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# Health effects associated with waterpipe smoking

Ziad M El-Zaatari,<sup>1</sup> Hassan A Chami,<sup>2,3</sup> Ghazi S Zaatari<sup>1</sup>

<sup>1</sup>Department of Pathology and Laboratory Medicine, American University of Beirut, Beirut, Lebanon

<sup>2</sup>Department of Internal Medicine, American University of Beirut, Beirut, Lebanon

<sup>3</sup>Boston University School of Medicine, Boston, Massachusetts, USA

## Correspondence to

Dr Ghazi Zaatari, Department of Pathology and Laboratory Medicine, American University of Beirut, P.O. Box 11-0236, Beirut, 110-72020 Lebanon; [zaatari@aub.edu.lb](mailto:zaatari@aub.edu.lb)

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## ABSTRACT

**Objective** It is widely held that waterpipe smoking (WPS) is not associated with health hazards. However, several studies have documented the uptake of several toxicants and carcinogens during WPS that is strongly associated with harmful health effects. This paper reviews the literature on the health effects of WPS.

**Data sources** Three databases-PubMed, MEDLINE and EMBASE-were searched until August 2014 for the acute and long-term health effects of WPS using the terms 'waterpipe' and its synonyms (hookah, shisha, goza, narghileh, arghileh and hubble-bubble) in various spellings.

**Study selection** We included original clinical studies, case reports and systematic reviews and focused on clinical human studies. ~10% of the identified studies met the selection criteria.

**Data extraction** Data were abstracted by all three authors and summarised into tables. Abstracted data included study type, results and methodological limitations and were analysed jointly by all three authors.

**Data synthesis** WPS acutely leads to increased heart rate, blood pressure, impaired pulmonary function and carbon monoxide intoxication. Chronic bronchitis, emphysema and coronary artery disease are serious complications of long-term use. Lung, gastric and oesophageal cancer are associated with WPS as well as periodontal disease, obstetrical complications, osteoporosis and mental health problems.

**Conclusions** Contrary to the widely held misconception, WPS is associated with a variety of adverse short-term and long-term health effects that should reinforce the need for stronger regulation. In addition, this review highlights the limitations of the published work, which is mostly cross-sectional or retrospective. Prospective studies should be undertaken to assess the full spectrum of health effects of WPS, particularly in view of its growing popularity and attractiveness to youth.

and the Western Pacific Region.<sup>4</sup> The perception of safety and harm reduction has been refuted by studies which documented the presence in waterpipe smoke of harmful toxicants and carcinogens<sup>5,6</sup> that are taken in by smokers and not filtered out by the passing through water.

Contrary to this misconception about the safety of WPS, several studies have demonstrated its adverse health effects on many organs but primarily the cardiovascular and respiratory systems where there is documentation of coronary artery disease (CAD) and obstructive pulmonary disease and increased risk to develop lung cancer. In addition, perinatal effects in smoking mothers, periodontal disease and other health effects have been described in this group of smokers. This paper is a narrative review of the current knowledge on the health effects of WPS and it draws recommendations for the work needed to determine the scope of disease in this group of smokers and highlights the importance of regulatory measures to curb this rapidly growing epidemic.

## METHODS

### Eligibility criteria

For a comprehensive evaluation of published data on the health effects of WPS, a minimally restrictive approach of study inclusion was adopted. All available original clinical studies (cohort, case-control and cross-sectional), systematic reviews, case reports and case series were included. Relevant abstracts and full text studies were also included. In vitro and animal studies were included but were not the main focus of this study. Publications that were not eligible were letters and editorials that did not represent original research, or publications that did not assess our main outcomes of interest, that is, effects or outcomes of WPS on human health.

### Search strategy

PubMed, MEDLINE and EMBASE databases were searched from the earliest studies on those databases until 27 August 2014. A medical librarian was consulted and agreed with the search strategy used. The PubMed search was carried out using a strategy employing synonyms of 'waterpipe': waterpipe OR hookah OR shisha OR goza OR narghileh OR arghileh OR hubble-bubble. MEDLINE was searched using previously reported strategies,<sup>7</sup> which helped identify further studies not found using the former strategy. EMBASE was searched using a modified version of the MEDLINE search, namely searching for terms in titles and abstracts only, including only English language hits for the term "guza", and combining the search terms "water pipe\*" or "argil\*" with the term "tobacco". This resulted in a more focused retrieval of studies from EMBASE, since applying the non-modified

## BACKGROUND AND INTRODUCTION

The worldwide prevalence of daily waterpipe smoking (WPS) is estimated to be 100 million<sup>1</sup> with alarming increasing popularity among the youth.<sup>2</sup> This global trend is on the rise as per several epidemiological studies and surveys due to the following factors: (1) the introduction of flavoured waterpipe tobacco with its reduced harshness, pleasant flavour and aroma;<sup>3,4</sup> (2) the misperception that it is 'healthier' than cigarette smoking;<sup>3</sup> (3) social acceptance and being an essential part of gatherings, and café and restaurant culture;<sup>3,4</sup> (4) internet, mass and social media;<sup>3,4</sup> (5) low cost;<sup>3</sup> (6) lack of waterpipe-specific policy and regulations towards its use;<sup>3,4</sup> and (7) immigration of people from Middle Eastern countries to the European Region, the Region of the Americas



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MEDLINE strategy to EMBASE retrieved a very large number of entries irrelevant to the present study.

### Selection process

The studies were selected based on the eligibility criteria outlined above. All three authors agreed on the studies to include in this review.

### Data abstraction

Each included study was reviewed thoroughly and the selected studies were organised and summarised into tables prior to analysis. The abstracted data included acute and long-term health effects and outcomes, populations studied and their demographic characteristics (age, gender, location), study design, methodological flaws such as inclusion of concurrent cigarette smokers or lack of control for other confounders and any other limitations.

### Data analysis

All three authors analysed the data according to their medical experience and knowledge. Strengths as well as flaws associated with the methodology of studies were critiqued. The results of the studies were presented in the context of all other available evidence.

## RESULTS

### Effects on the cardiovascular system

WPS has both acute and long-term effects on the cardiovascular system. WP acutely increases heart rate (HR) and blood pressure (BP) and can lead to decreased baroreflex sensitivity, HR variability and exercise capacity. Chronically, WPS is associated with CAD.

#### Acute cardiovascular effects

##### *Heart rate and blood pressure*

The acute cardiovascular effects of WPS were evaluated in multiple studies<sup>8–21</sup> conducted in the Middle East,<sup>8–10 12 13 16 19–21</sup> Europe<sup>11</sup> and the USA,<sup>14 15 17 18</sup> using an experimental interventional design. Studies that assessed HR and BP<sup>8–21</sup> measured them before and after WPS sessions that lasted 30–60 min after abstaining from WPS and in some cases from caffeine<sup>9 14</sup> or caffeine and alcohol<sup>12</sup> for varying periods of time. Studies primarily included young healthy participants, either men alone<sup>8 9 12 13</sup> or men and women,<sup>10 11 14–21</sup> and were conducted in indoor laboratory and café and outdoor environments. Flavoured tobacco (moassal) was most commonly used and the weight ranged from 5–20 g per WP. With few exceptions, significant increases in HR ranging from 4.1 to 16 bpm were observed,<sup>8–11 14–21</sup> as were increases in systolic<sup>8–13 16 21</sup> and diastolic<sup>8–12 14 16 20 21</sup> BPs ranging from 6.7 to 15.7 mm Hg and from 2.0 to 14 mm Hg, respectively. The results of these studies are summarised in [table 1](#). Two studies did not show a change in BP,<sup>15 18</sup> possibly related to lower achieved plasma nicotine levels (5.6 ng/mL compared to 19.1 and 60.3 ng/mL in studies that showed an increase in BP).<sup>8 16 18</sup> The difference in nicotine levels is influenced by multiple factors: the amount of tobacco used (20<sup>8</sup> vs 10 g),<sup>18</sup> the burning temperature and the puffing parameters.<sup>22</sup> Crossover studies comparing tobacco-based WPS versus WPS nicotine-free herbal or tea products<sup>14 18</sup> implicate nicotine as the mediator of HR increase. This is understandable considering its known sympathetic stimulation effect.<sup>23</sup> This may be a mechanism shared by WP and cigarettes, as in one crossover study which compared the acute effects of WPS and cigarette smoking.<sup>17</sup> Smoking one

cigarette for 5 min and smoking one WP for 45 min were associated with a similar increase in the nicotine level (10.2 vs 10.5 ng/mL) and a slightly smaller increase in HR (10.8 vs 16.8 bpm). The nicotine level and HR peaked earlier at 5–10 min after cigarette smoking but were higher at 30–45 min after WPS.<sup>17</sup> Another study showed a significantly larger acute increase in HR after 60–90 min of WPS compared with smoking an unspecified number of cigarettes (7.9 vs 0.3 bpm).<sup>21</sup>

##### *Other measures of cardiovascular function*

The acute effects of WPS on predictors of cardiovascular disease were also assessed in some of the aforementioned studies ([table 1](#)). Baroreflex sensitivity,<sup>12</sup> HR variability,<sup>14</sup> endothelial dysfunction,<sup>16</sup> exercise capacity<sup>13</sup> and blood flow<sup>20</sup> were measured before and after exposure to WPS following an experimental interventional design. The interbeat interval and baroreflex sensitivity dropped significantly from 846 to 709 ms and from 9.6 to 5.67 ms/mm Hg, respectively, in a group of young normotensive men after WPS.<sup>12</sup> However, the drop in pulse pressure and baroreflex sensitivity did not reach statistical significance. A transient decrease in HR variability, a measure of autonomic cardiac dysregulation and a predictor of CAD and mortality were observed after smoking both tobacco and nicotine-free WP products.<sup>14</sup> This suggests that smoke constituents other than nicotine impact HR variability. Exercise capacity was evaluated using cardiopulmonary exercise testing in young men after 48 h of abstinence from WPS and repeated a few days later after a 45 min WPS session at a café near the testing laboratory.<sup>13</sup> Both peak exercise capacity as measured by VO<sub>2</sub>max and peak O<sub>2</sub> pulse (oxygen extracted per heartbeat at peak exercise) decreased from 1.86 to 1.7 L/min and from 10.89 to 9.97 mL/beat, respectively. This drop in peak O<sub>2</sub> pulse was attributed to carbon monoxide (CO) induced impairment in vasodilation in the exercising muscle rather than a decrease in the cardiac stroke volume. Postocclusion peripheral forearm arterial and venous blood flow measured by plethysmography decreased significantly and postocclusion arterial vascular resistance increased following a 30 min self-paced WPS session in 53 young WP smokers demonstrating impaired flow-mediated vascular dilation, suggestive of endothelial dysfunction.<sup>20</sup> However, another study in 47 individuals found no change in endothelial function after WPS as measured by the endopat device.<sup>16</sup>

##### *Long-term cardiovascular effects*

The first publication on the association of WPS with long-term cardiovascular outcomes was an abstract reporting an increased odds of CAD with OR=2.2 (95% CI 0.9 to 5.4) in individuals who ever smoked WP and OR=0.7 (95% CI 0.3 to 1.9) in current WP smokers compared with individuals who never smoked.<sup>24</sup> Since then, more studies have evaluated this association including a cross-sectional study from Iran,<sup>25</sup> one prospective study<sup>26</sup> and one case-control study<sup>27</sup> from Bangladesh,<sup>26 27</sup> and three hospital-based cross-sectional studies from Lebanon,<sup>28</sup> Qatar<sup>29</sup> and Egypt.<sup>30</sup> Moreover, one community-based cross-sectional study from Jordan evaluated the association of WPS with hypertension.<sup>31</sup>

In a community-based cross-sectional study of 50 045 participants (40–75 years; 42% males) from Golestan province in Iran, WPS was significantly associated with self-reported prevalent heart disease (ischaemic heart disease or heart failure) after adjusting for demographics and cardiovascular risk factors including physical activity, body mass index (BMI), hypertension and diabetes (*p* for trend=0.04).<sup>25</sup> Heavy WP users with a history of >180 WP-years (WP smoked per day times number

**Table 1** Acute cardiovascular effects of waterpipe smoking: heart rate and blood pressure

Study	Population	Smoking abstinence	Smoking session time and setting	Tobacco type and amount	HR change bpm	SBP change mm Hg	DBP change mm Hg
Shafogoj 2002 <sup>8</sup>	18 previously healthy, normotensive men, avg. age 27 years, exclusive WP smokers	84 h	45 min in a well-ventilated laboratory	20 g moassal	+16	+6.7	+4.4
Shaikh 2008 <sup>9</sup>	202 men, mean age 33.2 years, cigarette smokers excluded	20 min*	30–45 min, in a café environnement	unspecified	+6.3	+15.7	+2.0
Hakim 2011 <sup>10</sup>	30 men and 15 women, mean age 32.3 (±23.4) years. Included 8 cigarette smokers	24 h	30 min in an outdoor environment	10 g moassal	+15.2	+12.5	+8.2
Kadhun 2014 <sup>11</sup>	49 men and 12 women, free of cardiorespiratory disease, ages 18–25 years, cigarette or other tobacco users excluded	Yes, unspecified duration	45–90 min in 6 WP cafes	unspecified	+14	+15	+10
Al-Kubati 2006 <sup>12</sup>	20 normotensive men, avg. age 27 (±6) years	12 h†	45 min in a laboratory	5 g moassal	NE	+13	+14
Hawari 2013 <sup>13</sup>	24 healthy men, average age 20.4 years	48 h	45 min at a café	unspecified	+2.4 (NS)	+10.3	NS
Cobb 2012 <sup>14</sup>	16 men and 16 women, healthy, age 18–50 years, regular cigarette users (>5 per day) excluded	12 h*	45 min in a laboratory	10 g flavoured tobacco	+4.1	+5 (NS)	+6.3
Shishani 2014 <sup>15</sup>	22 adults, avg. age 24 (±3) years, exclusive WP smokers	24 h	45–60 in an outdoor laboratory	unspecified	+8	NS	NS
Bentur 2014 <sup>16</sup>	33 men and 14 women, healthy, average age 24.9 (±6.2) years	24 h	30 min in an indoor environment	10 g moassal	+15.5	+8	+4
Eissenberg 2009 <sup>17</sup>	21 men, 10 women, healthy, avg. age 21.4 (±2.3) years, both WP and cigarette smokers	12 h	45 min in a laboratory environment	15 g flavoured tobacco	+6.3	NE	NE
Blank 2011 <sup>18</sup>	29 men, 8 women, healthy, avg. age 20 years	overnight	45 min in a ventilated laboratory	10 g flavoured tobacco	+8.6	+1.7 (NS)	NS
Al-Osaimi 2012 <sup>19</sup>	220 WP smokers	unspecified	30 min	unspecified	+15	NE	NE
Alomari 2014 <sup>20</sup>	34 men, 19 women, avg age 22.7 (±4.8) years, range 18–35 years	unspecified	30 min in a well-ventilated, air-conditioned room	10 g flavoured tobacco	+5.2	+1.7 (NS)	+2.4
Layoun 2014 <sup>21</sup>	87 men, 45 women, avg age 33.4 (±13.29) years, exclusive WP smokers	unspecified	45 min at restaurants in Beirut and Mt Lebanon	20 g moassal tobacco	+7.09‡	+0.7‡	+2.6‡

\*Also abstained from caffeine.

†Also abstained from caffeine and alcohol.

‡Statistical significance unspecified. DBP, diastolic blood pressure; HR, heart rate; NE, not evaluated; NS, not statistically significant; SBP, systolic blood pressure.

of smoking years) had 3.75 times the odds (95% CI 1.5 to 9.2 N=25) of heart disease compared to never users. Moderate to heavy WP users with >50 WP-years had 1.83 times the odds (95% CI 1.1 to 3.1 N=120) of heart disease compared to low users and never users (<50 WP-years). The limitations of this study are its cross-sectional design with the potential for recall bias, and the low prevalence of WPS with primarily light use, which could have biased against finding a significant association with heart disease in the non-heavy WP users. Indeed, the odds of heart disease in an ever WP user ( $\geq 1$  WP/week for 6-month) was 1.09 (95% CI 0.8 to 1.5 N=525) compared to never users. Furthermore, important CAD risk factors such as hyperlipidaemia and family history of CAD were not accounted for. In the large prospective community-based Health Effects of Arsenic Longitudinal Study (HEALS) that included 20 033 individuals in Arai-hazar, Bangladesh, women who ever smoked WP had 2.81 (95% CI 1.78 to 4.43) times the risk of death from any cause compared to non-WP smokers.<sup>26</sup> In men, only heavy smokers who reported smoking WP >5 times per day had increased risk of death from any cause (hazard ratio=1.35 95% CI 1.05 to 1.76) and from ischaemic heart disease (hazard ratio=1.96, 95% CI 1.05 to 3.63) compared to non-WP smokers. Although analyses were adjusted for age and BMI, 99% of WP smokers were cigarette or beedi smokers, making it impossible to isolate the effect of WPS. In another study, WPS was not associated with stroke-related death risk.<sup>27</sup>

Three hospital-based studies assessed the association of WPS and heart disease. The first evaluated the association with angiographically defined CAD in 1210 patients from four hospitals in Lebanon.<sup>28</sup> Patients with >40 WP-years smoking had three times the odds of severe stenosis (>70%) compared to non-smokers (OR=2.95 95% CI 1.04 to 8.33), adjusting for demographics and CAD risk factors—cigarette smoking, alcohol consumption, physical activity, diabetes, hypertension, hyperlipidaemia and family history of CAD. Furthermore, WPS was associated with the extent of CAD measured by the Duke CAD prognostic index. Although cigarette smoking history was adjusted for, there was a potential residual confounding effect due to the significant concurrent (29%) or previous cigarette smokers (12.2%). To minimise recall bias inherent to the cross-sectional design, participants were interviewed prior to their knowledge of CAD results. The second study investigated the outcome of acute coronary syndrome in 7930 hospitalised patients of whom 306 (3.9%) were WP smokers.<sup>29</sup> Although WP smokers were older than cigarette smokers, the age-adjusted in-hospital mortality was significantly higher in WP smokers (OR=1.8). Furthermore, WP smokers experienced significantly higher rates of recurrent ischaemia (26.9%) compared to cigarette smokers (14.1%). Finally, a third study, which included 287 patients referred for coronary revascularisation at a single centre in Egypt, reported that the Duke CAD prognostic index was highest among WP smokers (6.96, SD3.28) and mixed smokers (6.92, SD3.1), followed by cigarette smokers (6.14, SD3.02) and non-smokers (5.41, SD3.06).<sup>30</sup> Although CAD risk factors were more common among WP smokers and diabetes was more common in non-smokers, analyses adjusting for these factors were not reported, thus limiting this analysis. Furthermore, none of the females included in this study reported WP or cigarette smoking.

A recent study found a weak association between exclusive long-term WPS and increased BP and HR ( $p=0.05$ ,  $p=0.01$ , respectively).<sup>21</sup> Another community-based cross-sectional study found no association between exclusive WPS and hypertension in 14 310 healthy young adults (mean age  $31.4 \pm 14.2$  years, 48%

females), primarily university students.<sup>31</sup> Compared to non-smokers, BP and HR were significantly higher in participants who smoked cigarettes alone or cigarettes and WP concurrently, but not in pure WP smokers. However, the vast majority of WP smokers were light users who reported smoking one to two times per week. The study was further limited by a lack of adjustment for important predictors of hypertension and duration of smoking. Thus, although BP and HR are proven to acutely increase after WPS, such evidence for long-term increase is weak.

#### Mechanisms for WP-induced cardiovascular disease

Multiple mechanisms can mediate the association of WPS with cardiovascular disease. Flow-mediated dilation was lowest in otherwise healthy WP smokers followed by age-matched and sex-matched cigarette smokers and non-smokers, suggesting a higher degree of endothelial dysfunction.<sup>32</sup> Reduced HR variability (referred to above) and increased oxidative stress, the latter persisting after 2 weeks of sustained smoking,<sup>33</sup> are other possible mechanisms. Finally, enhanced thrombosis and oxidation of cholesterol are other potential mechanisms that were implicated in cigarette smoking<sup>34</sup> but have not been evaluated in WPS.

#### Effects on the respiratory system

Similar to the cardiovascular system, WPS has acute and long-term effects on the respiratory system. The former are reflected in increased respiratory rate (RR) and CO, in addition to changes in pulmonary function (PF) and exercise capacity. Chronically, CO levels may be elevated and PF can become permanently altered, leading to chronic obstructive pulmonary disease (COPD). Chronic bronchitis, emphysema and exacerbation of asthma are other pulmonary manifestations of WPS.

#### Acute respiratory effects

A number of experimental interventional studies, conducted from UAE,<sup>9</sup> Israel,<sup>10 16</sup> Jordan<sup>13</sup> and Lebanon,<sup>21</sup> in café,<sup>9 13</sup> restaurant,<sup>21</sup> other indoor<sup>16</sup> or outdoor environments,<sup>10</sup> measured the acute effect of WPS on the respiratory system (table 2). Four showed a significant increase in RR that varied between 2 and 3.5 breaths per minute after 30–45 min of WPS.<sup>9 10 13 16</sup> Four studies measured the acute effect on PF.<sup>10 13 16 21</sup> Forced expiratory flow (FEF<sub>25-75</sub>)<sup>10 13</sup> and peak expiratory flow rate<sup>10 16</sup> decreased significantly post-WPS, suggesting small airway dysfunction. However, there was no change in the main spirometric measurements: forced expiratory volume in 1 s (FEV<sub>1</sub>), forced vital capacity (FVC) and FEV<sub>1</sub>/FVC<sup>10 13 16 21</sup> or in gas exchange at rest as measured by diffusing capacity for carbon monoxide (DLCO).<sup>13</sup> Perceived dyspnoea as measured by the Borg scale increased at mid and peak exercise after WPS; however, using formal cardiopulmonary exercise testing, maximal ventilatory capacity, breathing reserve and oxygen saturation at peak exercise did not change after WPS.<sup>13</sup> An average significant decrease in oxygen saturation by 0.39% after a 30 min WPS session was reported in another study.<sup>19</sup> Overall, participants were young, healthy and smoked at their own pace. Smoking abstinence ranged from 20 min<sup>9</sup> to 48 h<sup>13</sup> before experimentation, with one study not specifying this type of control.<sup>21</sup> Two studies included both men and women and the participants smoked a controlled amount of the same tobacco.<sup>10 16</sup> One study included a passive smoking group with no significant changes in PF.<sup>16</sup>

#### CO Toxicity

WPS acutely leads to a marked CO inhalation and increased carboxyhaemoglobin (COHb) or exhaled CO when compared

**Table 2** Acute respiratory effects of water pipe smoking: change in respiratory rate and pulmonary function parameters

Study	Population	Smoking session duration	Tobacco type and amount	Included only healthy participants?	RR bpm	Difference in FEV <sub>1</sub> predicted*	Difference in FVC predicted*	Difference in FEV <sub>1</sub> /FVC %*	Difference in PEF <sub>r</sub> % predicted*	Difference in FEF <sub>25-75</sub> % predicted*
Shaikh 2008 <sup>9</sup>	202 men, 17+ years	45 min	Unspecified	No	+2	NE	NE	NE	NE	NE
Hakim 2011 <sup>10</sup>	30 men, 15 women, 18+ years, mean age 32.35 (±23.36) years, range 18.3–65.1 years	30 min	10 g double-apple flavoured moassal	Yes	+2.3	-1 (NS)	0	-1 (NS)	NE	-5
Hawari 2013 <sup>13</sup>	24 men, 18–26 years	45 min	Unspecified	Yes	+2	-0.08 L/sec (NS)	-0.05 L (NS)	NE	NE	-0.22 L/sec
Bentur 2014 <sup>16</sup>	39 men, 23 women, 47 active smokers, 18+ years, mean age 24.9 (±6.2) years	30 min	10 g double-apple flavoured moassal	Yes	+3.5	+0.1 (NS)	-0.7 (NS)	+1.0 (NS)	-3.6	-0.1 (NS)
Layoun 2014 <sup>21</sup>	87 men, 45 women, avg age 33.4 (±13.29) years, exclusive WP smokers	45 min	20 g moassal	No	NE	-1.21†	+1.69†	-2.28†	NE	NE

\*All pulmonary function values are changes (WP value after—WP value before). The units are % predicted, except FEV<sub>1</sub>/FVC, which is a % ratio, or otherwise specified.

†Statistical significance unspecified.

% pred, per cent predicted; FEF<sub>25-75</sub>, forced expiratory flow between 25% and 75% (middle half) of the FVC; FEV<sub>1</sub>, forced expiratory volume in 1 s; FEV<sub>1</sub>/FVC, ratio of FEV<sub>1</sub>/FVC; FVC, forced vital capacity; NE, not evaluated; NS, not statistically significant; PEF<sub>r</sub>, peak expiratory flow rate; RR, respiratory rate; unsp, unspecified.

to cigarette smokers<sup>17 35–37</sup> and non-smokers.<sup>36–38</sup> An acute increase in CO levels (exhaled CO or COHb) is demonstrated in smokers following a timed WPS session<sup>8 10 11 13–18 39–42</sup> after exiting WP cafés<sup>43</sup> or compared to non-WP cafés,<sup>44</sup> and among passive smokers.<sup>16 41 45</sup> COHb compromises the transportation of oxygen to various organs, including the brain, and can cause dizziness, headache, syncope and nausea. Acute CO poisoning after WPS is widely reported in the literature as case reports<sup>46–56</sup> and manifests with markedly elevated blood COHb levels and various symptoms that resolve after therapy. The increase in exhaled CO levels is probably tobacco-independent and related to charcoal as CO levels after tobacco-free WPS were similar to<sup>14 18</sup> or larger than<sup>15</sup> tobacco-based WPS.

### Long-term respiratory effects

#### Carbon monoxide

WPS may lead to a long-term increase in COHb to levels greater than those in cigarette smokers<sup>57</sup> and to polycythaemia.<sup>58 59</sup> In fact, WPS was a predictor of increased exhaled CO levels in Lebanese residents aged 40 and above.<sup>60</sup>

#### Pulmonary function

Several studies assessed PF in long-term WP smokers compared to non-smokers (table 3).<sup>21 61–71</sup> These cross-sectional studies were mostly community-based,<sup>61–66 68–71</sup> with one hospital-based study,<sup>67</sup> and were conducted in Iran,<sup>61 71</sup> Tunisia,<sup>62 63</sup> Kuwait,<sup>64</sup> Turkey,<sup>65 66</sup> Syria,<sup>67 68</sup> China<sup>69</sup> and Saudi Arabia.<sup>71</sup> PF was impaired as measured by FEV<sub>1</sub>,<sup>61 63 69–71</sup> FVC,<sup>21 61 70 71</sup> FEV<sub>1</sub>/FVC<sup>66 69 70</sup> or FEF<sub>25-75</sub>,<sup>61 63 71</sup> while two studies did not demonstrate impairment of these parameters.<sup>64 67</sup> Air trapping was reported in WP smokers in one study,<sup>62</sup> although other PF parameters such as total lung capacity<sup>62 63</sup> and DLCO<sup>65</sup> were not altered. While the results of these studies are inconsistent, a meta-analysis of six cross-sectional studies found that FEV<sub>1</sub> and FEV<sub>1</sub>/FVC were significantly reduced with a trend towards lower FVC in an obstructive pattern.<sup>72</sup> Furthermore, long-term WP smokers had a shorter 6 min-walk-test distance compared to healthy non-smokers.<sup>73</sup>

Studies that evaluated the associations between the total number of WPs,<sup>61 71</sup> total weight of tobacco smoked<sup>62</sup> or WP-years<sup>66</sup> and PF parameters reported a significant moderate negative correlation with FEV<sub>1</sub>  $r \sim -0.35$ ,<sup>61 62 66 71</sup> Other negative correlates of the amount of WP smoked include FVC  $r \sim -0.39$ ,<sup>61 71</sup> FEF<sub>25-75</sub>,<sup>61 62 71</sup> peak expiratory flow<sup>61 62 71</sup> and FEV<sub>1</sub>/FVC.<sup>62</sup> A significant positive correlation between the amount of WPS and functional residual capacity and residual volume was also reported.<sup>62</sup>

#### COPD, chronic bronchitis, emphysema, asthma and others

While studies on PF parameters provide preliminary evidence that WPS causes respiratory disease, a few studies have shown an association with frank clinical syndromes. The GOLD guidelines define COPD by the presence of FEV<sub>1</sub>/FVC <70% on spirometry.<sup>74</sup> Four cross-sectional community-based studies<sup>69 75–77</sup> and one hospital-based study<sup>67</sup> evaluated the association of WPS with COPD. These studies were conducted in Syria,<sup>67</sup> Lebanon,<sup>75</sup> the UAE,<sup>77</sup> China<sup>69</sup> and several Middle Eastern and North African Countries.<sup>76</sup> Two studies, using the GOLD spirometry-based definition of COPD, found an association between COPD and smoking the traditional<sup>75</sup> (OR=2.53, 95% CI 1.83 to 3.50) or Chinese WP (OR=10.61, 95% CI 6.89 to 16.34).<sup>69</sup> (The Chinese WP is similar to the regular traditional Middle Eastern WP, but the tobacco is lit directly without charcoal.) Both analyses adjusted for

**Table 3** Long-term effect of waterpipe smoking on pulmonary function

Study	Population	WP quantity	Tobacco type	Included only healthy participants?	Comparison	Diff in FEV <sub>1</sub> %pred*	Diff in FVC %pred*	Diff in FEV <sub>1</sub> /FVC %*	Diff in FEF25–75% pred*
Boskabady 2012 <sup>61</sup>	371 men, 301 women, average ages in 30s and 40s	Average (Avg) 1.17 (±0.53) WP smoked per week	Unspecified	Yes	WP vs non-smokers	−14.6	−21.9	NE	−13.8
					WP vs cigarette (normal inhalation)	−3.83 (NS)	−7.03	NE	−13.0
Ben Saad 2013 <sup>63</sup>	142 men age 35–60 years	Avg 36 (±22) WP-years	Tabamel (sweetened tobacco)	Yes	WP vs cigarette	+24.0	+14.0	+13.0	NE
Ben Saad 2011 <sup>62</sup>	110 men, age 20–60 years	Median 14 WP-years	Unspecified	Yes	WP vs reference values	†	†	†	†
Mutairi 2006 <sup>64</sup>	139 men, 13 women, age 24–65 years	unspecified	Moassal,	Yes	WP vs cigarette	−1.1 (NS)	NE	+0.5‡ (NS)	NE
					WP vs non-smokers	−12.2 (NS)	NE	−2.5‡ (NS)	NE
Aydin 2004 <sup>65</sup>	25 persons average age 49.2 (±12.2) years	Avg 23.7 (±8.3) years smoking 1–2 times/day	Unspecified	Yes	WP vs passive cigarette smokers	−2.5 (NS)	+0.9 (NS)	−5.6‡	−7.2 (NS)
Kiter 2000 <sup>66</sup>	397 men, age 18–85 years	Average 37 (±42) Jurak-years	Jurak (tobacco-fruit mixture)	No	WP vs non-smokers	−6.5	−5.86 (NS)	−3.02‡	−8.63
					WP vs cigarette	+3.01	−0.5 (NS)	+4.49‡	+5.08
Mohammad 2013 <sup>67</sup>	788 women, age 44 + years	Unspecified	Unspecified	No	WP vs cigarette	+5.3 (NS)	NE	+0.1 (NS)	NE
She 2014 <sup>69</sup>	1238, mostly men, age 40+ years	Average 28 (±11.2) years of 17.9 (±8.9) g tobacco/day	Chinese WP tobacco	Yes	WP vs non-smokers	−9.4	+6.1	−12.1	NE
					WP vs cigarette	−4.0	+7.1	−8.0	NE
					WP passive vs never-passive	−9.0	−6.6	−4.5	NE
					WP passive vs cigarette-passive	−6.9	−5.5	−3.0	NE
Al-Fayez 1988 <sup>70</sup>	441 men, 154 women smokers, 878 total participants, men 20–59 years, women 17–59 years	Not reported	Jurak (tobacco-fruit mixture)	Yes	WP smokers vs non-smokers				
					Males	−0.54 L	−0.43 L	−4.6	NE
					Females	−0.41 L	−0.19 L	−11.42	NE
Boskabady 2014 <sup>71</sup>	§	§	§	§	§	§	§	§	§
Layoun 2014 <sup>21</sup>	87 men, 45 women, avg age 33.4 (±13.29) years, exclusive WP smokers	Avg 11.12 (±17.27) WP/week	Moassal	No	WP vs non-smokers	−4.4 (NS)	−9.1	+5.56	NE
					WP vs cigarette	+1.63 (NS)	−2.28 (NS)	+4.28	NE

\*All pulmonary function values are differences (WP value—comparison group value). The units are % predicted, except FEV<sub>1</sub>/FVC, which is a % ratio, or otherwise specified.

†FEV<sub>1</sub> and FEF25–75 decreased compared to reference values; no comparison group was included. FVC and FEV<sub>1</sub>/FVC were non-significant in this comparison.

‡Per cent predicted value.

§Same as 2012 data.

% pred, percent predicted; % pred, per cent predicted comparison group; Diff, difference; FEF25–75, forced expiratory flow between 25% and 75% (middle half) of the FVC; FEV<sub>1</sub>, forced expiratory volume in 1 s; FEV<sub>1</sub>/FVC, Ratio of FEV<sub>1</sub>/FVC; FVC, forced vital capacity; NE, not evaluated; NS, no significant difference with comparison group; unsp, unspecified; unsp, unspecified.

possible confounders such as age and cigarette smoking. The association of WP with COPD was also ascertained using an epidemiological questionnaire-based definition ( $p < 0.026$  for having COPD symptoms compared to non-smokers).<sup>76</sup> In contrast, two studies found no association between WP and COPD, but were methodologically limited.<sup>67–77</sup> One included women only and did not account for the total quantity of WP smoked;<sup>67</sup> thus, women may have been exposed to less WP smoke than participants in other studies, accounting for the lack of association. In addition, this study included women as young as 20 years and did not pilot test its survey, report on randomisation methods or calculate the sample size.<sup>67</sup> The second study had a low COPD prevalence and inadequate power.<sup>77</sup>

WPS was also associated with chronic bronchitis and emphysema in cross-sectional studies from Lebanon,<sup>45 78 79</sup> Iran,<sup>61</sup> China<sup>69</sup> and a combination of Middle Eastern and North African countries.<sup>76</sup> Overall, the studies were robust in design including randomisation,<sup>69 76 78</sup> good survey designs,<sup>61 79</sup> adequate power<sup>61 78 79</sup> and controlling for cigarette smoking<sup>61 69 76</sup> and other confounders.<sup>78 79</sup> The associations between WPS and chronic bronchitis, using the standard definition (chronic cough with sputum production for 3 consecutive months for 2 years), were: adjusted OR=1.42, 95% CI 1.12 to 1.8,<sup>76</sup> adjusted OR=3.4 for >6 WP smoked per week,<sup>78</sup> and adjusted OR=5.65 for >20 WP-years.<sup>79</sup> Another study found that symptoms of chronic bronchitis, using the standard definition, were more severe in WPS compared to non-smokers ( $p=0.003$ ). An association between Chinese WPS and chronic bronchitis and emphysema was also reported; however, in contrast to other studies, the standard definition of chronic bronchitis was not used.<sup>69</sup> Another study that conducted a multivariable analysis found that chronic cough but not chronic sputum production was more prevalent in individuals with occupational exposure to WP smoke.<sup>45</sup>

The association of physician-diagnosed asthma in Lebanon with WPS was of borderline significance after adjusting for cigarette smoking and other variables.<sup>78</sup> Furthermore, data were collected by phone interviews, making the diagnosis unreliable. Another study from India reported an association between asthma and WPS but did not differentiate between WPS and other forms of smoking.<sup>80</sup> Therefore, an association between WPS and asthma remains inconclusive.

#### Mechanisms of WP-induced respiratory disease

Possible mechanisms of respiratory diseases in WPS were explored in *in vitro* and *in vivo* studies. WPS resulted in increased airway resistance, lung inflammation, oxidative stress<sup>81</sup> and catalase activity in animal lungs.<sup>82</sup> Rats exposed to WPS over several weeks had higher red blood cell counts and haematocrit, supporting an association with chronic polycythaemia.<sup>83</sup> WP smoke exposure led to decreased neutrophils, lymphocytes, eosinophils and interferon- $\gamma$  and higher nitric oxide in the bronchioalveolar lavage fluid of asthmatic mice, similar to cigarette smoke exposure, and thus may contribute to asthma exacerbations by suppressing helper T1 cells.<sup>84</sup> In humans, levels of inflammatory cytokines were decreased in the exhaled breath of WP smokers,<sup>16</sup> while the bronchioalveolar lavage fluid of WPS with COPD had increased metalloproteinase two and nine gene expression similar to that of cigarette smokers with COPD.<sup>85</sup> These findings need further investigation to understand their implication to human disease.

#### Association of WPS with cancer

WP smoke has *in vitro* been associated with genotoxicity and cellular changes that may lead to cancer. WP smokers had greater chromosomal aberrations by karyotype testing,<sup>86</sup>

increased sister chromatid exchanges in lymphocytes<sup>87</sup> and increased micronuclei in buccal mucosa cells.<sup>88</sup> A second study also found increased sister chromatid exchanges and chromosomal aberrations in addition to mitotic index and satellite associations in somatic chromosomes of WP smokers.<sup>89</sup> Exposure of human alveolar cells to WP smoke resulted in reduced cell proliferation, cell cycle arrest and increased doubling time.<sup>86</sup> Increased nuclear size, nuclear/cytoplasmic ratio and Feret ratio and decreased cytoplasm size were found in the oral mucosa cells of WP smokers.<sup>90</sup>

Several studies evaluated the association of WPS with cancer (table 4). In the HEALS project, current male WP smokers had 2.5 times the risk of cancer death (95% CI 1.08 to 5.82) compared to non-WP smokers.<sup>26</sup> As previously noted, 99% of WP smokers were cigarette or beedi smokers, making it impossible to isolate the effect of WPS. Furthermore, the small number of cancer related deaths precluded assessment of cancer mortality in women and in different subtypes of cancer.

#### Lung cancer

Several methodologically limited case-control studies from Lebanon,<sup>91</sup> India<sup>92–93</sup> and China<sup>94–95</sup> and one Chinese cohort study<sup>96</sup> support an association between WPS and lung cancer. A sixfold greater risk of lung cancer was noted among former Lebanese WP smokers<sup>91</sup> and in a group of current Indian WP smokers.<sup>92</sup> However, the association was not adjusted for confounders in the latter study and became non-significant after adjustment for confounders in the former study. In another study that adjusted for age and education, the odds of lung cancer in Indian male heavy WP smokers of >45 years were 4.44.<sup>93</sup> Three studies also found an association between WPS and lung cancer in China<sup>94–96</sup> and a meta-analysis reported a pooled OR of 2.12 for lung cancer in WPS.<sup>7</sup> However, the Chinese studies did not account for cigarette smoking<sup>92</sup> or Chinese long-stem pipe smoking<sup>95 96</sup> or control for other possible confounders.<sup>94</sup> Thus, while cigarette smoking is a well-established risk factor for lung cancer,<sup>97</sup> the evidence linking WPS and lung cancer is limited and more robust studies are needed to elucidate this relationship.

#### Oesophageal, gastric, bladder and other cancers

Three case-control studies from India<sup>98 99</sup> and Iran<sup>100</sup> and a meta-analysis support an association between WPS and oesophageal cancer. One study showed twice the risk (OR=1.85, 95% CI 1.41 to 2.44) of oesophageal squamous cell carcinoma in WPS and a higher risk of cancer with greater intensity, duration and cumulative WPS.<sup>98</sup> Another study found very high odds of oesophageal cancer (OR=21.4, 95% CI 11.6 to 39.5) among WP smokers; however, data on concomitant use of cigarettes or other forms of tobacco were lacking.<sup>99</sup> One study<sup>100</sup> that controlled for cigarettes and other confounders did not demonstrate significant association between exclusive WPS and oesophageal squamous cell cancer (OR=1.66, 95% CI 0.65 to 4.22).<sup>100</sup>

Two of four studies support an association of WPS with gastric cancer. A large prospective cohort study in Iran reported three times greater risk of gastric cancer (OR=3.4, 95% CI 1.7 to 7.1) in WPS after adjusting for cigarette smoking and other risk factors.<sup>101</sup> A significant association between WPS and gastric cancer was also observed in a case-control study available in abstract form, also from Iran.<sup>102</sup> One study reported a non-significant association with gastric cancer; however, the number of WP smokers included in the study was too small to measure the effect with confidence.<sup>103</sup> Another study reported associations with gastric and oesophageal cancers, but again the

**Table 4** Studies on associations of waterpipe smoking (WPS) and cancer

Study	Cancer type	Population	Study type	Controlled for cigarette smoking?	Adjusted for other confounders?	OR (95% CI)	Comments
Wu 2013 <sup>26</sup>	All cancer death	20 033 Bangladeshi individuals	Prospective community-based	No	Yes	Adjusted=2.5 (1.08 to 5.82)	
Auon 2013 <sup>91</sup>	Lung	150 Lebanese individuals	Case-control	Yes	Yes	6.0 (1.78 to 20.26)	Non-significant OR after adjustment for confounders
Koul 2011 <sup>92</sup>	Lung	751 Indian individuals	Case-control	No	No	5.8 (3.9 to 8.6)	
Gupta 2001 <sup>93</sup>	Lung	265 Indian individuals	Case-control	Yes	Yes	Adjusted=4.44 (1.2 to 16.44)	OR for Male heavy smokers older than 45 years
Lubin 1990 <sup>94</sup>	Lung	148 Chinese men	Case-control	No	No	*	Increased risk with cumulative exposure
Lubin 1992 <sup>95</sup>	Lung	1438 Chinese men	Case-control	Yes	Yes	Adjusted=1.8 (0.8 to 4.2)	Did not control for Chinese long-stem pipe smoking
Hazelton 2001 <sup>96</sup>	Lung	12 011 Chinese men	Case-control	Yes	Yes	*	Did not control for Chinese long-stem pipe smoking
Dar 2012 <sup>98</sup>	Oesophageal	2365 Indian individuals	Case-control	Yes	Yes	Adjusted=1.85 (1.41 to 2.44)	Higher risk with greater intensity, duration and cumulative WPS
Malik 2010 <sup>99</sup>	Oesophageal	330 Indian individuals	Case-control	No	Yes	Adjusted=21.4 (11.6 to 39.5)	
Nasrollahzadeh 2008 <sup>100</sup>	Oesophageal	871 Iranian individuals	Case-control	Yes	Yes	Adjusted=1.66 (0.65 to 4.22)	OR for >32 WP-years smoking
Sadjadi 2014 <sup>101</sup>	Gastric	928 Iranian individuals	Prospective cohort	Yes	Yes	Adjusted=3.4 (1.7 to 7.1)	
Karajibani 2014 <sup>102</sup>	Gastric	92 Iranian individuals	Case-control	†	†	†	Statistically significant association was observed
Shakeri 2013 <sup>103</sup>	Gastric	922 Iranian individuals	Case-control	Yes	Yes	Adjusted=1.1 (0.3 to 3.3)	Also non-significant for cumulative WP use. Included a small percentage of WP smokers
Gunaid 1995 <sup>104</sup>	Gastric and Oesophageal	3064 Yemeni Individuals	Cross-sectional	Unclear	No	Not calculated ( $\chi^2=2.646$ , $P<0.05$ )	Number of gastric cancer cases was too small to draw significant conclusions. Most WP smokers were also Qat chewers, and an individual effect could not be discerned.
Zheng 2012 <sup>105</sup>	Bladder	1134 Egyptian men	Case-control	Yes	Yes	Adjusted=1.1 (0.7 to 1.9) for urothelial cancer, Adjusted=0.5 (0.2 to 1.0) for squamous cancer	ORs for smoking >153 Hagar-years. ORs also insignificant for lesser exposures
Bedwani 1997 <sup>106</sup>	Bladder	308 Egyptian men	Case-control	Yes	Yes	Adjusted=0.8 (0.2 to 4.0)	
Hosseini 2010 <sup>107</sup>	Prostate	274 Iranian men	Case-control	Yes	Yes	OR=7.0 (0.9 to 56.9)	Adjusted OR for WP was also non-significant (but not reported)
Lo 2007 <sup>108</sup>	Pancreatic	388 Egyptian individuals	Case-control	No	Yes	Adjusted=1.6 (0.9 to 2.8)	WP smoking was also not exclusive of other non-cigarette forms of smoking
Feng 2009 <sup>109</sup>	Nasopharyngeal	1251 North African individuals	Case-control	No	Yes	Adjusted=0.49 (0.20 to 1.43)	Had small numbers of WP smokers

\*A single OR was not reported, but there was an increased risk based on mathematical modelling, which is beyond the scope of this paper.

†Only an abstract was available, which did not mention these variables.

number of waterpipe smokers was too small and thus probably confounded by concurrent Qat chewing.<sup>104</sup> Despite these two methodologically limited studies, the evidence remains supportive of an association with gastric cancer.

In contrast to the well-known association between cigarette smoking and bladder cancer,<sup>97</sup> two case-control studies<sup>105 106</sup> reported a weak or non-existent association between bladder cancer and WPS. The two studies controlled for cigarette smoking and other confounders.

The evidence for an association of WPS with other cancers, such as prostate,<sup>107</sup> pancreatic<sup>108</sup> and nasopharyngeal carcinoma,<sup>7 109</sup> is very weak.

### Obstetrical and perinatal outcomes

WPS has been associated with obstetric and perinatal complications including low birthweight (LBW),<sup>110–117</sup> infant mortality,<sup>118</sup> low APGAR scores,<sup>115</sup> and pulmonary complications at birth.<sup>116</sup> Studies were primarily retrospective or cross-sectional and were conducted in Lebanon,<sup>110 114–116</sup> Qatar,<sup>111</sup> Iran,<sup>112 113</sup> the Gaza Strip<sup>117</sup> and Cambodia.<sup>118</sup>

Controlling for various confounders such as gestational age, parity and various obstetrical complications, one retrospective study found 2.4 (95% CI 1.2 to 5.0) times greater odds of LBW (<2500 g) among exclusive WPS who smoked more than once a day.<sup>110</sup> This study is limited, however, by a lack of control for important confounders such as alcohol and other substance intake.<sup>110</sup> Another case-control study found 3.5 times greater odds (95% CI 1.1 to 12.6) of LBW among WPS mothers in multivariable-adjusted analysis but, like the first study, did not control for other substance intake.<sup>112</sup> In contrast, a retrospective study, which controlled for substance intake, found a non-significant association with LBW (OR=1.8, 95% CI 0.67 to 5.38).<sup>116</sup> Other studies that supported an association between LBW and WPS did not account for concomitant cigarette smoking.<sup>111 114 115</sup>

Passive WPS was also associated with LBW independent of cigarette and wood fuel smoke in a case-control study; however, the study had low numbers of passive WP smokers and may have suffered from recall bias.<sup>117</sup> While a meta-analysis of three of the aforementioned studies<sup>110 112 116</sup> reported an overall 2.12 times odds of LBW in association with WPS,<sup>7</sup> these and several additional studies<sup>111 114 115</sup> that support an association between WPS and LBW are methodologically limited with incomplete adjustment for confounders. Larger prospective cohort studies that control for important confounders are still needed.

Other adverse pregnancy outcomes were also assessed in the aforementioned and other studies. The intensity of non-exclusive WPS was inversely correlated with the APGAR scores among newborns at 5 and 10 min in a retrospective study that did not adjust for cigarette smoking.<sup>115</sup> A strong association with the risk of perinatal pulmonary complications (OR=3.65, 95% CI 1.52 to 8.75) was also demonstrated among children born to exclusive WPS mothers.<sup>116</sup> A higher risk of infant mortality among Southern Asian WP smokers was also reported in a cross-sectional study, but the association did not reach statistical significance after adjustment for confounders.<sup>118</sup> Furthermore, one Lebanese prospective study suggested that exclusive WPS may be associated with in vitro fertilisation failure (OR=0.41, 95% CI 0.15 to 1.09), after controlling for maternal age, number of embryos transferred and various causes of infertility.<sup>119</sup> An Egyptian case-control study found a weak association between WPS and male factor infertility (OR=2.5, 95% CI

1.0 to 6.3) after controlling for confounders including cigarette smoking.<sup>120</sup> Finally, exclusive WPS, like cigarette smoking, may influence the results of prenatal serum biomarkers and sonographical measurements used to screen for Down's syndrome as found in a Saudi cross-sectional study that did not adjust for confounders.<sup>121</sup> Thus, most studies on the above perinatal outcomes associated with WPS were methodologically limited and have not been replicated.

### Periodontal and oral disease

#### Periodontal disease

Several cross-sectional studies conducted in Saudi Arabia assessed periodontal disease in WP smokers. Periodontal disease is associated with WPS, manifested by a lower mean age-adjusted periodontal bone height,<sup>122</sup> larger probing depth,<sup>123</sup> and poor gingival health as measured by plaque levels and gingival index.<sup>124</sup> This is probably not attributable to a change in the periodontal microflora, but rather to changes in the periodontal pocket depth in smokers.<sup>125</sup> WPS is also associated with vertical periodontal bone defects, most severe among heavy WP smokers and separate from cigarette smoking effect.<sup>126</sup> In addition, WPS was associated with three times the risk of developing dry socket after dental surgery.<sup>127</sup> Overall, these cross-sectional studies provide supportive evidence for periodontal disease in exclusive WP smokers; however, adjustment for confounders was either absent<sup>127</sup> or incomplete in most cases.<sup>123 124 126</sup> Thus, more robust studies are still needed.

#### Oral lesions

Three cross-sectional studies from India,<sup>128</sup> Saudi Arabia<sup>129</sup> and Yemen<sup>130</sup> assessed the association of WPS with oral lesions. WPS was associated with a greater referral rate for oral lesions suspicious for cancer after adjusting for various confounders.<sup>128</sup> Other studies found insignificant or weak associations with suspicious oral lesions<sup>129</sup> and leukoplakia.<sup>130</sup> Thus, the evidence on the association of WPS and oral lesions remains inconclusive.

#### Larynx and voice

Two studies conducted in Lebanon demonstrated an effect of WPS on the larynx and voice.<sup>131 132</sup> A 30 min WPS session acutely resulted in thick mucus, dilated true vocal fold blood vessels, significantly decreased vocal turbulence index and habitual pitch, and caused changes in voice parameters in a small experimental study that included 18 men and women.<sup>132</sup> A cross-sectional study reported greater oedema, mucus and varix of the cords as well as lower vocal turbulence index and maximum phonation time in 42 long-term WP smokers compared to non-smokers; however, no confounders were taken into consideration.<sup>131</sup> Thus, the evidence supporting an effect of WPS on the larynx and voice is limited.

#### Osteoporosis

Three recently published abstracts support an association between osteoporosis and WPS. A prospective cohort study of 1190 women, followed up for an average of 3.5 years, found decreased bone mass density (BMD) and an increased risk of new fractures (hazard ratio of 3.73, 95% CI 1.89 to 5.16) among WP smokers compared to non-smokers, after adjusting for multiple confounders.<sup>133</sup> Decreased BMD (lumbar spine,<sup>134 135</sup> femur neck, total hip, total body<sup>135</sup>) was also associated with WPS in two other studies after adjustment for confounders including a cross-sectional study of 1880 postmenopausal women<sup>135</sup> and a retrospective cohort study of

60 WP smokers and 120 non-smokers.<sup>134</sup> Of note, these data are published in abstract form.

### Infectious disease

Three Egyptian cross-sectional studies found no risk for transmitting hepatitis C among WP users,<sup>136–138</sup> after adjusting for confounders in two of the studies.<sup>136 137</sup> A meta-analysis that pooled the results of these studies reached the same conclusion.<sup>7</sup>

A cluster of tuberculosis cases was reported among individuals who shared a marijuana WP; however, it was difficult to separate the effect of close contact from that of WP sharing.<sup>139</sup> Pulmonary aspergillosis was also reported in one WP smoker with leukaemia in association with a positive fungal culture from the tobacco used.<sup>140</sup> Despite these limited findings, the risk of infectious disease transmission through sharing WP, being a very common practice in WP cafes, certainly warrants further investigation.

### Other health outcomes

WPS has been associated with a variety of other health effects. A moderate association with WPS and mental health diagnoses was observed among a large sample of US college students.<sup>141</sup> WPS was also associated with greater BMI and risk for obesity after adjusting for cigarette smoking, number of chronic diseases, age, gender, income and marital status in a cross-sectional study of 2536 from Syria.<sup>142</sup> Further cross-sectional studies

reported elevated urine microalbumin,<sup>143</sup> low back pain<sup>144</sup> and increased risk of gastroesophageal reflux disease among exclusive WP smokers.<sup>145</sup> Increased attic retractions, which predispose to cholesteatomas and possibly hearing loss, were reported in 80 ears of WP smokers.<sup>146</sup> WPS was associated with other miscellaneous conditions in several case reports including a case of hand eczema after contact with a WP tube,<sup>147</sup> acute eosinophilic pneumonia,<sup>148</sup> two cases of squamous cell carcinoma and lower lip keratoacanthoma<sup>149</sup> and ulcerative colitis flare after discontinuing WPS.<sup>150</sup> Finally, WPS was associated with lower overall health-related quality of life in a cross-sectional study of 1675, after adjusting for cigarette smoking and other variables.<sup>151</sup> Overall, the findings of these single reports require further confirmation.

### CONCLUSIONS

This review outlined the spectrum of acute and long-term health effects of WPS on multiple organ systems. Health effects and outcomes associated with WPS are summarised in [box 1](#). The greatest impact demonstrated to date is on the cardiovascular and respiratory systems, most seriously leading to CAD and COPD encompassing chronic bronchitis and emphysema.

Although these studies provide evidence that WPS, like cigarette smoking, leads to impaired cardiovascular and PF and several adverse health outcomes, methodological limitations are noted in most studies. A number of studies did not control for concurrent cigarette or other tobacco smoking. Most are cross-sectional and some are exclusively hospital-based with incomplete adjustments for potential confounders. Other limitations, as found in a meta-analysis, include the heterogeneity and under-reporting of methods used to measure variables, poor sampling methods, limited assessment of gender and age as confounders, absence of blinding, incompleteness of data and absence of a standard exposure assessment tool.<sup>72</sup> Furthermore, most studies failed to report the specific type of tobacco used. The long-term effects of smoking traditional (non-flavoured) tobacco versus smoking flavoured (moassel) may be different and needs to be assessed, particularly with the difference in the profile of smokers of each tobacco type.

Thus, large, well-designed, prospective, longitudinal, community-based studies are needed to better assess the long-term health effects of WPS. In addition, future studies must account for the state of knowledge on the ingredients and emissions of flavoured tobacco products, puffing parameters and duration of smoking. Finally, the effect of passive WPS is another area that has been minimally studied and warrants further investigation. Despite all the stated limitations, there is enough evidence to suggest that WPS has harmful health effects and this knowledge should be used to educate the public to dispel the notions of safety of use, and design public health interventions and research work to fill in the gaps in knowledge on the health effects of WPS. This knowledge should guide regulators<sup>152</sup> on appropriate measures to curb this epidemic by implementing health warning labels on packages and in public places of use, banning of misleading information on contents and emissions, and limiting access to youth and minors.

#### Box 1 Adverse health effects associated with waterpipe smoking

##### Acute effects

- ▶ Increased heart rate
- ▶ Increased blood pressure
- ▶ Carbon monoxide intoxication
- ▶ Impaired pulmonary function (FEF25-75, PEFR)
- ▶ Decreased exercise capacity
- ▶ Larynx and voice changes

##### Long-term effects

- ▶ Ischaemic heart disease
- ▶ Impaired pulmonary function (FEV<sub>1</sub>, FVC, FEV<sub>1</sub>/FVC, FEF25-75, PEF, FRC, RV)
- ▶ Chronic obstructive lung disease
- ▶ Chronic bronchitis
- ▶ Emphysema
- ▶ Lung cancer
- ▶ Oesophageal cancer
- ▶ Gastric cancer
- ▶ Low birthweight
- ▶ Pulmonary problems at birth
- ▶ Periodontal disease
- ▶ Larynx and voice changes
- ▶ Lower bone density and increased fracture risk

FRC, functional residual capacity; FVC, forced vital capacity; PEF, peak expiratory flow; PEFR, peak expiratory flow rate; RV, residual volume.

## What this paper adds

## What is already known on this subject

- ▶ Waterpipe smoking is known to expose participants to a variety of potentially harmful toxicants.
- ▶ Numerous studies have been published assessing the clinical effects of waterpipe smoking on human health with emphasis on the cardiovascular and respiratory systems. The literature suggests that waterpipe smoking is also harmful to other organ systems.

## What important gaps in knowledge exist on this topic

- ▶ The extent to which waterpipe smoking harms human health is not well known.
- ▶ Most available studies are methodologically limited and have not been extensively reviewed. Thus, an assessment of the current literature is needed to support or refute the suspected harmful effects of waterpipe smoking and suggest what gaps need to be addressed in future work.

## What this paper adds

- ▶ This narrative review synthesises the published literature on the extent of the health effects of waterpipe smoking on multiple organ systems.
- ▶ This study offers a comprehensive review of the acute and long-term health effects of waterpipe smoking on multiple organs with emphasis on the salient ones.
- ▶ Despite the limitations of some published studies, there is supportive evidence of the harmful effects of waterpipe smoking that lead to morbidity and mortality in humans.
- ▶ This study underscores the need to use this knowledge to educate the public, to dispel misconceptions about safety, and to urge the regulators to undertake effective control measures.

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