



REVIEW

The growing epidemic of water pipe smoking: Health effects and future needs



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Summary

Water pipe smoking (WPS), an old method of tobacco smoking, is re-gaining widespread popularity all over the world and among various populations. Smoking machine studies have shown that the water pipe (WP) mainstream smoke (MSS) contains a wide array of chemical substances, many of which are highly toxic and carcinogenic for humans. The concentrations of some substances exceed those present in MSS of cigarettes. Despite being of low grade, current evidence indicates that WPS is associated with different adverse health effects, not only on the respiratory system but also on the cardiovascular, hematological, and reproductive systems, including pregnancy outcomes. In addition, association between WPS and malignancies, such as lung, oral and nasopharyngeal cancer, has been suggested in different studies and systematic reviews. Despite its long standing history, WPS research still harbors a lot of deficiencies. The magnitude of toxicants and carcinogen exposures, effects on human health, as well as the addiction and dependence potentials associated with WPS need to be studied in well-designed prospective trials. Unfortunately, many of the tobacco control and clean indoor policies have exempted water pipes. World wide awareness among the public, smokers, and policymakers about the potential health effects of WPS is urgently required. Furthermore, stringent policies and laws that control and ban WPS in public places, similar to those applied on cigarettes smoking need to be implemented.

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Contents

Introduction	1242
Searching the literature	1242
Description of modern water pipe	1242
Epidemiology of water pipe use	1243
Smoking machine and puff topography	1244
Toxic compounds and carcinogens in water pipe smoke	1244
Nicotine and nicotine-free dry particulate matter (NFDPM)	1244
Carbon monoxide and carboxyhemoglobin	1245
Polycyclic aromatic hydrocarbons (PAH)	1245
Nitrosamines and primary aromatic amines	1245
Volatile aldehydes, phenolic and furanic compounds	1246
Heavy metals, radioactive substances, and ultrafine particles	1246
Health effect of water pipe smoking	1246
Acute cardiopulmonary effects of water pipe	1246
Long-term non-malignant pulmonary effects of water pipe	1247
Long-term extra-pulmonary effects of water pipe	1248
Association of WPS and cancer	1248
Effects of WPS on pregnancy	1248
Comparative studies of water pipe and cigarettes	1249
Future research needs on WPS	1249
Conclusion	1250
Conflict of interest	1250
References	1250

Introduction

Cigarettes remain the most common form of consumed tobacco worldwide. However, another old form that is regaining popularity is water pipe (WP). The history of water pipe goes back to around four centuries ago in India [1] and its use has been a traditional habit in Asia and North Africa. While the use of water pipe has decreased in these regions during the last century [1], this social habit is witnessing resurrection since the early 1990's, not only in Eastern Mediterranean (EM) and North Africa, but also in the U.S., Europe, and some countries of South America such as Brazil [2] and even among new populations like college students and youth [3,4]. Despite the growing burden of this public health problem, high-quality trials looking at the long-term effects of water pipe smoking are still lacking, and those available carry some methodological limitations [5].

In this review, we will highlight the prevalence of WPS use in different countries and among various population categories, the smoking topography, and the constituents of the WPS including carcinogens and carbon monoxide. We will also discuss the acute and long-term adverse effects (pulmonary and extrapulmonary) of WPS, as well its effects on pregnancy and fertility. Moreover, we will review the pattern of use and dependence on WPS and studies that have compared WPS to cigarette use.

Searching the literature

Most of the major databases of medical literature (e.g. PubMed, Medline, and Embase) have not yet assigned

medical subject headings (MeSH) terms for WPS, a fact that makes comprehensive search difficult. We were able to find at least 32 names of WPS in the English literature, 8 different names of the tobacco forms used in WPS, and 11 terms for one of these forms, the moassel (Table 1). A PubMed search of the 32 different names of WPS and the 11 different terms of moassel up until June 2013, revealed 321 articles from reviews, case reports and research studies. The majority were of the epidemiological nature.

Description of modern water pipe

A modern water pipe is mainly made up of five parts: the head, the body, the water bowl, a hose, and a mouthpiece (Fig. 1). Around 10–20 g of tobacco are placed in the head [6]. Burning charcoal is placed on the head, separated from the tobacco by a fenestrated aluminum foil [7]. The body is formed of a metallic tube, often decorated with metal or wood, extending from the head to the water bowl, half-immersed in water, while the hose emerges from the top of the water bowl and ends with a mouthpiece from which the user inhales [2]. As the user inhales from the mouthpiece, vacuum is created in the water bowl, sucking smoke from the head through the body into water bowl. The passage of smoke through the water causes bubbles. Finally, the smoke will pass to the user via the hose [2].

The most commonly used tobacco for WPS is called "Moassel". Most moassels made for export are produced in Bahrain and Egypt where tobacco is fermented with molasses and fruit essence. Moassel is moist and pliable, making it easier to use than other WPS tobaccos. In

Table 1 List of water pipe terminology and used tobacco forms.

Water pipe terms	Tobacco terms
Water pipe	Moassel
Water-pipe	Mu'assel
Waterpipe	Mouassel
Hubble bubble	Mu'assel
Hubble-bubble	Moassel
Hubblebubble	Ma'ssel
Arghile	Massel
Argileh	Ma'assel
Arguileh	Maassel
Argeeleh	Mua'sel
Argela	Muassel
Argila	Mo'assel
Narghile	Jurak
Narghileh	Ajami
Narguileh	Ajamy
Narguile	Tumbak
Nargila	Tombac
Nargile	Tobamel
Nargileh	Tutun
Hookah	
Huqqa	
Hukkah	
Hukka	
Goza	
Borry	
Sheesha	
Shisha	
Shesha	
Shishe	
Chicha	
Qalyan	
Mada'a	

addition, it has a pleasant taste and aroma [1]. Another common type of used tobacco is called "Ajami"; a pure dark tobacco paste [6]. "Steam Stones" are new products that have been recently released into the market as a tobacco alternative for use with the water pipes. These are heat-treated porous materials soaked with glycerin and produce smoke-like vapor upon heating. While these have been marketed as a "healthy" alternative to tobacco water pipe smoking that is free of nicotine, tar, carbon monoxide, and carcinogens, nothing is yet known so far about their health-related risks [8].

Epidemiology of water pipe use

As mentioned earlier, WPS is increasing rapidly all over the world. Maziak described it as "the first tobacco use method since the cigarette that is showing all signs of a burgeoning global epidemic" [7]. In the BREATHE COPD study that included more than 60,000 adults from 11 countries from Middle East and North Africa [9], 3.5% of individuals reported WP use with the highest rate being from Lebanon and Saudi Arabia. However, this rate appears to be lower than what was previously reported especially since the

study population did not include individuals less than 40 years of age; a group that represents the predominant users of WP [10]. In a systematic review by Akl et al. [11], the prevalence of current WPS among adults was 6% in Pakistan, 4–12% in Arabic Gulf region, 9–12% in Syria and 15% in Lebanon. In another survey from North America, 8.8% of adults (age > 18 years) reported having ever used WPS with 11.4% reported current use [12].

A more alarming fact is the growing spread of WPS among teenagers and college students. In the Middle East, 43%–61.1% of the college students reported lifetime WPS and 5.6%–43.3% reported past-month or current use [3]. Among American and European college students, 1 in every 5 students reported past-year WPS use whereas lifetime WPS ranged from 15.1% to 41.0% and past-month smoking rates ranged from 7.2% to 21.1% [3]. The Global Youth Tobacco Survey (GYTS) examined the pattern of tobacco use by adolescents ages 13–15 years in large number of countries [13]. The GYTS reported that 10%–20% of students (ages 13–15) have smoked hookah within the past-month [14], with the highest prevalence among the Eastern Mediterranean region where the Lebanese GYTS reported that 33.9% of youth aged 13–15 years were current WP users [15]. In the United States, 6.8–15.1% of middle and high



Figure 1 A modern waterpipe.

school students reported ever WP smoking [14]. Arab-American youth reported significantly higher percentages of ever using WP (38% vs. 21%) and current use of WP (17% vs. 11%) than non-Arab-American youth [16]. In addition to being of Arab origin, male sex, cigarette smoking in the last 30 days, and family WP use were significant predictors of WPS use among American adolescents [16].

5.8%–24% of WP smokers report daily use, mostly in restaurants or cafés and with friends [17]. WP smokers are twice as likely to become cigarette smokers in the next 2 years compared with never smokers (relative risk = 2.1, 95% CI 1.2–3.4) [18]. The majority of WP smokers (86.5%) believe that they can quit anytime though only 28.4% of these are interested in quitting while around 60% had an unsuccessful quitting attempt in the last year; moreover, this belief is inversely related to the perceived dependence, with only 48.7% of those who thought they are WP-dependent believe they could quit [19].

A major factor that has helped in the rapid spread of WPS is public misconceptions about the health risks of WPS. Several studies have shown that the bulk of WP smokers perceive WPS as less harmful and less addictive than cigarette smoking, believe that harmful substances are being filtered out through the water bowl, and think that WP is more socially acceptable than cigarettes and it represents a good opportunity for gathering of friends and family [17,20,21]. Moreover, the most common perceived positive attributes of waterpipe tobacco smoking were the taste, smell, relaxing effects, and the opportunity to socialize with friends [22]. Another contributing factor is the exemption that allows WPS bars to remain in operation despite the passage of clean indoor air legislation in many cities [23]. Furthermore, WPS remains unregulated by many countries around the world.

Smoking machine and puff topography

Smoking topography data include the smoking puff frequency, duration and amount of smoke inhaled per each puff, as well as the total session duration. These parameters are needed for programming laboratory smoking machines used for smoke sampling and toxicological analysis. In 1962, Rakower and Fatal were the first to use a smoking machine to assess the mainstream smoke (MSS) of WP [24]. Several modern WPS machines studies were performed in Lebanon [25–28], Germany [29–32], and Switzerland [33]. Shihadeh et al. [34] conducted the first modern topographic study using 52 volunteer WP smokers and demonstrated that the mean number of puff cycles per average session (session of 61 min duration) was 171 with a puff volume of 530 ml, a duration of 2.6 s per puff, and an inter-puff interval of 17 seconds. Moreover, the magnitude of exposure to different smoke-related toxicants correlated closely with the smoking topography. The expired carbon monoxide concentration and plasma nicotine levels increased in proportion with the different topographic parameters [35,36].

The use of smoking machines for studying MSS of WP is widely criticized. Unlike cigarette smoke machine studies in which the topographic parameters are standardized by the Federal Trade Commission (FTC), WPS machine studies have used different puff frequencies, puff volumes, inter-

puff intervals, and session durations [37], resulting in significant variations in the reported amount of carbon monoxide, nicotine, tar and other compounds. In addition, some smoking topographic parameters and their effects on toxicant exposure were not investigated, namely the breath-hold time (BHT) prior to exhalation. In one cigarettes smoking study [38], the exposure to carbon monoxide (CO), measured by the expired-air CO, increased with longer BHT. To the best of our knowledge, the effect of BHT on WP-associated toxicant exposure is not reported so far.

Moreover, real-life smoking patterns of WP smokers are not as uniform as those used in laboratory studies, further complicating the interpretation of smoking machines results [39]. The smoking machines trials did not take into consideration other confounding factors that may affect the composition of the MSS, such as the amount and different types of tobacco used, the effect of moving or replacing the charcoal, and the size of the water bowl or hose [39].

Toxic compounds and carcinogens in water pipe smoke

Despite its long history and recent revival, the chemical constitution of WP MSS and tobacco has not been studied as extensively as that of cigarette smoking. Several compounds had been shown to be present in WP MSS and tobacco including nicotine, [25,30,40,41] nicotine-free dry particulate matter (NFDPM) or "tar" [25,30,40], carbon monoxide (CO) [25,30,41], polycyclic aromatic hydrocarbons (PAH) [25,28,30,41], nitrosamines and primary aromatic amines [29,30,41], furanic compounds [31], aldehydes [42], phenolic compounds [43], ultrafine particles [33], and even radioactive substances [44] and heavy metals [40]. A list of the hazardous and toxic compounds present in the MSS and tobacco of WP is summarized in Table 2.

Nicotine and nicotine-free dry particulate matter (NFDPM)

Nicotine is a main chemical present in different forms of tobacco and a major cause of tobacco dependence [45] and NFDPM is normally taken as an indication of the quantity of carcinogens present in the smoke of a cigarette [25].

The nicotine content differs according to the type of tobacco used in the water pipe: The average nicotine content in each WP head (20 g) of unflavored tobacco (Ajami) has 713 mg of nicotine/head whereas flavored tobacco (moassel) has 67 mg of nicotine/head [46]. The mainstream smoke (MSS) content of nicotine and NFDPM ranges between 2.25 and 7.75 mg/session and 242–949 mg/session respectively [25,30,40]. Schubert et al. reported that a single session (171 puffs of 530 ml and 2.6 s duration every 20 s) of WPS yields amounts of nicotine and tar that are, 10 times and 100 times more than those in a single 3R4F reference cigarette, respectively [30]. The amount of nicotine and NFDPM in the inhaled smoke increases with the intensity of the smoking regimen, such as with the increase in number and/or volume of each puff and/or the decrease in inter-puff interval [25,40]. Moreover, water in the bowl

Table 2 Hazardous and toxic compound in WP MSS and tobacco.

Nicotine and nicotine-free dry particulate matter (tar)
Carbon monoxide
Polycyclic aromatic hydrocarbons (16 PAHs were detected, most importantly, benzene [a]pyrene and Di-benzo[a,h]anthracene)
Tobacco-specific nitrosamines
N-nitrosornicotine
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
N-nitrosoanatabine
N-nitrosoanabasine
Primary aromatic amines (9 PAAs were detected; most importantly, 2-naphthylamines)
Volatile aldehydes mainly formaldehyde
Phenol compounds (7 phenol compounds were detected mainly phenol, catechol and hydroquinone)
Furanic compounds (6 furanic compounds were detected; mainly, 5-(hydroxymethyl)-2-furaldehyde, furfuryl alcohol and 2-furaldehyde)
Heavy metals (arsenic, chromium, lead, beryllium, nickel and cobalt)
Radioactive elements (Uranium, Thorium, Polonium, Radium, Lead, and Potassium) ^a
Ultrafine particles (Diameter ≤ 100 nanometers)

MSS, main stream smoke; WP, water pipe.

^a Radiactive substances were detected only in the WP tobacco. Only Polonium was also detected in MSS. Data about availability of other radioactive elements in WP smoke are not currently available.

reduces the amount of nicotine, but not the level of NFDPM in the MSS [40]. Furthermore, WP smokers will adjust their smoking behavior to take desired doses of nicotine, so they will continue smoking until their nicotine level is reached, thus diminishing the nicotine filtering effect of water [47].

As expected, the plasma nicotine level increases after WPS use [41,48–50]. Plasma nicotine boost correlates with total session time, cumulative puff duration, mean puff duration, and total smoke inhaled in the session [36]. The nicotine level triples in the first 5 min after starting WPS and continues to rise substantially until it reaches four times the pre-smoking level after 45 min, which is significantly higher than the nicotine level reached 45 min after smoking a single cigarette [49,50].

Carbon monoxide and carboxyhemoglobin

Several cases of water pipe-associated carbon monoxide (CO) poisoning have been reported in the literature [51–56], with reported levels of carboxyhemoglobin (COHb) ranging from 7.3% [55] to 31.1% [51]. CO has been reported to be present in water pipe MSS in levels exceeding those in cigarette smoke by several times [30]. Charcoal contributes to about 90% of the CO present in MSS of WP [57] and the use of a plastic hose, rather than a leather one, yields a higher CO level in the water pipe MSS due to escape of CO and dilution from air infiltrating through the porous wall of the leather hose [58].

Following a single WPS session, the end-expiratory CO levels increase by around 8 times compared to pre-smoking level [35,59]. The relative increase in exhaled CO is much larger in WP versus cigarette smokers [49,60]. The magnitude of increase in the expired-air CO is proportional to the total amount of smoke inhaled per session, total session time, number of puffs, duration of each puff, and the flow rate; on the other hand, it is inversely proportion to the inter-puff interval [35].

Carboxyhemoglobin (COHb) levels increase after WPS reaching a mean peak of 3.9–4.5% in 45 min [49,50],

although levels as high as 10.06% [61] and 17.1% [30] have been reported. Compared to cigarette smoking, the WPS mean peak COHb is 3–3.75-fold higher [49,50].

Polycyclic aromatic hydrocarbons (PAH)

Compared to cigarettes, few studies investigated the concentration of PAH in the mainstream smoke of water pipe. [25,28,30,41] PAH are organic pollutants that are produced by incomplete combustion of organic materials, including tobacco [41], and many of these compounds have been associated with carcinogenesis of several tumors, mainly lung, skin, colorectal and pancreatic cancers [62]. Sixteen PAHs have been detected and quantified in the mainstream smoke of WP, mostly naphthalene and phenanthrene [28,30]. The International Agency for Research on Cancer (IARC) classifies various chemicals into five categories according to human carcinogenic potentials, where IARC group 1 compounds are definite carcinogens, IARC group 2A and 2B chemicals are probable and possible carcinogens respectively, while IARC group 3 and 4 are “not classifiable as to its carcinogenicity to humans” and “Probably not carcinogenic to humans” respectively [63]. Although most of the detected PAH are IARC group 2B and group 3, the group 1 compound, Benzo[a]pyrene, and group 2A compound, Di-benzo[a,h]anthracene, are also detected. The concentrations of the majority of these PAH in water pipe smoke exceed those in cigarette smoking by several times [28,30]. Of note, WP smoke contains 20 times more PAH [28] and 3 times more Benzo[a]pyrene [30]. After WPS, the urine concentrations of PAH metabolites (2-naphthol and 2-hydroxyfluorene) double, further indicating that WPS is a significant source of exposure to this class of carcinogens [41].

Nitrosamines and primary aromatic amines

Tobacco-specific nitrosamines (TSNAs) are formed through the nitrosation of nicotine and other tobacco alkaloids. The

major TSNA are N-nitrosornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), N-nitrosoanatabine (NAT), and N-nitrosoanabasine (NAB) [64]. NNN and NNK are classified as group 1 human carcinogens by the IARC monographs, while NAT and NAB are group 3 [65]. NNN and NNK exposure have been associated with benign and malignant tumors of nasal cavity, lung, trachea, esophagus, pancreas and liver [64]. In contrast to PAH, WP tobacco and MSS contain lower amounts of all 4 TSNA compared to those of cigarette [30]. Urinary detection of 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol NNAL, a metabolite of NNK, is tobacco-specific and correlates with carcinogen uptake [66]. Following WPS, the urinary level of NNAL increases markedly and then decreases slowly [41]; and the levels increase in proportion to the number of tobacco heads (hagars) smoked [66].

Nine primary aromatic amines (PAA) have been detected in the mainstream smoke of water pipe [29]. One important detected PAA is 2-naphthylamine which is classified as IARC group 1 carcinogen and is closely associated with urinary bladder cancer in humans [67].

Volatile aldehydes, phenolic and furanic compounds

An important aldehyde that has been detected in the water pipe MSS in both particulate phase (40%) and gaseous state (60%) is formaldehyde [42]. A WPS session of 171 puffs, each of 2.6 s duration, yields the equivalent of 17 cigarettes in formaldehyde [42]. Formaldehyde is classified as IARC group 1 human carcinogen and was associated with nasopharyngeal carcinoma, sinonasal cancer, and leukemia [68]. The presence of water in the bowl and increasing amount of humectants in unburned tobacco decrease the level of formaldehyde in MSS [32].

Seven phenol compounds and several phenolic derivatives are detected in the MSS of water pipe [43]. WP smoke contains at least 3 times more phenolic compounds (mainly phenol, catechol, and hydroquinone) and about 1000 times more phenolic derivatives compared to cigarette smoke. Hydroxyquinone and catechol are tumor promoters and facilitate lung cancer metastasis and invasion [43].

Six furanic compounds have been reported to be present in the water pipe MSS, mainly 5-(Hydroxymethyl)-2-furaldehyde (HMF). Two furanic compounds, namely Furfuryl alcohol and 2-Furaldehyde, have been associated with tumorigenesis in rats, primarily nasal and hepatic tumors. Similar to aldehydes, water bowl filters more than 90% of all furanic compounds (except for HMF) present in the smoke [31].

Heavy metals, radioactive substances, and ultrafine particles

WP MSS contains a huge amount of heavy metals mainly arsenic, chromium, and lead, in addition to beryllium, nickel, and cobalt. Beryllium, chromium, arsenic and nickel are classified as IARC group 1 human carcinogens. They are associated with mesothelioma, lung, skin, laryngeal, and urinary bladder cancer [69].

Several radioactive elements were detected in the WP tobacco such as Uranium (238U), Thorium (234Th and 232Th), Polonium (210Po), Radium (226Ra), Lead (210Pb), and Potassium (40K) [44]. About 69% of 210Po present in moassel will be present in water pipe MSS [44]. Data about availability of other radioactive elements in WP smoke are not currently available.

Ultrafine particles are generally considered to be particles with at least one dimension of 100 nm or less [70]. They have been associated with lung fibrosis, inflammation, and even tumorigenesis in animal experiments [70]. Monn et al., [33] reported a huge amount of ultrafine particles in the water pipe MSS, with a mean diameter of 40 nm.

Health effect of water pipe smoking

Despite the re-emergence of WPS and its worldwide spread, there is a paucity of data regarding its health effects. Moreover, the available studies carry major methodological limitations making the evidence of low quality [5]. One of these limitations is the lack of exposure measurement tools that standardize the amount and type of tobacco, as well as the frequency and duration of WPS [5]. Another important methodological flaw is the lack of adjustment for confounding factors, such as environmental or occupational exposures and, most important, concomitant cigarette smoking [5]. However, the existing evidence is enough to draw a picture of highly hazardous behavior [71]. In 2007, the American Lung Association called water pipe smoking "*An Emerging Deadly Trend*" [72]. Water pipe has been associated with acute cardiopulmonary changes, long-term pulmonary and extrapulmonary consequences, genetic and cellular function alterations, as well as adverse pregnancy effects. These potential adverse health-related outcomes are summarized in Table 3.

Acute cardiopulmonary effects of water pipe

WPS for thirty minutes is associated with an increase in systolic blood pressure of 12–16 mmHg, an increase in diastolic blood pressure of 2–8 mmHg and a rise in heart rate and respiratory rate by 6–15 beats per minute and 2 breaths per minutes respectively [73,74]. In a placebo-controlled trial [26] in which 37 healthy individuals smoked WP with either active tobacco or flavor-matched tobacco-free placebo, subjects in the active tobacco group have a significantly higher heart rate and plasma nicotine level compared to the placebo arm, with no difference in carboxyhemoglobin levels in both arms, indicating that the acute cardiovascular changes associated with WP use are mainly secondary to nicotine. In addition, WPS is associated with a decreased baroreflex sensitivity, a risk factor for coronary disease [75].

Spirometric alterations also occur shortly after WPS [73]. The peak expiratory flow rate (PEFR) and forced expiratory flow between 25% and 75% of forced vital capacity (FEF_{25%–75%}) decrease significantly after 30 min of WPS, without a major change in other spirometric measures [73].

Table 3 Potential adverse health-related outcomes of WPS.

Acute cardiopulmonary effects
Increase in systolic and diastolic blood pressure, respiratory rate and heart rate
Decreased baroreceptors sensitivity
Decrease in PEF _R and FEF _{25%–75%}
Long-term non-malignant pulmonary effects
Decrease in FEV ₁ , FVC and FEV ₁ /FVC
Obstructive lung disease (small and large airways)
Chronic bronchitis
Impaired respiratory-related QOL
Transmission of respiratory pathogens e.g. <i>Mycobacterium tuberculosis</i> and <i>Aspergillus</i>
Long-term extrapulmonary effects
Periodontal disease
Benign vocal folds lesions
Vocal cord edema and varices
Ischemic heart disease and increased mortality due to ACS
Metabolic syndrome
Cellular and molecular effects
Endothelial cell dysfunctions and cell cycle arrest
Lymphocytes chromosomal aberrations
Increased plasma thromboxanes and prostaglandins
Malignant effects
Lung cancer
Bladder cancer
Esophageal cancer
Nasopharyngeal cancer
Oral dysplasia and cancers
Effects on pregnancy
Increased risk of LBW
Newborn pulmonary complications
Increased markers of Down's syndrome
Detrimental effects on in vitro fertilization outcomes

ACS, acute coronary syndrome; FEF_{25–75%}, forced expiratory flow between 25% and 75% of forced vital capacity; FEV₁, forced expired volume at 1 second; FVC, forced vital capacity; LBW, low birth-weight; PERP, peak expiratory flow rate; QOL, quality of life; WPS, waterpipe smoking.

Long-term non-malignant pulmonary effects of water pipe

Few studies examined the effect of WPS on the pulmonary function parameters with mixed results. Compared to nonsmokers, forced expiratory volume at 1 second (FEV₁), forced vital capacity (FVC), and FEV₁/FVC were non-significantly lower in WP smokers in four cross-sectional trials [76–79], while these parameters were significantly lower in two other studies [80,81]. One of these studies found a correlation between the intensity of WPS (1–2 WPS/day versus >2 WPS/day) and degree of spirometric impairment [80]. In a recent systematic review that included the above studies [82], WPS was associated with a statistically significant reduction in FEV₁ and a trend toward lower FVC and FEV₁. The same review found no significant differences in FEV₁ and FEV₁/FVC between WP smokers and cigarette smokers [82]. However, the methodological limitations of these studies, such as the lack of standardized tools to measure the degree of exposure, should be taken into considerations [82].

The observed reduction in FEV₁ with WPS suggests its role in developing obstructive pulmonary disease (OPD). In

a recent study that included 110 WP smokers [83], 14% had small airway OPD, 6% had large airway OPD and 36% had static hyperinflation; in addition, restrictive lung disease was found in 14% of this population. The association between WPS and chronic obstructive pulmonary disease (COPD) symptoms or chronic bronchitis was studied in 2 recent publications [84,85]. In one study that included 62,086 smokers (2174 WP smokers) from 11 countries in the Middle East and North Africa [85], WPS contributed to the development of productive cough (odds ratio(OR) = 1.29, $p = 0.007$), dyspnea (OR = 1.18, $p = 0.018$) and chronic bronchitis (OR = 1.42, $p = 0.026$) after adjustment to cigarette smoking. The relationship of WPS and development of chronic bronchitis was further studied in 833 Lebanese subjects (274 with chronic bronchitis, 559 controls) [84]. Previous WPS (OR = 6.4), previous mixed smoking (OR = 38.03), current mixed smoking (OR = 7.68), and ever WPS > 20 WP-years were significantly associated with chronic bronchitis ($p < 0.001$ for all) but current exclusive WPS was not (OR = 1.87, 95% CI: 0.74–4.72) [84]. Moreover, previous, but not current, WP smokers have more impaired respiratory-related quality of life compared to nonsmokers, as measured by the clinical COPD

questionnaire (CCQ), and the degree of impairment correlated positively with the cumulative dose of smoking in both current and previous WP smokers [86]. Some case reports and series have linked water pipe sharing to the transmission of some respiratory pathogens, mainly *Mycobacterium tuberculosis* and *Aspergillus* [87–89]; however, this association was not evaluated in well-designed clinical trials.

Long-term extra-pulmonary effects of water pipe

The adverse effects of WP are not only confined to the respiratory system, but also may affect other body organs and systems. WP smoking is associated with higher incidence of periodontal disease (OR = 3–5), such as periodontal bone height loss, plaque index and gingivitis [5]. In addition, WP smokers are three times more likely to develop post-third molar extraction dry socket than non-smokers ($p = 0.001$); however, they have a similar risk to that of cigarette smokers ($p = 0.083$) [90]. Hamdan et al. reported an incidence of benign vocal folds lesions in WP smokers of 21.5% [91]. Compared to nonsmokers, WP users have a higher incidence of vocal cord (VC) edema ($p = 0.012$), thick mucus between the free edge of VCs ($p = 0.026$) and VC varices ($p = 0.026$) [91]. Compared to cigarette smokers, there is no significant difference between incidence of VC polyps, cysts or edema; however, WP smokers have a higher incidence of thick mucus threads ($p = 0.005$) [91].

In an in vitro study [92], water pipe MSS condensate induced endothelial cell dysfunction and cell cycle arrest by exerting oxidative stress, inflammation, and impaired vasodilatory function and repair mechanism, providing evidence that WP is a risk factor for vascular disease. In another recent study, moderate-high WP use (defined as cumulative use >50 WP-year) versus never-low use (cumulative use ≤ 50 WP-year) was associated with higher prevalence of ischemic heart disease (OR = 1.83, 95% CI 1.10–3.07); however, the prevalence did not differ significantly between ever and never WP users (OR = 1.09, 95% CI 0.80–1.48) [93]. In an observational study that included around 8000 patients with acute coronary syndrome [94], WP smokers had a higher risk of recurrent ischemia (26.9% in WP group versus 14.1% in cigarette group, $p = 0.001$), need of mechanical ventilation, and death (8.5% in WP group versus 3.4% in cigarette group, $p = 0.008$) compared to cigarette and oral tobacco users. After adjustment for age and gender, the in-hospital mortality was significantly higher in WP smokers compared to cigarette users (OR = 1.8) [94].

Moreover, WPS is associated with increased frequency of lymphocytes chromosomal aberrations [95], elevated plasma levels of various thromboxanes and prostaglandins (indicating a significant increase of in vivo oxidative stress) [96], and in one case report [97], with secondary polycythemia. Age adjusted-prevalence of metabolic syndrome was significantly higher among current WP smokers (33.1%) compared with non-smokers (14.8%). Furthermore WP smokers were three times more likely to have metabolic syndrome (OR = 3.21, 95% CI 2.38–4.33) compared with non-smokers after adjustment for age, sex and social class [98].

Association of WPS and cancer

Despite the clear evidence that MSS of WP contains a wide range of carcinogens, many of which are definite human carcinogens, the contribution of WP use to carcinogenesis is not well-established, so far, in high-quality trials. The genotoxic effect of WP smoke was investigated by Yadav et al. [99]. The mitotic index, chromosomal aberrations, sister chromatid exchanges, and satellite associations were more frequent in WP smokers compared to nonsmokers [99]. WP was found to double the risk of lung cancer (OR = 2.12, 95% CI 1.32–3.42) in a systematic review that included six trials studying the association of WPS and lung cancer [5]. However, most of these studies were conducted using Chinese or Indian versions of WP that differ from the modern widespread WP in the type of tobacco and method of heating [5]. In the same systematic review, Akl et al. found no significant association between WP smoking and bladder cancer (OR = 0.8, 95% CI = 0.2–4.0), esophageal cancer (OR = 1.85, 95% CI 0.95–3.58), nasopharyngeal cancer (OR = 0.49, 95% CI 0.20–1.23) or oral dysplasia (OR = 8.33, 95% CI 0.78–9.47) [5]. The authors classified the evidence as low or very low since most of the included studies had methodological problems, mainly the lack of adjustment for important variables such as quantity and type of tobacco used, frequency and length of WP smoking, concomitant use of other forms of tobacco, and occupational or environmental exposures.

El-Hakim et al. reported 2 cases of squamous cell carcinoma (SCC) of lips and one case of lip keratoacanthoma associated with different forms of WPS [100]. To date, no clinical trial has evaluated the association of WPS and oral cancers. However, WPS use might predispose to oral cancers through exposures to carcinogens present in MSS, prolonged mechanical trauma and irritation from the mouthpiece, and infections triggered by WP sharing [71].

Effects of WPS on pregnancy

Tobacco smoking is a well-established risk factor for adverse pregnancy outcomes and complications. With the resurrection of WPS use and worldwide popularity, its prevalence among pregnant women is becoming more alarming. In Lebanon, 4–8.3% of pregnant women reported WPS during pregnancy [101–103]. A similar prevalence was also reported in Jordan where 8.7% of pregnant women were current WP smokers while 32.8% were exposed to WPS mostly from their partners and while they are at home [104]. WPS during pregnancy has been associated with

Table 4 Topographic comparison of water pipe and cigarettes.

Topographic parameters	Water pipe [34] mean (Range)	Cigarettes [111] mean (Range)
Puff duration (s)	2.60 (1.21–4.74)	2.03 (0.51–5.26)
Puff volume (ml)	530 (150–1220)	56.4 (17.6–159.1)
Puff rate (ml/s)	208 (94–397)	28 (14–54)
inter-puff interval (s)	15.48 (6.94–54.30)	26.5 (7.9–74.8)

about a two-fold increase in the risk of low birth-weight (LBW) [105–107]. In a systematic review, the pooled OR for association of WPS use with LBW and newborn pulmonary complications were 2.12 (95% CI 1.08–4.18) and 3.65 (95% CI 1.52–8.75) respectively [5]. Tamim et al. found no difference regarding LBW between women smoking WP in the first trimester and those initiating smoking in subsequent trimesters [106]. Moreover, WPS affects the first trimester markers of Down's syndrome, where it is associated with significant decrease in the levels of free β -human chorionic gonadotropin (β -hCG) and pregnancy-associated plasma protein A (PAPP-A) ($p < 0.001$ for both compared to nonsmokers) and a significant increase in fetal nuchal translucency thickness ($p < 0.001$ compared to nonsmokers) [108]. On the other hand, Hannoun et al. failed to show a statistically significant detrimental effect of WPS on in vitro fertilization outcome [109]. However, a larger prospective study with more objective measures of WPS exposure is needed to confirm these results.

Comparative studies of water pipe and cigarettes

As previously mentioned, many WP smokers believe that WPS carries less toxicant exposure and health risks compared to cigarette smoking [110]. WPS differs from cigarette smoking in several aspects; the type of tobacco, effects of different parts of WP, method of combustion and most importantly the puff topography (Table 4) [34,111]. Unlike cigarette smoking, there is no well-defined point at which the WP has been consumed. The smoker simply stops when the smoke is no longer appealing, whether due to a change in flavor as the tobacco is consumed, to a sense of satiation, or to a change in social setting [112]. Therefore, there is no clear duration of a WPS session, making the comparison of the toxicant yield of WPS to that of cigarette complicated. Two studies showed that, compared to a single cigarette, WPS for 45 min is associated with 3–3.75-fold greater carboxyhemoglobin levels, a similar peak nicotine level, and a 48.6–56-fold greater inhaled smoke volume [49,50]. One study reported a similar subjective effects profile (45-min WPS versus single cigarette), such as improvement of tobacco abstinence symptoms, increased rating of nicotine-related side effects, and pleasure and satisfaction feeling [50]. In a recent study [113], Jacob et al. showed that, when smoking an average of 3 WPS sessions (total time of 45.8 min) compared with smoking 11 cigarettes per day, WP use was associated with a significantly lower intake of nicotine, greater exposure to carbon monoxide, and a different pattern of carcinogen exposure with greater exposure to benzene and high molecular weight PAH, but less to tobacco-specific nitrosamines. Moreover, the side stream smoke of a WPS session (171 puffs at 17-s intervals, each of 530 ml volume) contains around 4 times the carcinogenic PAH and volatile aldehydes and 30 times the CO present in that of a single cigarette [114]. It is estimated that a WP smoker generates, during a 1-h session, carcinogens and toxicants in the exhaled mainstream smoke equivalent to 2–10 cigarette smokers, each smoking at a rate of two cigarettes per hour [114]. Al-Mutairi et al. found no significant difference in chronic

respiratory symptoms among WP and cigarettes smokers, although there was a trend of more chronic bronchitis symptoms in WP smokers [76]. In a study that included 254 women (77 WP smokers, 77 cigarette smokers, and 100 nonsmokers) from East Mediterranean region [81], WP use provoked more chronic bronchitis than cigarettes for the same quantity or duration ($p < 0.001$) but caused lesser loss of lung function (assessed by spirometric measures).

Future research needs on WPS

Despite the 400-year history of WPS and its recent resurrection, many of its aspects remain largely under-studied; nevertheless, the already-existing data, though weak, suggest that WP constitutes a major health hazard. In brief, studying WPS tends to be more complex compared to cigarette research for several reasons. First, the toxicant and carcinogens yields of WP were chiefly studied using smoking machines; moreover, unlike cigarette research where smoking machines studies are well standardized by FTC or other regimens, WP smoking machines studies do not take into consideration real-life factors that might affect the composition of WP smoke, such as the effect of different type of tobacco (moassel, ajami, etc.), the contribution and effect of charcoal replacement or movement, and the effects of different WP parts (hose and water bowl) [39]. One study, which used a real-time in situ sampling of WP smoke generated by a smoker, yielded higher nicotine and CO levels, compared to smoking machines studies [115]. Second, different terms (water pipe, sheesha, goza, hookah, etc.) have been used in the literature to describe the same machine; this has created confusion since these devices differ from each other and from the modern water pipe in shape, type of used tobacco, and the way of combustion [116]. Most studies had also used the form of WPS that is popular to the regions where they were conducted and therefore, the results (toxicant yields and health hazards) might not be applicable to other forms. Third, unlike cigarette smoking where the "pack-year" number is used to quantify the intensity of exposure, there is no similar index that has been validated to standardize the magnitude of WPS exposure. Fourth, the short- and long-term health hazards of WPS, especially cancer predisposition and adverse effects on pregnancy, have not been so far investigated in well-designed studies that take into consideration the multiple confounding factors. Fifth, tools to measure and treat nicotine dependence in cigarette smokers (e.g. Fagerstrom Test for Nicotine dependence) might not be applicable to assess WPS dependence due to intermittent nature, social setting, and time-consuming use of WPS [117]. A promising tool, the Lebanese Water pipe Dependence Scale (LWDS-11), a tool for measurement of WPS dependence and composed of 11 scale items in four subscales which measure nicotine dependence, negative reinforcement, psychological craving, and positive reinforcement [118], needs further improvement and confirmation.

Therefore, it is clear that WPS research still harbors a lot of deficiencies that need to be further studied. The 2005 World Health organization (WHO) Advisory Note on WPS [2] highlighted these areas (Table 5). The toxicant carcinogens

Table 5 WPS aspects requiring further research according to WHO [2].

1. Types and patterns of smoking across regions and cultures
2. National and global trends in WPS
3. Relation between the chemical and physical properties of the smoke and WP set-up and smoking condition (geometry of WP, amount/type of charcoal and tobacco, puffing topography, etc.)
4. Methods to evaluate toxicant yield, smoke exposure.
5. Relation between the smoking patterns and toxicant intake
6. Pharmacology and toxicology of smoke as assessed in laboratory tests and in actual use by people
7. Epidemiology of WP-associated disease risk
8. Influence of cultural and social practices on initiation and maintenance
9. Relationship between WPS and other forms of tobacco and other drugs
10. Development of prevention and cessation strategies

yields of WPS should be investigated in relation to the type of charcoal and tobacco used, the geometry of the device, and the real-time puff topography of the smokers. The smoking machines trials of WPS should be standardized in a manner similar to those of cigarette. Well-designed long-term prospective trials are needed to assess the health-related and pregnancy hazards. These studies should adjust for confounding factors, such as the concomitant exposures to other tobacco forms, environmental, or occupational risks, as well as, the intensity of exposure. Moreover, methods for quantification of WP exposure and dependence must be developed and validated. Cessation interventions, like those used in cigarette addiction, are needed to be investigated and developed. Finally, WPS tobacco control and regulation remains a seriously neglected issue and needs to be addressed by local health authorities.

Conclusion

WPS is a global epidemic affecting different age groups. It is associated with exposure to a wide range of toxic substances, many of which are of high carcinogenic potential; thus, confirming that it poses major public health threats. Even though it is of low quality, current clinical evidence indicates that this re-emerging smoking habit carries remarkable adverse health-related outcomes, including the predisposition to different types of cancer. These contributions need to be confirmed by future well-designed prospective studies. Moreover, objective tools for assessing WPS dependence, such as LWDS-11, need to be further developed and validated. Unfortunately, many of the tobacco control and clean indoor policies have exempted water pipes. World wide awareness among the public, smokers, and policymakers about the potential health effects of WPS is urgently required. Furthermore, stringent policies and laws that control and ban WPS in public places, similar to those applied on cigarettes smoking need to be implemented.

Conflict of interest

All authors report no conflict of interest.

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