Health effects associated with waterpipe smoking

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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.

BACKGROUND AND INTRODUCTION
The worldwide prevalence of daily waterpipe smoking (WPS) is estimated to be 100 million with alarming increasing popularity among the youth.2 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;3 4 (2) the misperception that it is ‘healthier’ than cigarette smoking;1 (3) social acceptance and being an essential part of gatherings, and café and restaurant culture;1 4 (4) internet, mass and social media;3 4 (5) low cost;3 (6) lack of waterpipe-specific policy and regulations toward its use;3 4 and (7) immigration of people from Middle Eastern countries to the European Region, the Region of the Americas and the Western Pacific Region.4 The perception of safety and harm reduction has been refuted by studies which documented the presence in waterpipe smoke of harmful toxicants and carcinogens5 6 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,7 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
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. WPS 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 conducted in the Middle East, Europe and the USA. Using an experimental interventional design, studies that assessed HR and BP measured them before and after WPS sessions that lasted 30–60 min after abstinence from WPS and in some cases from caffeine or coffee, for varying periods of time. Studies primarily included young healthy participants, either men alone or men and women, and were conducted in indoor laboratory and café and outdoor environments. Flavoured tobacco (moassal) was most commonly used and the weight ranged from 5 to 20 g per WP. With few exceptions, significant increases in HR ranging from 4.1 to 16 bpm were observed, as were increases in systolic and diastolic 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, 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). The difference in nicotine levels is in part explained by the fact that smoking an unspecifed WP 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. Another study showed a significantly larger acute increase in HR after 60–90 min of WPS compared with smoking an unspecifed number of cigarettes (7.9 vs 0.3 bpm).

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, HR variability, endothelial dysfunction, exercise capacity and blood flow 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. 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. 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. Both peak exercise capacity as measured by VO₂max and peak O₂ 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 O₂ 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 young WP smokers demonstrating impaired flow-mediated vascular dilation, suggestive of endothelial dysfunction. However, another study in 47 individuals found no change in endothelial function after WPS as measured by the endopat device.

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. Since then, more studies have evaluated this association including a cross-sectional study from Iran, one prospective study and one case–control study from Bangladesh, and three hospital-based cross-sectional studies from Lebanon, Qatar and Egypt. Moreover, one community-based cross-sectional study from Jordan evaluated the association of WPS with hypertension.

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). Heavy WP users with a history of >180 WP-years (WP smoked per day times number of years) were observed, smokers or lack of control for other confounders and any other limitations.

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

*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 (≥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 Araihazar, 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.26 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.27

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.28 Patients with >40 WP-years smoking had three time 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.29 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 non-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).30 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).21 Another community-based cross-sectional study found no association between exclusive WPS and hypertension in 14 310 healthy young adults (mean age 31.4±14.2 years, 48% females), primarily university students.31 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.25 Reduced HR variability (referred to above) and increased oxidative stress, the latter persisting after 2 weeks of sustained smoking,33 are other possible mechanisms. Finally, enhanced thrombosis and oxidation of cholesterol are other potential mechanisms that were implicated in cigarette smoking34 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,9 Israel,10 Jordan13 and Lebanon,21 in cafe,9 13 restaurant,21 other indoor16 or outdoor environments,10 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.9 10 13 16 Four studies measured the acute effect on PF.9 10 13 16 21 Forced expiratory flow (FEF25-75)%10 13 and peak expiratory flow rate10 16 decreased significantly post-WPS, suggesting small airway dysfunction. However, there was no change in the main spirometric measurements: forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC) and FEV1/FVC10 13 16 21 or in gas exchange at rest as measured by diffusing capacity for carbon monoxide (DLCO).13 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.13 An average significant decrease in oxygen saturation by 0.39% after a 30 min WPS session was reported in another study.19 Overall, participants were young, healthy and smoked at their own pace. Smoking abstinence ranged from 20 min2 to 48 h15 before experimentation, with one study not specifying this type of control.21 Two studies included both men and women and the participants smoked a controlled amount of the same tobacco.10 16 One study included a passive smoking group with no significant changes in FEV1.16

CO Toxicity
WPS acutely leads to a marked CO inhalation and increased carboxyhaemoglobin (COHb) or exhaled CO when compared
to cigarette smokers\textsuperscript{17–18} and non-smokers.\textsuperscript{16–18} An acute increase in CO levels (exhaled CO or COHb) is demonstrated in smokers following a timed WPS session\textsuperscript{8–10\textsuperscript{11–13}–17–19–21–23–24–25–26} after exiting WP cafés\textsuperscript{x3} or compared to non-WP cafés,\textsuperscript{x4} and among passive smokers.\textsuperscript{16–19–21–22} 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\textsuperscript{16–20} 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\textsuperscript{14–15} or larger than\textsuperscript{16} 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\textsuperscript{57} and to polycythemia.\textsuperscript{58–59} In fact, WPS was a predictor of increased exhaled CO levels in Lebanese residents aged 40 and above.\textsuperscript{60}

Pulmonary function

Several studies assessed PF in long-term WP smokers compared to non-smokers (table 3).\textsuperscript{21–61–75} These cross-sectional studies were mostly community-based,\textsuperscript{61–66–68–71} with one hospital-based study,\textsuperscript{67} and were conducted in Iran,\textsuperscript{61–71} Tunisia,\textsuperscript{62–65} Kuwait,\textsuperscript{64} Turkey,\textsuperscript{65–66} Syria,\textsuperscript{67} China\textsuperscript{69} and Saudi Arabia.\textsuperscript{71} PF was impaired as measured by FEV\textsubscript{1},\textsuperscript{61–63–65–69–71} FEV\textsubscript{1}/FVC\textsuperscript{66–67} or FEF25–75\textsuperscript{61–63–71} while two studies did not demonstrate impairment of these parameters.\textsuperscript{64–66} Air trapping was reported in WP smokers in one study,\textsuperscript{72} although other PF parameters such as total lung capacity,\textsuperscript{62–63} DLCO\textsuperscript{65} were not altered. While the results of these studies are inconsistent, a meta-analysis of six cross-sectional studies found that FEV\textsubscript{1} and FEV\textsubscript{1}/FVC were significantly reduced with a trend towards lower FVC in an obstructive pattern.\textsuperscript{72} Furthermore, long-term WP smokers had a shorter 6 min-walk-test distance compared to healthy non-smokers.\textsuperscript{73}

Studies that evaluated the associations between the total number of WPs,\textsuperscript{61–71} total weight of tobacco smoked\textsuperscript{62} or WP-years\textsuperscript{66} and PF parameters reported a significant moderate negative correlation with FEV\textsubscript{1} \(r\sim-0.35\),\textsuperscript{61–62–66–71} Other negative correlates of the amount of WP smoked include FVC \(r\sim0.39\),\textsuperscript{61–71} FEV\textsubscript{1}/FVC\textsuperscript{66–67}, peak expiratory flow\textsuperscript{61–62–71} and FEV\textsubscript{1}/FVC.\textsuperscript{62} A significant positive correlation between the amount of WPS and functional residual capacity and residual volume was also reported.\textsuperscript{62}

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\textsubscript{1}/FVC <70% on spirometry.\textsuperscript{74} Four cross-sectional community-based studies\textsuperscript{69–71–74–75} and one hospital-based study\textsuperscript{67} evaluated the association of WPS with COPD. These studies were conducted in Syria,\textsuperscript{67} Lebanon,\textsuperscript{75} the UAE,\textsuperscript{76} China\textsuperscript{69} and several Middle Eastern and North African Countries.\textsuperscript{76} Two studies, using the GOLD spirometry-based definition of COPD, found an association between COPD and smoking the traditional\textsuperscript{75} (OR=2.53, 95\% CI 1.83 to 3.50) or Chinese WP (OR=10.61, 95\% CI 6.89 to 16.34).\textsuperscript{77} (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

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>WP quantity</th>
<th>Tobacco type</th>
<th>Included only healthy participants?</th>
<th>Comparison</th>
<th>Diff in FEV₁ %pred*</th>
<th>Diff in FVC %pred*</th>
<th>Diff in FEV₁/FVC %*</th>
<th>Diff in FEF₂₅–₇₅% pred*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boskabady 2012</strong></td>
<td>371 men, 301 women, average ages in 30s and 40s</td>
<td>Average (Avg) 1.17 (±0.53) WP smoked per week</td>
<td>Unspecified</td>
<td>Yes</td>
<td>WP vs non-smokers WP vs cigarette (normal inhalation)</td>
<td>−14.6</td>
<td>−21.9</td>
<td>NE</td>
<td>−13.8</td>
</tr>
<tr>
<td><strong>Ben Saad 2013</strong></td>
<td>142 men age 35–60 years</td>
<td>Avg 36 (±22) WP-years</td>
<td>Tabakel (sweetened tobacco)</td>
<td>Yes</td>
<td>WP vs cigarette</td>
<td>+24.0</td>
<td>+14.0</td>
<td>+13.0</td>
<td>NE</td>
</tr>
<tr>
<td><strong>Ben Saad 2011</strong></td>
<td>110 men, age 20–60 years</td>
<td>Median 14 WP-years</td>
<td>Unspecified</td>
<td>Yes</td>
<td>WP vs reference values</td>
<td>t</td>
<td>t</td>
<td>t</td>
<td>t</td>
</tr>
<tr>
<td><strong>Mutairi 2006</strong></td>
<td>62 persons average age 9.2 (±12.2) years</td>
<td>Avg 23.7 (±8.3) years smoking 1–2 times/day</td>
<td>Unspecified</td>
<td>Yes</td>
<td>WP vs cigarette WP vs non-smokers</td>
<td>−14.6</td>
<td>∼21.9</td>
<td>∼13.8</td>
<td>∼10.0</td>
</tr>
<tr>
<td><strong>Aydin 2004</strong></td>
<td>25 persons average age 18.2 (±12.2) years</td>
<td>Avg 23.7 (±8.3) years smoking 1–2 times/day</td>
<td>Jurak (tobacco-fruit mixture)</td>
<td>No</td>
<td>WP vs non-smokers WP vs cigarette WP vs passive cigarette smokers</td>
<td>−1.1 (NS)</td>
<td>+2.49 (NS)</td>
<td>+5.08</td>
<td>NE</td>
</tr>
<tr>
<td><strong>Kiter 2000</strong></td>
<td>397 men, age 18–85 years</td>
<td>Average 28 (±11.2) years of 17.9 (±8.9) g tobacco/day</td>
<td>Chinese WP tobacco</td>
<td>Yes</td>
<td>WP vs non-smokers WP vs cigarette WP vs cigarette passive</td>
<td>−9.4</td>
<td>−6.1</td>
<td>−12.1</td>
<td>NE</td>
</tr>
<tr>
<td><strong>Mohammad 2013</strong></td>
<td>788 women, age 44 + years</td>
<td>Not reported</td>
<td>Jurak (tobacco-fruit mixture)</td>
<td>Yes</td>
<td>WP vs non-smokers WP vs cigarette WP vs passive cigarette passive</td>
<td>−9.4</td>
<td>−6.1</td>
<td>−12.1</td>
<td>NE</td>
</tr>
<tr>
<td><strong>She 2014</strong></td>
<td>1238, mostly men, age 40+ years</td>
<td>Average 28 (±11.2) years of 17.9 (±8.9) g tobacco/day</td>
<td>Chinese WP tobacco</td>
<td>Yes</td>
<td>WP smokers vs non-smokers WP smokers vs non-smokers</td>
<td>−9.4</td>
<td>−6.6</td>
<td>−4.5</td>
<td>NE</td>
</tr>
<tr>
<td><strong>El-Fayez 1988</strong></td>
<td>441 men, 154 women smokers, 878 total participants, men 20–59 years, women 17–59 years</td>
<td>Not reported</td>
<td>Jurak (tobacco-fruit mixture)</td>
<td>Yes</td>
<td>WP smokers vs non-smokers WP smokers vs non-smokers</td>
<td>−9.4</td>
<td>−6.6</td>
<td>−4.5</td>
<td>NE</td>
</tr>
<tr>
<td><strong>Boskabady 2014</strong></td>
<td>§</td>
<td>§</td>
<td>§</td>
<td>§</td>
<td>§</td>
<td>§</td>
<td>§</td>
<td>§</td>
<td>§</td>
</tr>
<tr>
<td><strong>Layoun 2014</strong></td>
<td>87 men, 45 women, age 33.4 (±13.29) years, exclusive WP smokers</td>
<td>§</td>
<td>§</td>
<td>§</td>
<td>§</td>
<td>§</td>
<td>§</td>
<td>§</td>
<td>§</td>
</tr>
</tbody>
</table>

*All pulmonary function values are differences (WP value—comparison group value). The units are % predicted, except FEV₁/FVC, which is a % ratio, or otherwise specified.

1FEV₁ and FEF₂₅–₇₅ decreased compared to reference values; no comparison group was included. FVC and FEV₁/FVC were non-significant in this comparison.

1†Per cent predicted value.

1Per cent predicted value; % pred, per cent predicted comparison group; Diff, difference; FEF₂₅–₇₅, forced expiratory flow between 25% and 75% (middle half) of the FVC; FEV₁, forced expiratory volume in 1 s; 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). In contrast, two studies found no association between WP and COPD, but were methodologically limited. One included women only and did not account for the total quantity of WP smoked; 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. The second study had a low COPD prevalence and inadequate power.

WPS was also associated with chronic bronchitis and emphysema in cross-sectional studies from Lebanon, Iran, China and a combination of Middle Eastern and North African countries. Overall, the studies were robust in design including randomisation, good survey designs, adequate power and controlling for cigarette smoking and other confounders. 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 1.87; adjusted OR=3.4 for >6 WP smoked per week; and adjusted OR=5.65 for >20 WP-years. 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. 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.

The association of physician-diagnosed asthma in Lebanon with WPS was of borderline significance after adjusting for cigarette smoking and other variables. 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. 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 vitro and in vivo studies. WPS resulted in increased airway resistance, lung inflammation, oxidative stress and catalase activity in animal lungs. Rats exposed to WPS over several weeks had higher red blood cell counts and haematocrit, supporting an association with chronic polycythaemia. WP smoke exposure led to decreased neutrophils, lymphocytes, eosinophils and interferon-γ and higher nitric oxide in the bronchoalveolar lavage fluid of asthmatic mice, similar to cigarette smoke exposure, and thus may contribute to asthma exacerbations by suppressing helper T1 cells. In humans, levels of inflammatory cytokines were decreased in the exhaled breath of WP smokers, while the bronchoalveolar lavage fluid of WPS with COPD had increased metalloproteinase two and nine gene expression similar to that of cigarette smokers with COPD. 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 and increased sister chromatid exchanges in lymphocytes and increased micronuclei in buccal mucosa cells. 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. Exposure of human alveolar cells to WP smoke resulted in reduced cell proliferation, cell cycle arrest and increased doubling time. Increased nuclear size, nuclear/cyttoplasmic ratio and FeRet ratio and decreased cytoplasm size were found in the oral mucosa cells of WP smokers.

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. 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, India and China and one Chinese cohort study support an association between WPS and lung cancer. A sixfold greater risk of lung cancer was noted among former Lebanese WP smokers and in a group of current Indian WP smokers. 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. Three studies also found an association between WPS and lung cancer in China and a meta-analysis reported a pooled OR of 2.12 for lung cancer in WPS. However, the Chinese studies did not account for cigarette smoking or Chinese long-stem pipe smoking or control for other possible confounders. Thus, while cigarette smoking is a well-established risk factor for lung cancer, 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 and Iran 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 WP. 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. One study 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). 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. A significant association between WPS and gastric cancer was also observed in a case–control study available in abstract form, also from Iran. 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. Another study reported associations with gastric and oesophageal cancers, but again the
<table>
<thead>
<tr>
<th>Study</th>
<th>Cancer type</th>
<th>Population</th>
<th>Study type</th>
<th>Controlled for cigarette smoking?</th>
<th>Adjusted for other confounders?</th>
<th>OR (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu 2013</td>
<td>All cancer death</td>
<td>20,033 Bangladeshi individuals</td>
<td>Prospective community-based</td>
<td>No</td>
<td>Yes</td>
<td>Adjusted=2.5 (1.08 to 5.82)</td>
<td></td>
</tr>
<tr>
<td>Auon 2013</td>
<td>Lung</td>
<td>150 Lebanese individuals</td>
<td>Case-control</td>
<td>Yes</td>
<td>Yes</td>
<td>6.0 (1.78 to 20.26)</td>
<td>Non-significant OR after adjustment for confounders</td>
</tr>
<tr>
<td>Koul 2011</td>
<td>Lung</td>
<td>751 Indian individuals</td>
<td>Case-control</td>
<td>No</td>
<td>No</td>
<td>5.8 (3.9 to 8.6)</td>
<td></td>
</tr>
<tr>
<td>Gupta 2001</td>
<td>Lung</td>
<td>265 Indian individuals</td>
<td>Case-control</td>
<td>Yes</td>
<td>Yes</td>
<td>Adjusted=4.44 (1.2 to 16.44)</td>
<td>OR for Male heavy smokers older than 45 years</td>
</tr>
<tr>
<td>Lubin 1990</td>
<td>Lung</td>
<td>148 Chinese men</td>
<td>Case-control</td>
<td>No</td>
<td>No</td>
<td>*</td>
<td>Increased risk with cumulative exposure</td>
</tr>
<tr>
<td>Lubin 1992</td>
<td>Lung</td>
<td>1438 Chinese men</td>
<td>Case-control</td>
<td>Yes</td>
<td>Yes</td>
<td>Adjusted=1.8 (0.8 to 4.2)</td>
<td>Did not control for Chinese long-stem pipe smoking</td>
</tr>
<tr>
<td>Dar 2012</td>
<td>Oesophageal</td>
<td>2365 Indian individuals</td>
<td>Case-control</td>
<td>Yes</td>
<td>Yes</td>
<td>Adjusted=1.85 (1.41 to 2.44)</td>
<td>Higher risk with greater intensity, duration and cumulative WPS</td>
</tr>
<tr>
<td>Malik 2010</td>
<td>Oesophageal</td>
<td>330 Indian individuals</td>
<td>Case-control</td>
<td>Yes</td>
<td>No</td>
<td>Adjusted=21.4 (11.6 to 39.5)</td>
<td></td>
</tr>
<tr>
<td>Nasrollahzadeh 2008</td>
<td>Oesophageal</td>
<td>871 Iranian individuals</td>
<td>Case-control</td>
<td>Yes</td>
<td>Yes</td>
<td>Adjusted=1.66 (0.65 to 4.22)</td>
<td>OR for &gt;32 WP-years smoking</td>
</tr>
<tr>
<td>Sadjadi 2014</td>
<td>Gastric</td>
<td>928 Iranian individuals</td>
<td>Prospective cohort</td>
<td>Yes</td>
<td>Yes</td>
<td>Adjusted=3.4 (1.7 to 7.1)</td>
<td></td>
</tr>
<tr>
<td>Karajibani 2014</td>
<td>Gastric</td>
<td>92 Iranian individuals</td>
<td>Case-control</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>Statistically significant association was observed</td>
</tr>
<tr>
<td>Shakeri 2015</td>
<td>Gastric</td>
<td>922 Iranian individuals</td>
<td>Case-control</td>
<td>Yes</td>
<td>Yes</td>
<td>Adjusted=1.1 (0.3 to 3.3)</td>
<td>Also non-significant for cumulative WP use. Included a small percentage of WP smokers</td>
</tr>
<tr>
<td>Gunaid 1995</td>
<td>Gastric and Oesophageal</td>
<td>3604 Yemeni Individuals</td>
<td>Cross-sectional</td>
<td>Unclear</td>
<td>No</td>
<td>Not calculated ($\chi^2=2.646$, P&lt;0.05)</td>
<td>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.</td>
</tr>
<tr>
<td>Zheng 2012</td>
<td>Bladder</td>
<td>1134 Egyptian men</td>
<td>Case-control</td>
<td>Yes</td>
<td>Yes</td>
<td>Adjusted=1.1 (0.7 to 1.9)</td>
<td>ORs for smoking &gt;153 Hagar-years. ORs also insignificant for lesser exposures</td>
</tr>
<tr>
<td>Bedwani 1997</td>
<td>Bladder</td>
<td>308 Egyptian men</td>
<td>Case-control</td>
<td>Yes</td>
<td>Yes</td>
<td>Adjusted=0.8 (0.2 to 4.0)</td>
<td></td>
</tr>
<tr>
<td>Hosseini 2010</td>
<td>Prostate</td>
<td>274 Iranian men</td>
<td>Case-control</td>
<td>Yes</td>
<td>Yes</td>
<td>OR=7.0 (0.9 to 56.9)</td>
<td>Adjusted OR for WP was also non-significant (but not reported)</td>
</tr>
<tr>
<td>Lo 2007</td>
<td>Pancreatic</td>
<td>388 Egyptian individuals</td>
<td>Case-control</td>
<td>No</td>
<td>Yes</td>
<td>Adjusted=1.6 (0.9 2.8)</td>
<td>WP smoking was also not exclusive of other non-cigarette forms of smoking</td>
</tr>
<tr>
<td>Feng 2009</td>
<td>Nasopharyngeal</td>
<td>1251 North African individuals</td>
<td>Case-control</td>
<td>No</td>
<td>Yes</td>
<td>Adjusted=0.49 (0.20 to 1.43)</td>
<td>Had small numbers of WP smokers</td>
</tr>
</tbody>
</table>

* 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.\textsuperscript{104} 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,\textsuperscript{97} two case-control studies\textsuperscript{103, 106} 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,\textsuperscript{107} pancreatic\textsuperscript{108} and nasopharyngeal carcinoma,\textsuperscript{109} is very weak.

### Obstetrical and perinatal outcomes

WPS has been associated with obstetric and perinatal complications including low birthweight (LBW),\textsuperscript{110-117} infant mortality,\textsuperscript{118} low APGAR scores,\textsuperscript{119} and pulmonary complications at birth.\textsuperscript{116} Studies were primarily retrospective or cross-sectional and were conducted in Lebanon,\textsuperscript{110, 114-116} Qatar,\textsuperscript{111} Iran,\textsuperscript{112, 113} the Gaza Strip\textsuperscript{117} and Cambodia.\textsuperscript{118}

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.\textsuperscript{110} This study is limited, however, by a lack of control for important confounders such as alcohol and other substance intake.\textsuperscript{110} Another case-control study found 3.5 times greater odds (95% CI 1.1 to 12.6) of LBW among WPS mothers at birth.\textsuperscript{116} Studies were primarily retrospective or cross-sectional and were conducted in Lebanon,\textsuperscript{110} Qatar,\textsuperscript{111} Iran,\textsuperscript{112, 113} the Gaza Strip\textsuperscript{117} and Cambodia.\textsuperscript{118}

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.\textsuperscript{117} While a meta-analysis of three of the aforementioned studies\textsuperscript{110, 112, 116} reported an overall 2.12 times odds of LBW in association with WPS,\textsuperscript{7} these and several additional studies\textsuperscript{111, 114, 115} that support an association between LBW and WPS did not account for concomitant cigarette smoking.\textsuperscript{111, 114, 115}

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.\textsuperscript{113} 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.\textsuperscript{116} 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.\textsuperscript{118}

Furthermore, one Lebanese prospective study suggested that exclusive WPS may be associated with increased fetalisation 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.\textsuperscript{119} 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.\textsuperscript{120} 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.\textsuperscript{121} Thus, most studies on the above perinatal outcomes associated with WPS were methodically 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,\textsuperscript{122} larger probing depth\textsuperscript{123} and poor gingival health as measured by plaque levels and gingival index.\textsuperscript{124} This is probably not attributable to a change in the periodontal microflora, but rather to changes in the periodontal pocket depth in smokers.\textsuperscript{125} WPS is also associated with vertical periodontal bone defects, most severe among heavy WP smokers and separate from cigarette smoking effect.\textsuperscript{126} In addition, WPS was associated with three times the risk of developing dry socket after dental surgery.\textsuperscript{127} Overall, these cross-sectional studies provide supportive evidence for periodontal disease in exclusive WP smokers; however, adjustment for confounders was either absent\textsuperscript{127} or incomplete in most cases.\textsuperscript{123, 124, 126} Thus, more robust studies are still needed.

### Oral lesions

Three cross-sectional studies from India,\textsuperscript{128} Saudi Arabia,\textsuperscript{129} and Yemen\textsuperscript{130} 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.\textsuperscript{128} Other studies found insignificant or weak associations with suspicious oral lesions\textsuperscript{129} and leukoplakia.\textsuperscript{130} 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.\textsuperscript{131, 132} 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.\textsuperscript{132} 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.\textsuperscript{131} 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.\textsuperscript{133} Decreased BMD (lumbar spine,\textsuperscript{134, 135} femur neck, total hip, total body)\textsuperscript{135} was also associated with WPS in two other studies after adjustment for confounders including a cross-sectional study of 1880 postmenopausal women\textsuperscript{132} and a retrospective cohort study of
60 WP smokers and 120 non-smokers. 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, after adjusting for confounders in two of the studies. A meta-analysis that pooled the results of these studies reached the same conclusion.

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. Pulmonary aspergillosis was also reported in one WP smoker with leukemia in association with a positive fungal culture from the tobacco used. 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. 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. Further cross-sectional studies reported elevated urine microalbumin, low back pain and increased risk of gastroesophageal reflux disease among exclusive WP smokers. Increased attic retractions, which predispose to cholesteatomas and possibly hearing loss, were reported in 80 ears of WP smokers. WPS was associated with other miscellaneous conditions in several case reports including a case of hand eczema after contact with a WP tube, acute eosinophilic pneumonia, two cases of squamous cell carcinoma and lower lip keratoacanthoma and ulcerative colitis flare after discontinuing WPS. Finally, WPS was associated with lower overall health-related quality of life in a cross-sectional study of 1673, after adjusting for cigarette smoking and other variables. 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. 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 (moassal) 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 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 (FEV1, FVC, FEV1/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.

Contributors The idea for this manuscript arose in consultation with the scientific committee for the Second International Conference on Waterpipe Smoking Research (GSZ is a member of this committee). The literature search was performed by ZME, with GSZ overseeing the search. All authors contributed to the writing and editing of this article. GSZ is the guarantor.

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