal places displayed is 2 for values< 1; 1 for values ≥ 1 and < 10; 0 for values≥ 10

i Charcoal vs Electric Head p = p value for main outcome: charcoal pre-post change vs electric head pre-to-post change; dependent *t*-test for normally distributed cardiac measures, Wilcoxon signed-rank test for skewed CO measures; two-tailed alpha level p < 0.05 (bolded)

[a] M ± SD = arithmetic mean and standard deviation

[b] GM (95%CI) = geometric mean and 95% confidence interval

[c] M Δ = difference in mean levels for: Charcoal vs Electric Head; Charcoal vs Non-Smoker; Electric Head vs Non-Smoker—separately at pre-session and at post-session

[d] p = p value from (dependent or independent (as appropriate) *t*-test of equality of arithmetic means; two-tailed alpha level *p* < 0.05 (bolded)

[e] Residual WPT = grams of WPT remaining at end of a smoking session; an initial 10 g WPT was loaded in the waterpipe head; weights determined using an analytical balance

[f] mmHg = millimeters of mercury

[g] Mean Δ = post-session minus pre-session arithmetic mean level for each of 2 sessions: charcoal and electric head

[h] *t*-test p = p value from a dependent, matched-pairs *t*-test of equality of arithmetic means; two-tailed alpha level *p* < 0.05 (bolded)

[i] Charcoal vs Electric Head p = p value for main outcome: charcoal pre-post change vs electric head pre-to-post change; dependent *t*-test; two-tailed alpha level $p < 0.05$ (bolded)
[j] Median (q1-q3) = 50th percentile; (q1-q3) = interquartile range, from first quartile 1 (q1; aka 25th percentile) to the third quartile 3 (q3; aka 75th percentile) of the distribution
[k] Ratio = ratio of GM levels: Charcoal/Electric Head; Charcoal/Non-smoker; Electric Head/Non-Smoker—separately at pre and post
[m] CO = carbon monoxide; CO in the ambient air was measured using a CO analysis monitor (Micro+pro™ Smokerlyzer® Covita, Bedfont, US)
[n] ppm = parts per million
[o] GM ratio = ratio of post-session to pre-session GM biomarker levels for each of 2 sessions: charcoal and electric head
[p] GM Δ = post-session GM value minus pre-session GM value
[q] Signed-rank test p = p value from Wilcoxon matched-pairs signed-rank test; two-tailed alpha level $p < 0.05$ (bolded)
[r] Exhaled breath CO measurements were taken using the Smokerlyzer® CO analysis monitor

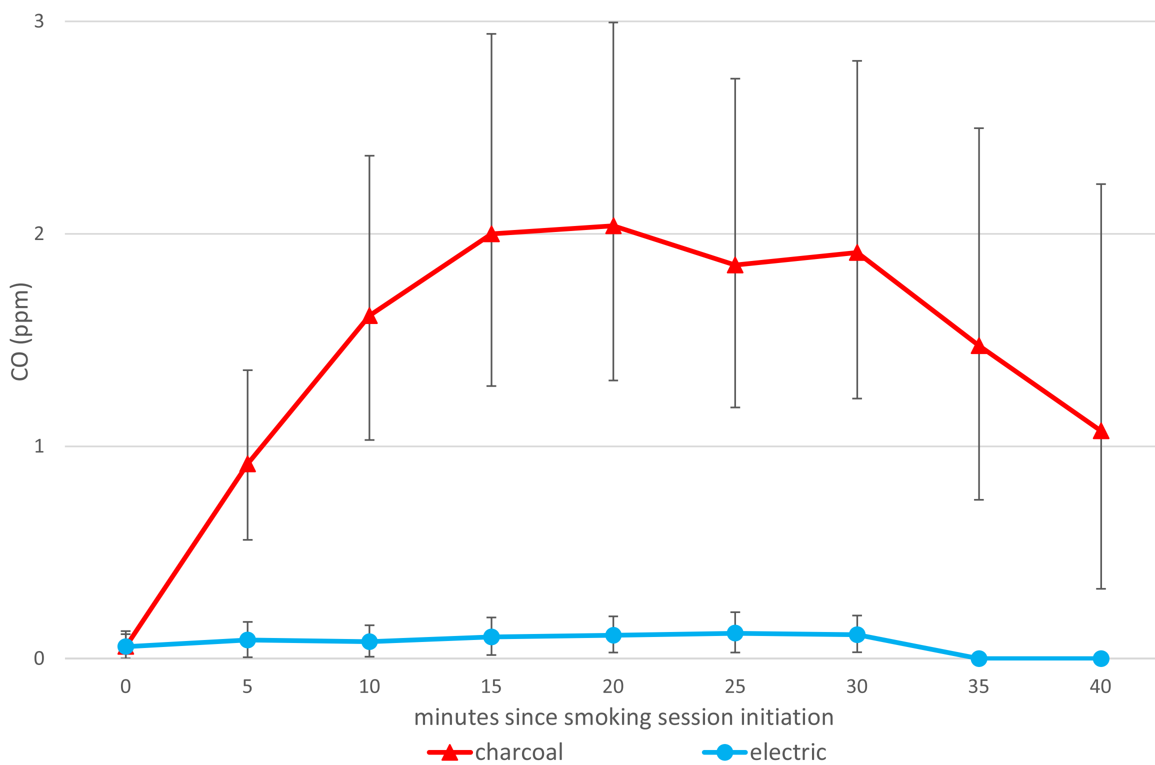

Fig. 2. Ambient air carbon monoxide concentrations (ppm) during home waterpipe tobacco smoking sessions using charcoal or electric heating. Points on the line plots represent geometric means, and error bars indicate 95% confidence intervals. Abbreviations: CO = carbon monoxide; ppm = parts per million.

4.1. Ambient Air CO and Smoking Location

We found significantly higher ambient air CO levels around smokers who smoked charcoal heated WPT indoors compared to outdoors (Fig. 4), and more than half of our participants smoked WPT inside their homes. A study outside the U.S. found that CO levels inside WPT smoker homes were significantly higher than in non-smoker homes [49]. We previously found that indoor air and surfaces in WPT smokers' homes, compared to non-smokers' homes, were highly contaminated with nicotine, and we also found that children living in WPT smokers' homes were exposed to WPT smoke toxicants [50]. Consequently, WPT smokers should be encouraged to avoid indoor smoking to protect non-smokers.

A study demonstrated that WPT smoking substantially increases indoor CO levels in smoking rooms and adjacent rooms [49]. Elevated CO levels generated during WPT smoking are expected to decrease after smoking sessions end; however, the duration of elevated CO levels may persist for hours in poorly ventilated environments [49,51]. Future studies should quantify post-WPT smoking CO decay rates under varying ventilation, room volume, and charcoal combustion conditions to determine the duration of elevated CO concentrations and characterize factors influencing indoor CO clearance.

4.2. Blood pressure and heart rate

Similar to findings of a recent review of the adverse effects of WPT use on cardiovascular health [52], we found significant elevation of diastolic blood pressure immediately following both types of heating methods. However, the pre-to-post increase in heart rate was significantly greater for the charcoal session than for the electric session (Table 2).

4.3. Urinary biomarkers of toxicity (Table 3)

4.3.1. Cotinine (nicotine metabolite)

Similar to a human study in a clinical smoking chamber [34], we found pre-to-post changes in urinary cotinine levels were not significantly different between the two WPT heating methods—charcoal and electric. In contrast, laboratory machine-smoking charcoal heated WPT resulted in 1.4 times higher increase in mainstream nicotine compared to machine-smoking with the same ceramic electric head used in this study [35]. Another machine-smoking study found that WPT temperature and nicotine yields more than doubled when WPT was electrically heated using a charcoal-like electric heating element vs charcoal heating [37]. However, a laboratory-based study found nicotine yields were ~20% lower for a metal electric head and a charcoal-like electric

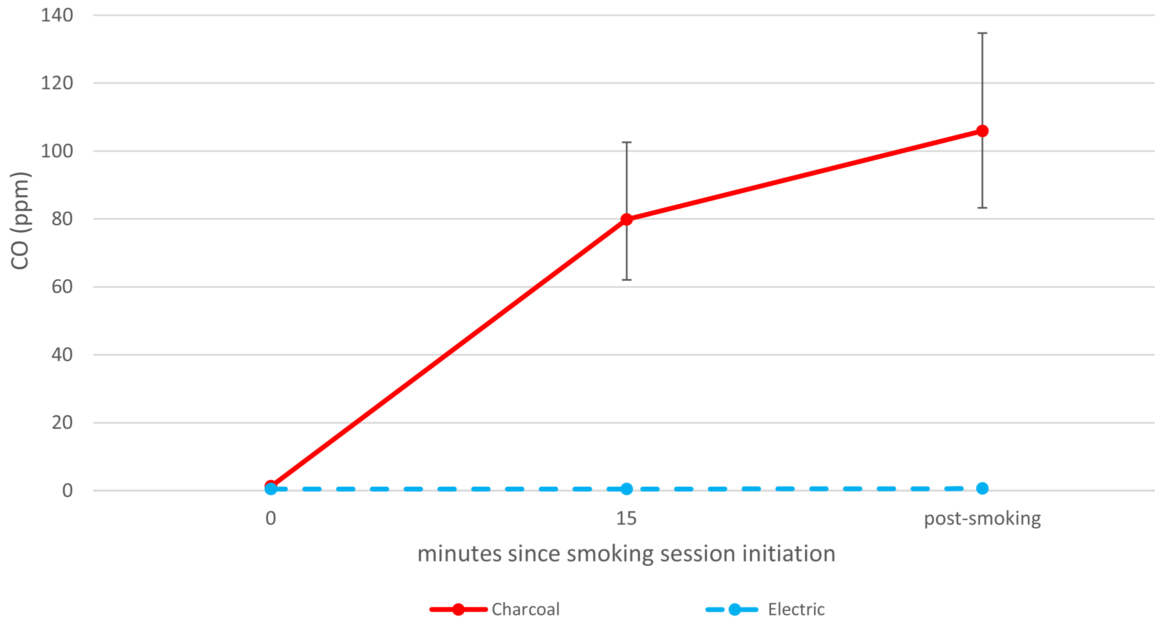

Fig. 3. Exhaled breath carbon monoxide concentrations (ppm) during home waterpipe tobacco smoking sessions using charcoal or electric heating. Points on the line plots represent geometric means, and error bars indicate 95% confidence intervals. Abbreviations: CO = carbon monoxide; ppm = parts per million. Error bars for the electric-heating condition are not readily visible because their magnitude is small relative to the y-axis scale required for the charcoal-heating condition.

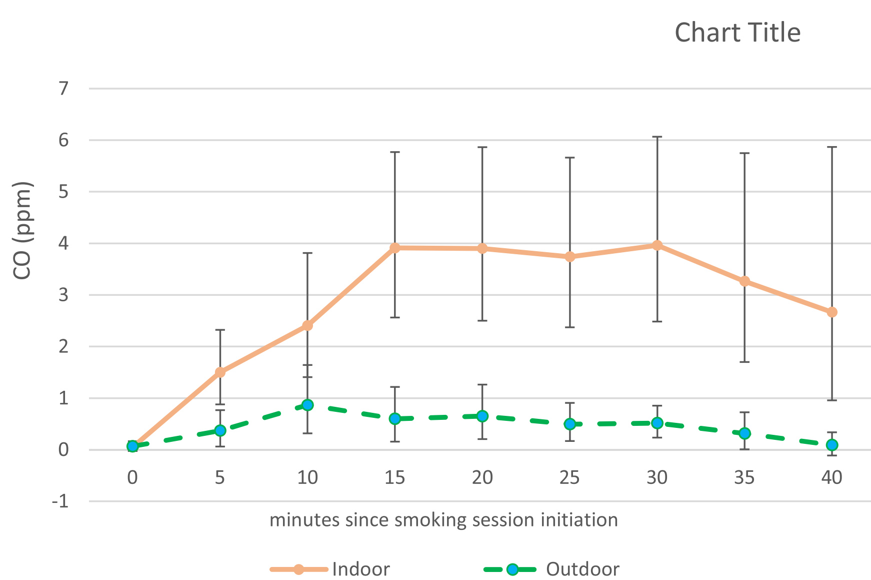

Fig. 4. Ambient air carbon monoxide concentrations (ppm) during charcoal-heated home waterpipe tobacco smoking sessions by smoking location (indoor versus outdoor). Points on the line plots represent geometric means, and error bars indicate 95% confidence intervals. Abbreviations: CO = carbon monoxide; ppm = parts per million.

element, but not significantly different for a ceramic electric head [38]. Discrepancies among machine-smoking WPT study findings [35,37,38] could result from differences in WPT products, electric heating devices, temperature settings, heated surface areas, and puffing topography.

Had participants using an electric heating head extended their smoking sessions to durations more comparable to those observed with charcoal heating, nicotine uptake would likely have increased because nicotine exposure is influenced, in part, by heating conditions and cumulative aerosol inhalation over time. However, the magnitude of this increase would require empirical verification through biomarker measurements [53–56].

4.3.2. *SPMA (benzene metabolite)*

Benzene is generated primarily by burning charcoal [57]. We previously found that urinary SPMA levels in WPT smokers increased significantly 2.2 times after smoking charcoal heated WPT in a home social event [50]. A clinical research center study also found a significant increase in urinary SPMA levels after smoking charcoal heated WPT [29]. In our study, we found pre-to-post changes in levels of urinary SPMA did not significantly differ between the two methods of heating WPT. However, compared to non-smokers, urinary SPMA levels of WPT smokers after smoking charcoal heated WPT were 6.6 times higher, but only 1.7 times higher after smoking electrically heated WPT. A human chamber study detected benzene in WPT smoker's exhaled breath after smoking charcoal heated WPT, but not after smoking electrically heated

Table 3
Creatinine-corrected urinary biomarkers: 1) from 50 waterpipe tobacco (WPT) smokers using a) charcoal heated WPT, and b) electrically heated WPT; and 2) from 25 non-smokers. [a].

	WPT heated by Charcoal		**WPT heated by an Electric Head**		**Non-Smoker**		**Charcoal vs Electric Head**		**Charcoal vs Non-Smoker**		**Electric Head vs Non-Smoker**	
Cotinine (ng/mg)[b]							Ratio[c]	p[d]	Ratio[c]	p[d]	Ratio[c]	p[d]
Pre-Smoking												
Median (25–75 %ile)	0.45	(0.13–11.85)	0.64	(0.15–18.4)	0.02	(0.01–0.09)						
% above LOD[e] (Freq/n)[f]	98%	(49/50)	86%	(43/50)	60%	(15/25)						
GM (95% CI)[g]	1.34	(0.59–3.04)	1.22	(0.48–3.11)	0.03	(0.02–0.05)	1.1	0.981	50.9	**< 0.001**	46.2	**< 0.001**
Post-Smoking												
Median (25–75 %ile)	31.4	(17.0–61.2)	21.1	(12.9–46.8)	0.02	(0.01–0.09)						
% above LOD (Freq/n)	100%	(50/50)	100%	(50/50)	40%	(10/25)						
GM (95% CI)[g]	34.9	(24.1–50.5)	26.4	(18.3–38.0)	0.03	(0.02–0.05)	1.3	0.131	1327	**< 0.001**	1002	**< 0.001**
GM ratio,[h] GM Δ[i]	26.1	33.6	21.7	25.2								
Signed-rank test p [j]		**< 0.001**		**< 0.001**								
Charcoal vs Electric Head p [k]								0.115				
SPMA (pmol/mg) [m]												
Pre-Smoking												
Median (25–75 %ile)	0.72	(0.15–4.3)	0.37	(0.07–0.97)	0.15	(0.12–0.44)						
% above LOD[e] (Freq/n)[f]	78%	(39/50)	70%	(35/50)	76%	(19/25)						
GM (95% CI)[g]	0.70	(0.41–1.18)	0.30	(0.18–0.49)	0.21	(0.15–0.29)	2.3	**0.018**	3.4	**0.005**	1.5	0.328
Post-Smoking												
Median (25–75 %ile)	2.44	(0.46–5.02)	0.38	(0.08–1.37)	0.15	(0.12–0.44)						
% above LOD (Freq/n)	84%	(42/50)	76%	(38/50)	84%	(21/25)						
GM (95% CI)[g]	1.35	(0.78–2.33)	0.34	(0.20–0.57)	0.21	(0.15–0.29)	4.0	**0.001**	6.6	**< 0.001**	1.7	0.212
GM ratio,[h] GM Δ[i]	1.94	0.65	1.14	0.04								
Signed-rank test p [j]		0.141		0.776								
Charcoal vs Electric Head p [k]								0.619				
1-HOP (pmol/mg) [n]												
Pre-Smoking												
Median (25–75 %ile)	0.40	(0.24–0.67)	0.57	(0.25–0.98)	0.24	(0.15–0.31)						
% above LOD[e] (Freq/n)[f]	100%	(49/49)	100%	(47/47)	96%	(23/24)						
GM (95% CI)[g]	0.41	(0.31–0.54)	0.55	(0.42–0.71)	0.25	(0.17–0.36)	0.74	**0.031**	1.6	**0.010**	2.2	**< 0.001**
Post-Smoking												
Median (25–75 %ile)	0.46	(0.22–0.86)	0.45	(0.23–0.69)	0.24	(0.15–0.31)						
% above LOD (Freq/n)	100%	(48/48)	98%	(46/47)	96%	(24/25)						
GM (95% CI)[g]	0.47	(0.34–0.65)	0.48	(0.35–0.66)	0.25	(0.17–0.36)	0.98	0.788	1.9	**0.010**	1.9	**0.007**
GM ratio,[h] GM Δ[i]	1.16	0.06	0.88	−0.07								
Signed-rank test p [j]		0.743		**0.048**								
Charcoal vs Electric Head p [k]								0.085				

[a] All values and percentages are rounded up; number of decimal places displayed is 2 for values< 1; 1 for values ≥ 1 and < 10; 0 for values≥ 10
[b] Cotinine, a metabolite of nicotine; Limit of Detection (LOD) = 0.03 ng/mL. <LOD values were replaced with (LOD/2): 0.015 ng/mL
[c] Ratio = ratio of GM biomarker levels between sessions: charcoal/electric head; charcoal/non-smoker; electric head/non-smoker—for pre-session and post-session
[d] p = p value for Wilcoxon signed-rank test or Mann-Whitney *U* test (as appropriate) of biomarker level difference between sessions; two-tailed alpha level p < 0.05 (bolded)
[e] % above LOD = percentage of urine samples above the LOD
[f] Freq/n = frequency of urine samples with levels above the LOD / n size of urine samples minus missing values due to laboratory interference
[g] GM (95% CI) = geometric Mean (95% Confidence Interval)
[h] GM Ratio = ratio of post-session to pre-session geometric mean biomarker levels for each of the 3 sessions: charcoal, electric head, and non-smoker
[i] GM Δ = change in geometric mean value from pre-session to post-session
[j] Signed-rank test p = p value from Wilcoxon signed-rank test of difference between pre-session and post-session; two-tailed alpha level p < 0.05 (bolded)
[k] Charcoal vs Electric Head = p value for main outcome: Wilcoxon signed-rank test of charcoal pre-to-post change vs electric head pre-to-post change; two-tailed alpha level p < 0.05 (bolded)
[m] SPMA = S-Phenylmercapturic acid, a metabolite of benzene; LOD = 0.10 pmol/mL. <LOD values were replaced with (LOD/2): 0.05 pmol/mL
[n] 1-HOP = 1-hydroxypyrene, metabolite of pyrene, a polycyclic aromatic hydrocarbon; LOD = 0.12 pmol/mL. <LOD values replaced with (LOD/2): 0.06 pmol/mL

WPT [36].

4.3.3. 1-HOP (pyrene metabolite)

Two machine-smoking WPT studies showed that compared to charcoal, electrically heating WPT resulted in significantly lower pyrene, benzo[*a*]pyrene and total PAHs yields [35,38]. In our study, pre-to-post increases in levels of urinary 1-HOP were not significantly different between the two methods of heating WPT; however, for both heating methods, urinary 1-HOP levels after smoking were significantly higher than in non-smokers.

4.4. Subjective Reactions to Electric Heating (eTables 1–3)

Consistent with a previous study [36], the majority of participant smokers found smoking electric vs charcoal heated WPT was less satisfying, less appealing, and less enjoyable; thought the smoke was harsher and hurt their throat; and felt smoke was significantly less dense, allowing fewer fun smoke tricks. We previously found that "having fun" with the smoke was one reason smokers enjoyed smoking WPT [58,59], and a machine-smoking study found WPT produced little aerosol when electrically heated [11].

4.5. High temperature of electrically heated WPT

A machine-smoking WPT study replicating the conditions and components of our two-session in-home human study found that the maximum WPT temperature in the electric head was 300°C - 380°C, depending on the power supply setting, vs ~150°C for charcoal heated

WPT (supplementary figures S-2, S-3, S-4 in Brinkman et al., 2020 [35]). Higher electrically heated WPT temperatures were also reported in other machine-smoking WPT studies [11,37,60]. High WPT temperatures, due partly to the minimal effect of the electric head's adjustable (1–9 scale) temperature dial (**eFigure 3**), were likely related to participants' negative subjective reactions, e.g. warm, harsh smoke, charred tobacco (**eTables 1, 2**).

Previous studies reported that compared to charcoal heating, while electric heating resulted in lower yields of CO and PAHs, the higher temperatures of WPT from electric heating led to more intense thermal degradation (pyrolysis) of the WPT mixture and additives (e.g., glycerin and flavorings), and thus to greater emissions of toxic and carcinogenic compounds (e.g., acrolein and furans) [35,55].

To prevent negative subjective reactions from WPT smokers and adverse health effects, electric heating devices should be regulated to prevent overheating and excessive thermal degradation of WPT.

4.6. WPT consumption

We calculated WPT consumption as: [initial WPT weight (10 g)] minus [Residual WPT (weight of WPT remaining after smoking)]. Residual WPT in the electrically heated session was visually more charred and weighed 1.5 g less than residual charcoal heated WPT, even though the time spent smoking in the electric session was significantly shorter by 4.8 min (Table 2). The lower weight of the residual electrically heated WPT implies that the charring effect associated with higher WPT temperature was responsible for the greater WPT consumption during the electric smoking session.

4.7. Limitations

WPT smoker participants smoked alone at home, using one type and brand of WPT, charcoal, electric heater, and disposable plastic hose. WPT smokers typically smoke in social settings [59,61], so measurement values in our study may differ from those WPT smokers typically experience in home gatherings or hookah lounges, where multiple smokers contribute to side-stream emissions [58,62]. A machine-smoking WPT study showed that air-tight plastic hoses, such as those we used exclusively, resulted in more than double the CO yields of the popular but highly permeable leather hoses [63]. Our spot urine samples may not have assessed peak levels of metabolites of benzene (9–13-hour half-life) [64,65] and pyrene (6–18-hour half-life) [66]. Given these considerations, our convenience sampling strategy, sample size of 50, participants aged 21–35 years, and missing responses to some open-ended questions, results may not well represent the general population of WPT smokers.

4.8. Recommendations for Future Research

Future research should collect data using various WPT brands/types, charcoal brands/types, types of hoses, and waterpipe device styles; include WPT smokers who typically use a WPT electric heater to rule out the effects of inexperience in using the heater; use larger sample sizes and group smoking sessions; sample different populations including older adults with various socio-demographic backgrounds; conduct experimental studies in laboratory smoking chambers where potential ambient sources of benzene, pyrene and nicotine are controlled; collect 24 h spot urine samples; determine exposure levels to other Harmful and Potentially Harmful Constituents (HPHC) using various types of electric heating devices vs charcoal, as others have found increases in mainstream toxic yields of volatile aldehydes and semi-volatile furan when investigating electrically heated WPT compared to charcoal [35,36,38,67,68].

In our within-subjects trial, each smoking participant smoked first in a charcoal heated session followed by an electric heated session after a one-week washout period before each of the two sessions. To control for carryover, habituation, or learning from one session to the next, other research designs can be tested, such as the counterbalancing design.

Our visual inspection comparing the charring of WPT that occurred in each smoking session was a subjective procedure and it was to some degree corroborated by the difference between the two sessions in the weight of the residual WPT at completion of the session—explained in the WPT consumption section of the Discussion. We were unable to find any literature describing a categorization or scale of tobacco charring that might provide a more quantitative assessment. Still, our finding would seem to merit further exploration as a possible flag for associations.

5. Conclusion

Compared with charcoal heating, smoking WPT heated with an electric heating head was associated with smaller increases in ambient air CO, exhaled breath CO, and heart rate. Pre-to-post-session change in levels of urinary metabolites of nicotine, benzene, and pyrene did not differ by type of WPT heat source. Urinary SPMA (benzene metabolite) levels at the end of the smoking session were higher than non-smoker levels when the WPT was heated by charcoal, but not when the WPT was heated by electric head.

Nevertheless, while participants reported that smoking electrically heated WPT was healthier and cleaner, they also found it less satisfying, less enjoyable, and less appealing, and made their throat hurt. To eliminate those barriers to the use of electric heads for heating, it is imperative that the heating device not overheat the WPT to avoid increased exposure to toxicants due to excessive thermal degradation of WPT. That objective could be accomplished by the U.S. Food and Drug Administration, which has the authority to impose restrictions on design and operational features of waterpipe devices and components [38,69,70]; other national regulatory bodies may also have this leverage. Ensuring precise, consistent control of electric heating of WPT could almost entirely prevent generation of CO from WPT smoking. Also, our finding that ambient air CO levels were significantly higher when participants used charcoal to heat WPT inside their homes, rather than outdoors, should encourage WPT smokers to avoid charcoal heated indoor smoking to protect non-smokers and children from exposure to CO.

CRediT authorship contribution statement

Nada O.F. Kassem: Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Sandy Liles:** Writing – review & editing, Writing – original draft, Validation, Software, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Noura O. Kassem:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Flora K. Zaki:** Writing – review & editing, Writing – original draft, Validation, Formal analysis, Data curation.

Ethics approval

The study was approved by San Diego State University's Institutional Review Board (IRB# 2445100; Approval date: December 5, 2016).

Declaration of Generative AI and AI-assisted technologies in the writing process

In preparing our Responses to Reviewers, the authors used ChatGPT to clarify terminology, find appropriate references, and solicit criticisms of, and alternatives to, language. After using this tool, the authors vetted the source material retrieved by ChatGPT, reviewed and edited the content, and take full responsibility for the content of the publication.

Funding

Research reported in this publication was supported by the United States Food and Drug Administration, the Center for Tobacco Products, and the National Institute on Drug Abuse of the National Institutes of Health under Award Number R01DA042471 to Nada O.F. Kassem, and was supported in part by the Tobacco-Related Disease Research Program under Award Numbers T30IR0894 and T32IR4777 to Nada O.F. Kassem.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the authors' institutions, the National Institutes of Health, the U.S. Food and Drug Administration, or the Tobacco-Related Disease Research Program.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank our participants, our research assistants (Shadeh A. Rassoulkhani, Mayra Z. Duran, Cyrielle Jeanne Pagharion, Krystle Liz E. Diaz, Rahwa G. Weldeselase, Tamara Vu, Warda Haq), our Center for Behavioral Epidemiology and Community Health (CBEACH) and Hookah Tobacco Research Center (HTRC) support staff (Jennifer A. Jones and Benjamin Nguyen). We thank Drs. Nathan G. Dodder and Eunha Hoh, and Linda Chu, Jade Wong, Kaylen Wilson, and Pamela Olguin of the School of Public Health, San Diego State University, San Diego, CA, for cotinine and creatinine laboratory analyses. We also thank Stephen S. Hecht, and Steven G. Carmella at the Masonic Cancer Center, University of Minnesota, Minneapolis, MN, for SPMA and 1-Hop laboratory analyses.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.toxrep.2026.102303.

Data Availability

Data will be made available on request. Data, codebook, metadata, protocols, etc. will be made available for research purposes upon legitimate request to the corresponding author.

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