A Systematic Review of Effects of Waterpipe Smoking on Cardiovascular and Respiratory Health Outcomes

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ABSTRACT

BACKGROUND: Waterpipe smoking (WPS) is a social custom common in many Middle Eastern, North African, and Asian countries and has become increasingly popular in the US, especially among youth; however, WPS smoking may be increasing in the US adult population as well. There is a common belief among waterpipe (WP) smokers that WPS is less harmful than smoking cigarettes. Thus, this review aims to systematically explore the literature on the effects of WP tobacco smoking with a particular focus on cardiovascular and respiratory health outcomes as well as on oxidative stress, immunity, and cell cycle interference health outcomes.

METHODOLOGY: We conducted a systematic review, guided by the criteria of The Preferred Reporting Items for Systematic Reviews and Meta-Analyses, using the following online databases MEDLINE, CINAHL, ScienceDirect, PMC, and Cochrane Library. Results were summarized qualitatively.

RESULTS: Forty studies met the inclusion criteria established for this review. Based on the existing evidence, several cardiovascular and respiratory physiologic health indicators and conditions have been shown to be negatively affected by WPS. In addition to the effects of nicotine and chemical toxicant exposures, WPS was significantly associated with an increase in heart rate, blood pressure, and lower pulmonary function test results, as well as a number of health conditions such as lung cancer, alterations in oxidative stress, immunity, and cell cycle interference.

CONCLUSION: The current literature provides evidence that WPS is associated with a number of negative health indicators and outcomes. There is need for more research related to WPS and its effects on health so that appropriate campaigns and prevention interventions can be implemented to control the epidemic increase of WPS in the US.

KEYWORDS: waterpipe smoking, hookah, cardiovascular disease, respiratory system illness, health effects, cancer

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Introduction

Waterpipe smoking (WPS), commonly known as hookah smoking, is a growing worldwide social phenomenon practiced in group settings such as hookah bars or cafés in which patrons purchase waterpipe (WP) tobacco and then share it during smoking sessions. WPS is a symbol of social sharing and cultural identity.[1–4] The unregulated social aspect of smoking WP, combined with the myth that WPS is less harmful than smoking cigarettes, makes it difficult for those newly exposed to WPS to recognize the potential harmful effects, particularly when evidence is still being established. WPS sessions vary in length, ranging from 30 to 90 minutes,[5–7] depending on the number of those sharing or the number of tobacco pouches used during a smoking session. A single WPS session may involve 50 to 100 times the smoke volume inhaled from a single cigarette.[8–16] In one study, once-a-day WP smokers were found to have levels of plasma nicotine concentration comparable to those of 10 cigarettes/day smokers,[8,17] and evidence suggests that WP use is associated with health risks comparable to those caused due to cigarette smoking.[18] WPS is also associated with nicotine addiction[19] and includes negative health consequences from secondhand smoke exposure.[20]

Despite the evidence, most WP users are misinformed about the risks of use. Of particular concern is WP use in the Eastern Mediterranean Region (which includes Middle Eastern and North African countries). Prevalence of WPS in this region is the highest in the world, ranging between 20% and 70%.[6] WPS appears to be on the rise, especially among youth and college-age young adults.[9–11,21,22] Research focused on WPS and WP secondhand smoke is garnering attention in the US and across the globe; however, there continues to remain a gap in knowledge about WPS and WP secondhand

smoke in the US in comparison to other countries such as those in the Middle East. The World Health Organization's (WHO) report on research for universal health coverage notes that smoking is responsible for about six million deaths annually worldwide; more than five million of these deaths occur in primary smokers, and the remainder die as a result of secondhand smoke exposure.[23,24] Despite the remarkable success of public health policies in regulating and reducing cigarette smoking, WPS has been flourishing worldwide, thus emphasizing the importance of strict tobacco control policies and regulations that are also WP oriented. Monitoring and regulating tobacco use should target not only cigarette smoking but also all forms of tobacco in order to combat the worldwide spread of WPS and the misconception that it is less harmful than other forms of tobacco.[18]

Two systematic reviews conducted by Akl et al[25] and El-Zaatari et al[26] did an excellent job of summarizing the health effects of WPS on multiple organ systems. The systematic review presented here offers additional evidence by extending the search to include CINAHL, ScienceDirect, PMC, and Cochrane Library databases. Additionally, our systematic review adds five additional studies to the previously published systematic review[26] and includes a comprehensive focus and inclusion of studies reporting cardiovascular and respiratory health outcomes as well as on oxidative stress, immunity, and cell cycle interference health outcomes. This review is important in order to compel evidence about the direct association between cardiovascular, respiratory illness, and WPS. In addition, this review is important to develop scientifically based regulatory policies with regard to WPS and WP secondhand smoke exposure, as tobacco control policy makers need reliable up-to-date scientific evidence to inform concerns aimed at: (1) establishing health warning campaigns and label packaging that identifies the known risks of WPS, (2) prevention of the sale of WP tobacco to minors, and (3) targeting prevention control and taxation similar to those used to combat cigarette smoking.

Thus, the aim of this systematic review was to assess the most up-to-date published literature in order to synthesize the evidence about the effects of WPS and exposure to WP secondhand smoke on health outcomes. The research question was: How does WPS affect the cardiovascular, respiratory, and immunity-related health outcomes of people who smoke waterpipe?

Methodology

Protocol development. We developed the protocol specifying all aspects of the review methods before commencing the review. These included the following: inclusion criteria for studies, search strategy, screening method, abstraction, quality assessment, and data analysis. This aspect of the design was planned to minimize the effect of our possible bias on the review.

Search strategy. The review of the literature was conducted between May and August 2015 by searching articles published in English using the following electronic databases: MEDLINE, CINAHL, ScienceDirect, PMC, and Cochrane Library. Our literature search was restricted to articles published between January 1, 2005, and August 31, 2015. Search terms included combinations of the following: "waterpipe," "water-pipe," "water pipe," "hookah," "shisha," "narghile," "narguile," "hubble bubble," "goza," "respiratory system illness," "cardiovascular diseases," "health concerns," "health effects," "cancer," and "cardiorespiratory." We included original research studies conducted inside and outside of the US if published in English.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[27] outlined this literature search and review. All of the originally retrieved articles were saved in an EndNote library. Using the EndNote library search box, these articles were screened for duplicates, the search terms, and the word "review" in the title. Articles were deleted from the EndNote library if their titles were duplicates, did not contain the key terms, or had the words "review," "expert's opinion," or "qualitative." Abstracts of the remaining articles were also scanned for the search terms and the words "review," "expert's opinion," and "qualitative." Articles were deleted from the library if their abstracts did not contain the search terms or had the words "review," "expert's opinion," and "qualitative." Abstracts and full texts of the remaining articles were read to check for their relevance to the searched topics. Additional articles were excluded because they were literature reviews. The remaining articles were included in this systematic review.

Data abstraction. The data abstraction form was piloted over five studies and used to abstract general information about the paper, where the study was conducted, study characteristics, populations studied, design features that affected the quality of the study and the validity of the results, outcome measures, and quality assessment data. Abstraction was performed in duplicate independently. Any disagreement was resolved by discussion.

Data analysis. Four reviewers extracted data from the papers; two reviewers worked independently on each paper and then amalgamated the results. Discrepancies were resolved by referral back to the original papers and discussion. We did not combine the results of the studies because of the heterogeneity of design, outcomes, and populations. In our narrative analysis, we consider the results in relation to the design and quality of the studies.

Results

Our search of the literature identified 59 potentially relevant articles, but only 40 met the inclusion criteria (Fig. 1). The 40 articles regarding the effects of WPS on health outcomes were thoroughly reviewed. A review across the 40 articles resulted in the effects of WPS being categorized into four areas of focus by health outcome: (1) cardiovascular, (2) respiratory, and (3) oxidative stress, immunity, and cell cycle interference. Research studies involving humans (n = 37/40) were mainly conducted in the Middle East (28/37; 75.7%). Other human research studies were conducted in the US (5/37; 13.5%), the

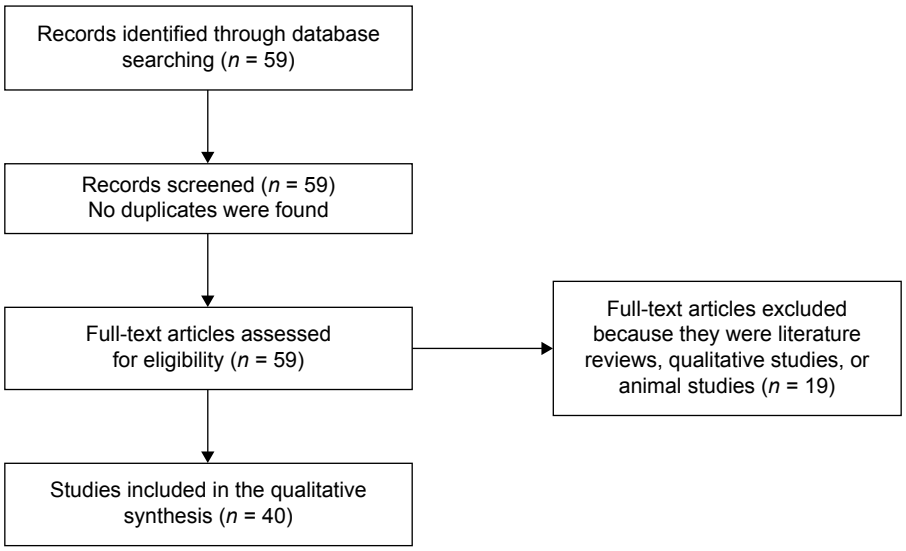

Figure 1. Process of the literature search.

United Kingdom (1/37; 2.7%), the Czech Republic (1/37; 2.7%), China (1/37; 2.7%), and Bangladesh (1/37; 2.7%), and one study was conducted in both the Middle East and North Africa (2.7%). In vitro studies (n = 2) and articles that did not provide information regarding participant age (n = 4) were excluded from calculation of participants' average age.

Twelve studies used a case–control study design.[7,15,28–37] A cross-sectional design (n = 12) was also used in many studies.[38–49] Other study designs included a quasi-experimental design (n = 3),[50–52] a time series (n = 2),[14,53] cohort (n = 2),[54,55] single group pretest–postest (n = 2),[56,57] experimental (n = 2),[58,59] a crossover design (n = 2),[60,61] secondary analysis (n = 1),[62] repeated measures (n = 1),[63] and case report (n = 1).[64]

Cardiovascular outcomes.

Overview. As seen in Table 1, 15 articles examined cardiovascular outcomes and focused on multiple blood pressure factors such as mean arterial pressure, vascular resistance, systolic and diastolic blood pressure, and mean blood pressure.[14,15,26,39,40,50,54] In addition, factors such as heart rate, heart rate variability, and blood flow obstruction were examined.[14,15,38,51,54,55,60,61] There was some overlap among studies examining cardiovascular outcomes and respiratory outcomes.[39,51,55] Also, other cardiovascular studies included variables such as toxic metals and cancer and overall stroke-related mortalities.[28,29,54,62]

Synthesis of results. Several cardiovascular outcomes are affected by WPS (Table 1). Vascular resistance demonstrated a significant increase after the use of WPS.[14,15] Significant increases were noted among all studies that examined heart rate and systolic, diastolic, and mean blood pressure.[38,39,41,47,50,51,54–56,60,61,63] There was a *drastic* increase in heart rate (50 beats per minute) noted in approximately 10% of participants 30 minutes following WPS in one study.[60] Heart rate variability significantly decreased after WPS.[60]

Also noted among WPS users was more severe coronary artery disease compared to nonsmokers and those who only smoked cigarettes.[30] One study found a moderate effect on venous outflow and vascular resistance.[15] Indeed, WPS users were 1.96 times more likely to die from cardiovascular disease than nonsmokers, and WP users had more coronary artery disease than nonsmokers.[62]

Respiratory outcomes.

Overview. Twenty-one articles (Table 2) examined respiratory parameters. Nine respiratory studies focused on the effects of WPS on either overall pulmonary function parameters or components of pulmonary function such as forced expiratory volume.[32,33,35,42,47,50,52,53,56,65] Nearly half (10 of 21) explored respiratory symptoms (shortness of breath, cough, and wheezing) or diseases (chronic pulmonary obstructive disorder, chronic bronchitis, and asthma).[32–34,43–46,49,52,56] Two studies examined lung cancer as an outcome variable of WPS.[31,36] One study explored the concept of *lung age* as a descriptor of WPS use, and one study explored the concept of respiratory quality of life.[48,56] Finally, one case study focused on severe carbon monoxide poisoning from smoking WP.[64]

Synthesis of results. There is evidence of the negative effects of WPS on respiratory outcomes (Table 2). Compared to individuals who did not smoke, WPS users had significantly ($P < 0.05$) lower scores on overall pulmonary function tests (PFTs).[16,32,33] The forced expiratory volume significantly ($P < 0.001$) decreased in individuals in the WPS group compared to nonsmokers ($P < 0.05$) and after WPS use.[42,56] Two studies, however, found no difference in forced expiratory volume between WPS and cigarette use, and one study demonstrated a significant ($P < 0.05$) decrease in forced expiratory volume of cigarette smokers compared to WPS users.[47,35,52] WP users demonstrated PFTs comparable (no significant difference between groups) to individuals who smoked cigarettes and deeply inhaled.[33]

Table 1. WPS and cardiovascular effects.

STUDY	STUDY DESIGN & LOCATION	SAMPLE SIZE & CHARACTERISTICS	STUDY PURPOSE/ AIMS	FINDINGS	COMMENTS/LIMITATIONS
Alomari et al, 2015	Case-control design Jordan	• Age range: 18–35 years old • Average age in years (Mean ± SD) = 22.7 ± 4.8 • N = 53 • Convenience sampling	• Determine effect of water-pipe smoking on the vascular function. • Investigate whether the effect of water-pipe smoking can be reversed through lifestyle changes (exercising).	• There was a moderate effect on the venous outflow (d = 0.30) and post-occlusion vascular resistance (d = 0.32) along with a small effect on the forearm post-occlusion blood flow (d = –0.19) after waterpipe smoking. • While resting blood flow had a strong correlation with habitual physical activity (r = 0.50), vascular resistance had a moderate correlation with physical fitness (r = –0.40). • Both venous capacitance and post-occlusion blood flow had a moderate relationship with handgrip strength (r = 0.30). • Resting venous capacitance had a moderate relationship with walking for 6 minutes (r = 0.30).	• Small sample size. • No clear description of demographics of the sample.
Alomari et al, 2014	Time-series design Jordan	• Age range: 18–35 years old • Average age in years (Mean ± SD) = 22.7 ± 4.8 • N = 53 • Convenience sampling	Investigate how waterpipe (WP) smoking affects central and peripheral cardiovascular systems.	• Mean arterial blood pressure ($P = 0.02$), diastolic blood pressure ($P = 0.013$), rate pressure product ($P = 0.002$), heart rate ($P = 0.003$) and vascular resistance after occlusion ($P = 0.003$) increased significantly after waterpipe smoking. • Waterpipe smoking led to significant decrease in after occlusion blood flow ($P = 0.035$) and outflow ($P = 0.012$). • Post-smoking changes in the periphery significantly correlated with changes in the central cardiovascular components ($P < 0.05$). • After WP smoking, there is a weak positive relationship between changes in resting blood flow (Bf) and heart rate (HR) (r = 0.36, $P = 0.008$). • After WP smoking, there is a weak positive relationship between changes in resting Bf and resting blood flow (RPP) (r = 0.35, $P = 0.01$). • After WP smoking, there is weak negative relationship between changes in resting vascular resistance (Vr) and HR (r = –0.3, $P = 0.024$). • After WP smoking, there is a weak positive relationship between changes in resting Vr and diastolic blood pressure (DBP) (r = 0.3, $P = 0.036$). • After WP smoking, there is a positive relationship between changes in resting Vr and mean arterial pressure (MAP) (r = 0.32, $P = 0.024$).	• Small sample size. • No clear description of demographics of the sample.
Cobb et al, 2012	Cross-over study design United States of America	• Age range: 18–50 years old • Average age in years (Mean ± SD) = 21.6 ± 2.7 • N = 32 (69% non-White, 31% White) • Convenience sample	Determine the extent of carbon monoxide (CO), plasma nicotine level exposure on heart function after smoking tobacco-based and a tobacco-free waterpipe products.	• Heart rate variability significantly ($P < 0.01$) decreased after waterpipe smoking. • Although both products increased CO, only tobacco-based product ($P < 0.01$) increased plasma nicotine, blood pressure, and heart rate. • Use of tobacco-free product led to more smoke inhalation.	• No clear description of demographics of the sample (possible selection bias).
Hakim et al, 2011	Double-blind, quasi-experimental, prospective design Israel	• Age range: 18.3–65.1 years old • Average age in years (Mean ± SD) = 32.35 ± 23.36 • N = 45 • Convenience sampling	Examine how 30-minutes of waterpipe (WP) smoking affects inflammatory and cardiorespiratory systems along with carboxyhemoglobin (COHb) levels.	• WP smoking significantly increased COHb levels from 1.47% ± 0.57% (median 1.4) to 9.47% ± 5.52% (median 7.4), $P < .001$. • WP smoking significantly increased systolic and diastolic blood pressures (systolic, 119.52 ± 12.07 mmHg vs 131.98 ± 17.8 mmHg; diastolic, 74.84 ± 7.89 mmHg vs 82.98 ± 12.52 mmHg, respectively; $P < .001$). • WP smoking significantly increased heart rate from 80.39 ± 9.92 beats/min to 95.59 ± 17.41 beats/min, $P < .001$.	• No clear description of demographics of the sample. • Measurement of "general feeling" is too abstract. • Exhaled breath condensate was performed only on 20 participants.

				• WP smoking significantly increased respiratory rate 14.36 ± 1.63 breaths/min to 16.68 ± 2.24 breaths/min, $P < .001$. • WP smoking significantly decreased peak expiratory flow rate ($P = 0.0004$).	• No assessment was done on reversibility of the symptoms.
Kadhum et al, 2014	Cross-sectional design United Kingdom	• Age range: 18–25 years old • Average age was not reported • N = 61 (38% Asian-Arabian, 31% Asian-Pakistani, 20% Asian-Indian, 7% Black-African, 5% White-British) • Convenience sampling	Examine how shisha (waterpipe) smoking affects the cardiovascular system.	• Waterpipe smoking significantly increased heart rate from 77 to 91 bpm ($P < 0.001$), mean arterial blood pressure from 96 mmHg to 108 mmHg ($P < 0.001$), and carbon monoxide from an average of 3 to 35 ppm ($P < 0.001$). • Carbon monoxide did not have a significant relationship with differences in systolic blood pressure, diastolic blood pressure, heart rate, and mean arterial pressure.	• Variability in smoking time (45–90 minutes) may have influenced the results.
Khlifi et al, 2015a	Case-control study Tunisia	• Adults • Specific age range was not reported • Average age in years (Mean) = 44.91 • N = 261 • Convenience sampling	Determine the nature of the relationship between nasal polyposis (NP) and metal blood levels.	• The control group (1.2 μg/L) had significantly ($P = 0.008$) lower metal blood levels of arsenic (As) compared to patients with NP (2.1 μg/L). • Non-smokers had significantly lower arsenic blood levels than tobacco smokers ($P = 0.031$). • NP disease was significantly associated with shisha (waterpipe) smoking (OR = 14.1, $P < 0.001$), environmental exposure (OR = 10.1, $P < 0.001$), and high levels of blood As (OR = 2.1, $P = 0.026$). • All four stages of NP disease were significantly associated with Cr blood levels ($P = 0.004$).	• Arsenic levels may vary depending on the shisha producer. • High As blood levels may have occurred through concurrent environmental exposure and shisha consumption.
Khlifi et al, 2015b	Case-control study Tunisia	• Adults • Specific age range was not reported • Average age in years (Mean) = 44.91 • N = 261 • Convenience sampling	Evaluate whether exposure to cadmium (Cd) and nickel (Ni) is related to pathogenesis of Nasosinusal Polyposis (NSP).	• Compared to non-consumers, tobacco consumers, both controls ($P = 0.001$) and patients ($P = 0.018$) had significantly higher Ni and Cd concentrations. • NSP had the most significant correlation with shisha smoking (OR = 14.1, $P < 0.001$), environmental exposure (OR = 10.1, $P < 0.001$), high levels of blood Cd (OR = 3.5, $P = 0.027$), and occupational exposure (OR = 1.7, $P = 0.040$). • All four stages of NSP correlated significantly with Ni blood levels in both the right ($P = 0.001$) and left ($P = 0.007$) nasal cavities.	• It is possible that the Ni and Cd levels are due to concurrent environmental exposure, cigarette smoking, tobacco chewing, and shisha consumption.
Selim et al, 2013a	Case-control design Egypt	• Age range: 25–35 years old • Average age in years (Mean) = 29.1 • N = 70 • Convenience sampling	Examine and compare how shisha (waterpipe) and cigarette smoking affect endothelial function.	• Compared to cigarette smokers (12 ± 3.4%) and non-smokers (21.5 ± 2.5%), shisha (7.9 ± 3.8%) smokers had a significantly impaired flow-mediated dilation ($P < 0.001$).	• The utilized brachial artery duplex ultrasonography needs to be verified as a reliable measuring tool for endothelial function.
Selim et al, 2013b	Prospective cohort design Egypt	• Adults • Specific age range and average age were not reported • N = 287 • Convenience sampling	Examine whether shisha (waterpipe) smoking affects the health of coronary artery.	• Smokers of both shisha and cigarettes had significantly higher systolic blood pressure ($P = 0.009$) and heart rate ($P < 0.001$) than exclusively cigarette smokers, shisha smokers, or non-smokers. • Exclusively shisha smokers had a significantly higher Duke Jeopardy Score (DJ) and severity of coronary artery disease ($P = 0.012$). • 71.43% of shisha smokers with coronary artery disease (CAD) had an elevated DJ score (>6), which was significantly different from the rest of the groups with CAD ($P = 0.008$).	• Study results may have been influenced by the medications participants took at the time of the study. • Generalizability of the study may have been limited by the reduced diversity in the sample.

(*Continued*)

Table 1. (*Continued*)

STUDY	STUDY DESIGN & LOCATION	SAMPLE SIZE & CHARACTERISTICS	STUDY PURPOSE/ AIMS	FINDINGS	COMMENTS/LIMITATIONS
				• Systolic blood pressure ($P = 0.001$) and resting pulse ($P < 0.001$) were significantly higher in shisha smokers. • Compared to non-shisha smokers (5.762 ± 3.062), shisha smokers (6.961 ± 3.238) had a significantly higher mean DJ score ($P = 0.004$).	
Wu et al, 2013	Secondary analysis of national data Bangladesh	• Age range: 18–75 years old • Average age was not reported • N = 20,033	Determine the association between hookah, cigarette/bidi smoking and mortality related to cancer, all-cause, and cardiovascular disease (CVD).	• Hookah smoking had a weak association with cancer and all-cause mortality. • Hookah and cigarette/bidi smoking were not significantly related to CVD-related mortality. • The hazard ratios (HR) of hookah and cigarette smoking were not distinguished because most of the sample smoked both products. • Female hookah smokers had an increased risk of all-cause mortality (HR 2.81, 1.78 4.43). • After adjusting for cigarette smoking, hazard ratios for deaths related to cancer and associated with hookah smoking decreased from 1.38 (95% CI 0.86 2.22) to 1.21 (95% CI 0.74 1.99). • Compared to non-smokers, people who smoked hookah at least once every other day were 1.96 (95% CI 1.05 3.63) more likely to have a death related to ischemic heart disease. • Hookah smoking was related to 8.9% and 7.5% of all-cause deaths in women and men, respectively.	• Results of this study should have been adjusted for environmental exposure to smoke and air pollution. • Due to differences in product production, bidi and cigarettes should have been analyzed separately.
Shaikh et al, 2008	Cross-sectional design United Arab Emirates	• Age range: 17 and older • Average age in years (Mean) = 33.16 • N = 202 • Convenience sampling	Evaluate acute symptoms of waterpipe (WP) smoking (WPS) on cardiovascular and respiratory systems of WP smokers in Ajman, United Arab Emirates (UAE).	• There was a significant increase ($P < 0.001$) in heart rate (6.30 ± 0.60 bpm), diastolic blood pressure (2 ± 0.7 mmHg), systolic blood pressure (16 ± 1 mmHg), and respiratory rate (2 ± 2 breathes/min). • Among the studied WP smokers, 77% of these adults chose WPS for leisure and 92% considered WPS harmful to health.	• Convenience sampling. • Only one gender (male) is studied. • Observations are made on only one day out of participants' lives (i.e., increase in BP or HR could be due to stress or other factors, such as diet).
Al-Kubati et al, 2006	Cross-sectional design Czech Republic	• Age range: 20–40 years old • Average age in years (Mean ± SD) = 27.2 ± 6.4 • N = 20 • Convenience sampling	Determine acute results of waterpipe (WP) smoking (WPS) on blood pressure (BP), heart rate (HR), and the baroreflex control of HR.	• There was a significant increase in mean BP (82 ± 10 to 95 ± 11 mmHg, $P = 0.0001$), diastolic BP (67 ± 11 to 81 ± 11 mmHg, $P = 0.0002$), and systolic BP (110 ± 13 to 123 ± 12 mmHg, $P = 0.004$). • There was a significant decrease in baroreflex sensitivity (9.16 ± 4 to 5.67 ± 3 ms/mmHg, $P = 0.003$), baroreflex sensitivity as HR changes per change of pressure (0.013 ± 0.005 to 0.011 ± 0.004 Hz/mmHg, $P = 0.3$ ns), pulse pressure (43 ± 10 to 41 ± 9 mmHg, $P = 0.46$ ns), and the inter-beat interval (846 ± 100 to 709 ± 109 ms, $P = 0.0003$).	• Small sample size. • Only evaluation of acute effects of WPS.
Shishani et al, 2014	Repeated-measures design United States of America	• Age range: 18–30 years old • Average age in years (Mean ± SD) = 23 ± 3.1	Evaluate smoking behaviors along with subjective and physiological effects of nicotine on young adult occasional waterpipe smokers.	• Compared to the non-nicotine condition, there was a significant increase in heart rate ($F = 7.92$, $P = 0.01$, partial $\eta^2 = 0.31$) and over time nicotine interaction ($F = 12.64$, $P = 0.01$, partial $\eta^2 = 0.41$). • Compared to the non-nicotine condition, the nicotine condition led to a significant increase in smoking duration ($P = 0.004$) and amount of puffs taken ($P = 0.03$).	• Small sample size. • Smoking occurred in laboratory, rather than natural, setting.

		• N = 22 (82% Caucasian, 4.5% African American, 4.5% Asian, 4.5% Hispanic, and 4.5% Middle Eastern) • Convenience sampling		• There was a significant decrease in the duration of puffs taken ($P = 0.03$) and the volume inhaled with each puff ($P = 0.02$). • The nicotine condition differed significantly from the non-nicotine condition in providing the factor headrush $F = 9.69$, $P < 0.001$, partial $\eta^2 = 0.31$), and the time by nicotine interaction ($F = 8.17$, $P = 0.02$, partial $\eta^2 = 0.30$).	
Eissenberg et al, 2009	Two-condition crossover design United States of America	• Age range: 18–50 years-old • Average age in years (Mean ± SD) = 21.4 ± 2.3 • N = 31 (71% Caucasian, 9.7% Asian, 3.2% African American, and 1.6% mixed or other ethnicity). • Convenience sampling	Analyze toxicant exposure to waterpipe (WP) tobacco and cigarette smoking in a controlled laboratory setting.	• Compared to pre-smoking condition, heart rate was significantly elevated at 5, 10, 15, 20, 25, and 35 minutes during the cigarette session and at 5-minute intervals during the waterpipe session (P's < 0.001). • There was a significant ($P < 0.001$) increase in carbon monoxide level by 23.9 ppm for WP smoking (SD = 19.8) and 2.7 ppm for cigarette use (SD = 1.8). • Compared to cigarette use (M = 1.3%, SD = 0.5; $P < 0.001$), carboxyhemoglobin was three time higher after WP smoking (M = 3.9%, SD = 2.5, $P < 0.001$). • There was similarity between peak nicotine levels in the two sources (waterpipe M = 10.2 ng/mL, SD = 7.0; cigarette M = 10.6 ng/mL, SD = 7.7). • Compared to cigarette smoking (1.0 L), WP smoking led to a significantly higher mean total puff volume ($P < 0.001$).	• Small sample size. • Concurrent cigarette smoking in participants. • Laboratory, rather than natural, setting.
Al-Osaimi et al, 2012	Cohort design Kuwait	• Age range: 18–66 years old • Average age (Mean) = 41 • N = 220 • Convenience sampling	Evaluate acute effects of waterpipe smoking (WPS) on heart rate and oxygen saturation.	• Compared to baseline, WPS significantly decreased participants' oxygen saturation by an average of 0.39% ($P < 0.001$). • After adjustment for gender and age, the only variables associated with change in oxygen saturation (more than 2% decrease) were asthma (OR = 3.4, 95% CI = 1.3–9.3) and history of smoking (OR = 2.4, 95% CI = 1.02, 5.7). • Compared to baseline, WPS significantly increased heart rate by an average of 15 bpm ($P < 0.001$). • After adjustment, increase in heart rate by over 15 bpm was explained by male gender, younger age, frequent shisha smoking, and change in head weight by more than 4 g. • After 30 minutes of WPS, a drastic increase in heart rate of over 50 bpm was observed in only 6.4% of participants. • After 30 minutes of WPS, heart rate levels over 200 bpm were observed in 3.6% of participants.	• Convenience sample.

Table 2. WPS and respiratory effects.

STUDY	STUDY DESIGN	SAMPLE SIZE & CHARACTERISTICS	STUDY PURPOSE/ AIMS	FINDINGS	COMMENTS/LIMITATIONS
Aoun et al, 2013	Case-control design Lebanon	• Age range: 18 years and older • Average age in years (Mean) = 59.74 • N = 150 • Convenience sampling	Investigate whether there is any relationship between lung cancer, waterpipe smoking, and electricity generator exposure (a potential source of diesel exhaust to the community).	• The main risk factors of lung cancer among Lebanese women are use of heating fuel (ORa = 9.76/95% CI: 2.15–44.30/ $P = 0.003$) and cigarette smoking (ORa = 9.12/95% CI: 1.81–46.00/$P = 0.007$). • The main risk factors of lung cancer in Lebanese men are family history of cancer (ORa = 8.75/95% CI: 1.22–63.03/$P = 0.031$), consuming low quantities of fruits and vegetables (ORa = 10.54/95% CI: 1.76–63.24/$P = 0.010$), living near an electricity generator (ORa = 13.26/95% CI: 1.85–95.04/$P = 0.010$), and cigarette smoking (ORa = 156.98/95% CI: 5.90–417.4/$P = 0.003$). • Bivariate analysis revealed that waterpipe smoking was associated with a higher risk of lung cancer in males ($P < 0.009$).	• No clear description of demographics of the sample. • There is a possibility of selection and admission bias. • Authors admit to have a small number of participants who smoked waterpipe. • Authors believe some of the participants smoked both waterpipe and cigarettes.
Blank et al, 2011	Quasi expermintal I design United States of America	• Age range: 18–50 years old • Average age in years (Mean ± SD) = 20.5 ± 2.1 • N = 37 (8% African-American, 19% Asian, 54% Caucasian, 3% Hawaiian/Pacific Islander, and 16% mixed/other ethnicity) • Convenience sample	Investigate what health effects result from nicotine exposure during waterpipe tobacco smoking.	• The mean plasma nicotine concentration (3.6 ± 0.7 ng/mL) and heart rate (8.6 ± 1.4 bpm) significantly increased after waterpipe tobacco smoking ($P < 0.05$). • Placebo had no effect on these measurements (0.1 ± 0.0 ng/mL; 1.3 ± 0.9 bpm). • Both tobacco (3.8 ± 0.4%; 27.9 ± 2.6 ppm) and placebo (3.9 ± 0.4%; 27.7 ± 3.3 ppm) significantly increased carboxyhemoglobin and expired Carbon Monoxide ($P < 0.05$). • Both waterpipe and placebo reduced symptoms of nicotine/ tobacco abstinence and increased its direct effects.	• Participants are occasional users (2–5 smoking episodes/month). • Study results may not be applicable to more frequent smokers. • Study results from the solitary condition may differ from effects of group smoking.
Boskabady et al, 2014	Case-control design Iran	• Age range: 20–70 years old • Average age in years (Mean) = 44.72 • N = 673 • Cluster sampling	• Examine the prevalence of waterpipe smoking among the population of Mashhad. • Determine how quantity and duration of waterpipe smoking affect respiratory system and results of pulmonary function test (PFT).	• Compared to nonsmokers, waterpipe smokers showed significantly lower results on the PFT ($P < 0.05$ to $P < 0.001$). • Waterpipe smokers had significantly higher severity and prevalence of respiratory symptoms compared to nonsmokers ($P < 0.05$ to $P < 0.001$). • There was no statistically significant correlation between smoking duration, amount of smoking, total waterpipe smoking, and the respiratory symptoms. • Smoking duration, rate, and total amount of waterpipe smoking (except for maximum expiratory flow at 25%) had negative correlation with results of the PFT ($P < 0.05$ to $P < 0.001$).	• Subjective self-report of respiratory symptoms may have influenced the study results. • No clear description of demographics of the sample.
Boskabady et al, 2012	Case-control design Iran	• Age range: 20–70 years old • Average age in years (Mean) = 44.72 • N = 673 • Stratified sampling	Compare respiratory symptoms (RS) and results of pulmonary function test (PFT) between deep (S-DI) and normal (S-NI) inspiration cigarette smokers along with waterpipe smokers (WP).	• Nonsmokers had significantly higher results of PFT than WP, S-DI, and some S-NI smokers ($P < 0.05$ to $P < 0.001$). • Compared to nonsmokers, waterpipe smokers had significantly lower values for FVC ($P < 0.0001$), FEV_1 ($P < 0.0001$), MMEF ($P = 0.008$), PEF ($P = 0.0002$), MEF_{75} ($P < 0.0001$), MEF_{50} ($P = 0.003$), MEF_{25} ($P = 0.019$). • Most of the PFT values in S-NI were significantly higher than those in S-DI and WP smokers ($P < 0.05$ to $P < 0.001$). • Compared to nonsmokers, waterpipe smokers had significantly more wheezing ($P = 0.026$), chest tightness ($P = 0.0009$), and coughing ($P = 0.017$). • Compared to nonsmokers, waterpipe smokers had significantly more severe wheezing ($P = 0.006$), chest tightness ($P = 0.047$), coughing ($P = 0.004$), and sputum production ($P = 0.003$).	• No clear description of demographics of the sample. • Imitation of inspiration during regular smoking appears to be subjective.

				• Except for sputum production, nonsmokers had significantly lower prevalence of RS than the three groups of smokers ($P < 0.05$ to $P < 0.001$). • Except for the wheezing in S-NI, nonsmokers had significantly lower severity of RS compared to the S-DI and WP ($P < 0.05$ to $P < 0.001$). • Duration, rate, and total amount of WP smoking had negative correlation with PFT results ($P < 0.05$ to $P < 0.001$). • WP smoking did not have significant correlation with RS.	
Joseph et al, 2012	Cross-sectional design Lebanon	• Age range: 40 years and older • Average age in years (Mean) = 54.48 • N = 2,201 • Cluster sampling	Describe the differences between Lebanese nonsmokers and smokers in relation to the respiratory quality of life, using data from a cross-sectional national study on the prevalence of Chronic Obstructive Pulmonary Disease (COPD).	• Independent of the respiratory disease status, nonsmokers had a higher respiratory quality of life compared to smokers. • After adjusting for COPD severity, cumulative smoking of cigarettes and waterpipe, lower education, and environmental factors serve as independent predictors of a reduced respiratory quality of life.	• Data analysis included cumulative effect of cigarette and waterpipe smoking. • Clinical COPD Questionnaire needs to be compared to an equivalent, established questionnaire. • No clear description of demographics of the sample.
Koubaa et al, 2015	Time-series design Tunisia	• Age range: 18 years and older • Average age in years (Mean ± SD) = 44.7 ± 4.5 • N = 33 • Convenience sampling	Determine how interval exercise training program affects aerobic capacity and pulmonary function of hookah and cigarette smokers.	• Before the exercise intervention, the non-smokers had significantly higher pulmonary function than the hookah and cigarette smokers. • Hookah and cigarette smoking resulted in significantly lower values of forced expiratory volume at 1 second (FEV_1) ($P < 0.001$), peak expiratory flow (PEF) ($P < 0.001$), and forced expiratory flow ($FEF_{50\%}$ $P < 0.001$ and $FEF_{25–75\%}$ $P = 0.004$). • The 12-week exercise training program significantly increased peak expiratory flow (PEF) in the hookah smoker group ($P < 0.05$) and both PEF and forced expiratory volume in 1 second in the cigarette smoker group ($P < 0.01$). • In the non-smoker and cigarette smoker groups, the intervention improved VO2max (4.4 and 4.7%, respectively) versus VO2max (6.7 and 5.6%, respectively), and the recovery index (7.9 and 10.5%, respectively).	• Small sample size. • There is no control group.
Meo et al, 2014	Cross-sectional design Saudi Arabia	• Teenage and young adult males • Age range: 17–33 years old • Average age in years (Mean ± SD) = 21.54 ± 0.41 • N = 146 • Convenience sample	Evaluate how Fractional Exhaled Nitric Oxide (FeNO) and lung function are affected by shisha (waterpipe) smoking.	• Shisha smokers had a significantly decreased lung function (FEV_1, $P = 0.0001$; FEV_1/FVC ratio, $P = 0.0001$; FEF-25%, $P = 0.005$; FEF-50% $P = 0.0001$; FEF-75%, $P = 0.0001$; and FEF-75–85%, $P = 0.010$) compared to the non-smokers. • Compared to control group, shisha smokers had significantly reduced levels of the FeNO ($P = 0.022$).	• Small sample size. • The sample consists of only men. • There is no clear description of the sample's demographics.
Mohammad et al, 2013	Cross-sectional design Syria	• Children, teenage, and adult females • Age range: 6 years and older • Average age in years (Mean) = 28.61 • N = 788 • Convenience sample	Determine how different smoking patterns influence chronic respiratory disease in women.	• While cigarette smoke was significantly associated with doctor-diagnosed COPD ($P < 0.05$), narghile smoking was not. • Airway obstruction, defined by the standards of Global initiative for chronic Obstructive Lung Disease (GOLD), was significantly associated with passive smoking of either narghile or cigarettes ($P < 0.05$).	• Authors admit the possibility that the participants had asthma, rather than COPD. • Study participants never had lung-function tests or had been treated with inhalers in order to apply definitions from GOLD.

(*Continued*)

Table 2. (*Continued*)

STUDY	STUDY DESIGN	SAMPLE SIZE & CHARACTERISTICS	STUDY PURPOSE/ AIMS	FINDINGS	COMMENTS/LIMITATIONS
Salameh et al, 2012	Case-control design Lebanon	• Age range: 40 years and older • Average age in years (Mean) = 53.09 • N = 833 • Convenience sampling	Investigate whether there is an association between chronic bronchitis, waterpipe smoking, and waterpipe dependence.	• Chronic bronchitis had a significant association ($P < 0.001$) with current mixed smoking (OR = 7.68), previous mixed smoking (OR = 38.03), and previous waterpipe smoking (OR = 6.4). • Current exclusive waterpipe smoking did not significantly correlate with chronic bronchitis (OR = 1.87, 95% CI: 0.74–4.72). • Chronic bronchitis had a significant association with current waterpipe dependence (OR = 3.74, $P < 0.001$). • Waterpipe smoking for more than twenty years has a significant association with chronic bronchitis ($P < 0.001$).	• Reduced power of study due to low number of participants with waterpipe smoking. • Selection bias may have occurred due to participants' preference for appointment with specific doctors. • In addition, sampling bias may have occurred because some of the participants came from the same family. • Limited generalizability due to mixed non-respiratory diagnoses in participants in the control group.
Tageldin et al, 2012	Cross sectional design Algeria, Egypt, Jordan, Lebanon, Morocco, Saudi Arabia, Syria, Tunisia, Turkey, United Arab Emirates, and Pakistan	• Age range: 40 years old and older • Average age in years (Mean) = 51.55 • N = 61, 551 • Convenience sampling	Determine and describe respiratory symptoms present in people with suspected COPD.	• After adjustment for cigarette use, waterpipe smoking was significantly associated with productive cough ($P = 0.007$), chronic bronchitis ($P = 0.026$), and breathlessness ($P = 0.018$). • Cigarette ($P < 0.001$) and waterpipe ($P = 0.026$) smokers had significantly higher frequency of COPD symptoms compared to non-smokers.	• Results for waterpipe smokers should have been adjusted for air pollution and occupational exposure. • Misdiagnosis of COPD and prior tuberculosis exposure may have influenced the study results.
Waked et al, 2009	Cross-sectional design Lebanon	• Age range: 16 years old and older • Average age in years (Mean ± SD) = 39.0 ± 16.4 • N = 425 • Convenience sampling	• Describe the population of waterpipe smokers. • Evaluate relationship between waterpipe smoking, cigarette smoking, and respiratory diseases.	• Waterpipe smokers had a significantly higher rate of cigarette smoking ($P < 0.0001$). • Over one-third of exclusively waterpipe users smoke it more than seven times a week. • Exclusively waterpipe smokers reported having higher rates of chronic respiratory diseases and chronic bronchitis than people who don't smoke at all.	• Selection bias of only talking to people with phone may have influenced the study results. • Cross-sectional investigation shows only a glimpse of participants' experience.
Zeidan et al, 2014	Cross-sectional design Lebanon	• Age range: 18–35 years old • Average age in years (Mean) = 24.07 • N = 147 • Empirical sampling	Evaluate how second hand smoke (SHS) relates to exhaled carbon monoxide levels and respiratory symptoms.	• Occupational exposure to waterpipe smoke (adjusted odds ratio (ORa) = 7.08) and to cigarette smoke (ORa = 6.06) were predictors of chronic cough. • Higher frequency of exposure to cigarette smoke ($\beta = 1.14$) and waterpipe smoke ($\beta = 1.46$) increased carbon monoxide levels.	• Generalizability may be limited because waterpipe smokers were demographically different from the rest of the sample. • Sampling bias may have occurred because people with health problems may have left the workforce. • Cross-sectional design prevents temporal association.
Hawari et al, 2013	Single group pre-test post-test design Jordan	• Males • Age range: 18–26 years old • Average age in years (Mean) = 20.4 • N = 24 • Convenience sampling	Define acute symptoms of waterpipe tobacco smoking (WTS) on smokers' respiratory and cardiovascular systems.	• After the WTS, there was a significant ($P < 0.05$) increase in baseline respiratory rate (from 17.7 to 19.7 breath/min), CO level (from 3.7 to 24.4 ppm), and perceived exertion (measured by the Borg scale) at mid and peak exercise. • There was a significant ($P < 0.05$) decrease in oxygen consumption (from 1.86 to 1.7 L/min) and forced expiratory flow over the middle half of the forced vital capacity (from 5.51 to 5.29 L).	• Small sample size.

				• There was a significant ($P < 0.05$) increase in baseline resting systolic blood pressure (from 118.9 to 129.2 mmHg), pulse pressure (from 45.3 to 55.6 mmHg), and pulse pressure product (from 9.9 to 11.1 mmHg/min). • During exercise after WTS, oxygen pulse significantly ($P < 0.05$) decreased (from 10.89 to 9.97 mL/beat) and the heart rate-oxygen consumption relationship significantly increased (from 3.52 to 3.91 beats/mL/kg).	
Layoun et al, 2014	Cross-sectional design Lebanon	• Age range: 18 years old and older • Average age in years (Mean) = 33.44 • N = 132 • Convenience sampling	Determine acute and chronic changes in function of pulmonary and cardiovascular systems after waterpipe (WP) smoking under real life conditions.	• There was no significant differences between WP and cigarette smoking in terms of respective mean values of forced expiratory volume at 1 s (FEV_1), 6 s (FEV_6), percentage of FEV_1/FEV_6, diastolic and systolic blood pressures. • Compared to cigarette use, WP smoking led to a significantly ($P < 0.007$) higher heart rate. • Function of pulmonary and cardiovascular systems was observed to be affected by duration of smoking, age at first WP and quantity of smoking. • Smoking WP of a larger size significantly increased diastolic blood pressure ($P < 0.011$). • Smoking WP of a smaller size significantly increased FEV_6 ($P < 0.045$).	• Convenience sampling. • Concurrent use of cigarettes among participants.
Ben Saad et al, 2013	Case-control design Tunisia	• Males • Age range: 35–60 years old • Average age in years (Mean) = 46.49 • N = 142 • Convenience sampling	Compare pulmonary function of waterpipe smokers (WPS) and exclusive cigarette smokers (ECS).	• Both ECS and WPS participants consumed similar amounts of tobacco (36922 waterpipe-years vs. 35919 pack years). • Compared to ECS, WPS had a significantly higher forced expiratory volume (FEV_1) (60921 vs. 84912%), forced vital capacity (FVC) (76918 vs. 90912%), and FEV_1/FVC (83917 vs. 9997%). • A similar percentage of restrictive ventilatory-defect (RVD) was observed among ECS (31%) and WPS (36%). • Compared to ECS, WPS had a significantly lower percentage of large-airway-obstructive-ventilatory-defect (LAOVD) (58 vs. 8%) and lung hyperinflation (57 vs. 36%).	• Convenience sample.
Ben Saad et al, 2011	Cross-sectional study Tunisia	• Males • Age range: 20–60 years old • Average age in years (Mean ± SD) = 34 ± 10 • N = 110 • Convenience sampling	Determine how many waterpipe smokers (WPS) suffer from obstructive ventilatory defect (OVD), restrictive ventilatory defect (RVD), and/or static hyperinflation (SHI). To compare the estimated and chronological lung ages of WPS.	• Among the WPS participants, 6% had large airway OVD, 14% had small airway OVD, 14% had RVD, and 36% had SHI. • Compared to chronological lung age of the participants, estimated lung age was significantly higher (34 ± 10 years vs. 47 ± 18 years, $P < 0.05$).	• Small sample size. • Contradictory conclusions.
Mutairi et al, 2006	Quasi-experimental design Kuwait	• Age range: 24–65 years old • Average age in years (Mean) = 36.96 • N = 152 (Middle Easterners) • Convenience sampling	Determine and compare nicotine and cotinine levels in exclusive waterpipe smokers (WPS) and exclusive cigarette smokers (ECS).	• WPS, ECS, and non-smokers had comparable spirometric values. • Compared with ECS, chronic WPS had chronic respiratory symptoms at a significantly younger age ($P < 0.05$).	• This study could benefit from randomization of subject selection and subject assignment to groups.

(*Continued*)

Table 2. (*Continued*)

STUDY	STUDY DESIGN	SAMPLE SIZE & CHARACTERISTICS	STUDY PURPOSE/ AIMS	FINDINGS	COMMENTS/LIMITATIONS
			Evaluate if there is a relationship between the nicotine, cotinine levels and the respiratory, metabolic indices in WPS and ECS.	• Neither the spirometric variables (FEV_1%, FEV_1/FVC%) nor the lipid profile variables (HDL, LDL, HDL/LDL, TG) showed significant difference between WPS, ECS, and non-smokers. • Compared to ECS (1321.4 ng/mL), WPS (677.6 ng/mL) had significantly ($P = 0.008$) lower mean cotinine concentration in urine. • Compared to ECS (1487.3 ng/mL), WPS (440.5 ng/mL) also had significantly ($P < 0.0001$) lower mean nicotine concentration in urine.	
She et al, 2014	Cross-sectional design China	• Age range: over 40 years of age • Average age in years (Mean) = 55.51 • N = 1,238 • Random-digit phone sampling	Determine whether Chinese waterpipe smoking (WPS) and exposure among the Chinese population is related to the risk of developing COPD.	• Compared to ever non-smokers, the risk of developing COPD was significantly increased for Chinese water-pipe smokers (adjusted OR, 10.61; 95% CI, 6.89–16.34; $P < 0.001$), Chinese water-pipe passive smokers (adjusted OR, 5.50; 95% CI, 3.61–8.38, $P < 0.001$), cigarette smokers (adjusted OR, 3.18; 95% CI, 2.06–4.91; $P < 0.001$), and cigarette passive smokers (adjusted OR, 2.52; 95% CI, 1.62–3.91, $P < 0.001$). • Compared to cigarette exposure, WPS gives off more fine particulate 2.5 matter (PM2.5). • Tissue inhibitor of metalloproteinase-1 and ChemR23 could possibly serve as COPD protein biomarkers.	• Design of the Chinese waterpipe is different from the Arabic waterpipe.
Koul et al, 2011	Case-control design India	• Age range was not reported • Average age in years (Mean) = 58.07 • N = 651 • Convenience sampling	To evaluate if there is an association between waterpipe smoking (WPS) and lung cancer in the Kashmir population.	• Compared to not smoking anything at all, WPS significantly increased the risk for developing lung cancer by nearly six times (OR 5.83, 95% CI 3.95–8.60, $P < 0.0001$). • There was a positive association between the severity of smoking and risk of developing lung cancer (chi-square 72.09, $P = 0.000$).	• Convenience sample.
Feng et al, 2009	Case-control design Algeria, Morocco, Tunisia	• Age range and average age were not reported • N = 1,251 • Convenience sampling	Evaluate exposure of North Africans to tobacco, cannabis, domestic fumes, alcohol intake, and lifestyle specific to North Africa in relation to the risk of developing nasopharyngeal carcinoma (NPC).	• Waterpipe smoking was not associated with the risk of developing NPC and undifferentiated carcinoma. • Marijuana smoking ($P < 0.025$) and exposure to domestic cooking fumes from *kanoun* (compact charcoal oven) ($P < 0.05$) significantly increased the risk of developing NPC. • Alcohol was not associated with the risk of developing NPC.	• Convenience sample.
Wang et al, 2015	Case report Australia	• One 20-year-old woman	To report the first Australian case of severe carbon monoxide poisoning cause by waterpipe use for one hour.	• Patient appeared lethargic. • Po2 (mmHg) venous level was 19.	• Findings from case report may not be applicable to the rest of the population.

Of those individuals who smoked cigarettes, normal inhalation was associated with better PFT scores than deep inhalation.[33] Evidence also supports the possible serious health risks of passive smoking, as airway obstruction was significantly associated ($P < 0.05$) with WP and cigarette smoking.[43]

Severity and prevalence of unspecified respiratory symptoms were reported to be significantly greater in WPS users than in nonsmoking individuals.[32,33] Shortness of breath ($P = 0.018$), chronic cough ($P = 0.007$), and bronchitis ($P = 0.026$) were found to be significantly associated with WPS.[44] Chronic bronchitis and chronic obstructive pulmonary disease (COPD) were significantly associated ($P < 0.05$) with WPS.[34,43,44,49] Passive WPS was significantly ($P < 0.05$) associated with COPD in one study[43] and was a significant ($P < 0.05$) risk for developing COPD in another.[49]

There was a significant ($P < 0.05$) relationship between WPS and lung cancer in the two studies examining this relationship. In addition, a third study demonstrated that WPS users were six times more likely ($P < 0.0001$) to develop lung cancer than nonsmokers.[36]

Oxidative stress, immunity, and cell cycle interference outcomes.

Overview. Evidence of oxidative stress and immune factors such as white blood cell count and markers of inflammation is demonstrated in Table 3. The four studies were diverse in their focus and included cellular disruption,[7,57–59] inflammation, and impairment of cellular oxygen delivery by measuring carboxyhemoglobin (COHb) and carbon monoxide levels. Studies from the cardiovascular and respiratory categories also examined COHb and carbon monoxide levels.[46,50,51,56,60,61]

Synthesis of results. Two in vitro studies examined cellular changes in aortic cells[58,59] and alveolar cells.[58] Cellular damage was noted via apoptosis[10] and cell cycle arrest.[7,58,59] One study explored the levels of inflammatory markers (cytokines) in the exhaled breath condensate of active WPS.[57] Anti-inflammatory cytokines (interleukin-4, 10, and 17) significantly ($P < 0.01$) decreased after WPS exposure.[57] COHb levels were significantly higher in both the active ($P < 0.00001$) and passive ($P = 0.003$) WPS groups after exposure to WPS.[57] Compared to cigarette use, the COHb level increased threefold after WPS ($P = 0.0002$).[50,61]

Other outcomes.

Overview. There were several other chemical toxicants associated with WPS that were included as outcome variables and that were included in this review, including elements such as arsenic, cadmium, chromium, nickel, and nicotine.[28,29,51] Associated health conditions also included cancers such as bladder, esophageal, and nasopharyngeal cancers.[25,37]

Synthesis of results. There were significant differences noted in the lung tissue of the WP smokers. The literature suggests that WPS increases certain levels of substances that may also have long-term negative health effects associated with nicotine. Nicotine levels were measured in four studies.[51,60,61,63] One study found nicotine levels to only be significantly elevated in the cigarette use group;[60] one study found nicotine levels significantly increased after WPS use ($P < 0.05$);[51] and in contrast, one study found similar nicotine levels between cigarette use and WPS use.[61] One study found there to be a significant ($P = 0.01$) interaction between nicotine and increased heart rate as well as nicotine and smoking duration ($P = 0.004$).[63] Arsenic was significantly lower in nonsmokers than smokers ($P < 0.05$).[28] Nickel and cadmium levels were noted to be more significantly ($P < 0.05$) elevated in smokers (WP and cigarette users) than in nonconsumers of tobacco.[29] Nasal polyposis (soft, painless, noncancerous growths on the lining of nasal passages or sinuses) was significantly associated with WPS.[28,29] This condition was also related to higher concentrations of blood metal (arsenic and chromium) levels.

Discussion

This systematic review has shown that WPS is associated with several health indicators such as increased vascular resistance, increased heart rate, increased blood pressure, lower PFT scores, shortness of breath, chronic cough, and health conditions such as bronchitis and chronic bronchitis, COPD, lung cancer, nasal polyposis, cellular damage, low immunity, and low birth weight. These results are in agreement with Akl et al[25] and El-Zaatari et al,[26] which reinforce the message that WPS is associated with poor health outcomes. This review supports the growing evidence that WP users had more coronary artery and cardiovascular diseases than nonsmokers. Passive WPS was also significantly associated with COPD in two studies. However, this review did not find that WPS was significantly associated with oral dysplasia, esophageal cancer, nasopharyngeal cancer, or bladder cancer.

This review demonstrates that the poor health outcomes associated with WPS are similar to those well-established for cigarette smoking. As most of the studies meeting the inclusion criteria for this systematic review were conducted outside of the US (33/40; 82.5%), it confirms the need for additional study among US populations, particularly with the recognized growing increase in WPS among youth and college-age young adults.[2,66] More study is also needed of secondhand exposure. As noted in the "Results" section and Table 1, the evidence supporting the negative health effects of WPS on particularly the cardiovascular and respiratory systems (two of the identified four health outcome categories for this review) is wide and varied. Although research findings on the general health effects of WPS within the US should result in similar findings, this type of information is needed given the rapidly growing exposure, experimentation, and use of WPs in the US, which may be expanding beyond youth and college-age groups as the number of hookah cafés continues to grow and WP tobacco and its products are purchased via the Internet. As a result, WPS and its related secondhand smoke exposure risks ultimately threaten all the public health gains made in reducing cigarette use over the past decade.[67] It is therefore imperative that research studies be conducted in the US in

Table 3. WPS, oxidative stress, and inflammation in the lung and heart.

STUDY	STUDY DESIGN	SAMPLE SIZE & CHARACTERISTICS	STUDY PURPOSE/ AIMS	FINDINGS	COMMENTS/LIMITATIONS
Rammah et al, 2013	Experimental design Lebanon	• Human aortic endothelial cells (HAEC)	Assess the changes in cell viability, reactive oxygen species (ROS) generation, inflammatory and vasodilatory markers and in vitro angiogenesis of human aortic endothelial cells in response to waterpipe smoke condensate exposure.	• Exposure to waterpipe smoke condensate (WSC) resulted in apoptosis, cell cycle arrest, and oxidative stress in HAEC. • Following exposure to WSC, HAEC cells had inflammation and obstruction of endothelium-dependent vasodilation (activated phosphorylation of p65 and prevented phosphorylation of adenosine monophosphate-activated protein kinase/endothelial cell nitric oxide synthase (AMPK/eNOS). • HAEC cells were obstructed from angiogenesis and had limited motility after exposure to WSC.	• Study results are limited by the effect of WSC in vitro.
Rammah et al, 2012	Experimental design Lebanon	• Alveolar type II cells, vascular endothelial cells, genes involved in cell cycle arrest and inflammation	Investigate cytotoxicity and mutagenicity of the waterpipe smoke condensate (WSC). Examine how WSC changes the cellular profile of A549.	• The highest tested doses of WSC were significantly toxic for TA102 and TA97a strains ($P < 0.05$). • Using the p53–p21 pathway, cell stopped its cycle and initiated senescence following the WSC exposure. • An immune response regulator (Toll-like Receptor-4) and matrix metalloproteinases (MMP-2 and MMP-9) had an increased transcriptional expression after exposure to WSC.	• Prokaryotic living organism was used. • The solvent used does not occur naturally in lungs. • Results were limited by the range of tested doses of WSC.
Shihadeh et al, 2014	Case-control design Lebanon	• Age range: 18–50 years old • Average age was not reported • N = 33 • Convenience sampling	Evaluate how human alveolar cells are influenced by tobacco-free and tobacco-derived waterpipe smoke.	• There was no significant difference between tobacco-derived and tobacco-free waterpipe smoke. • Halt of cell cycle at G0/G1, reduced cell proliferation, and prolonged cell doubling time resulted from both tobacco-derived and tobacco-free waterpipe smoke.	• Study generalizability may have been limited by the sample of occasional waterpipe smokers.
Bentur et al, 2014	Single group pre-test, post-test design Israel	• Age range: 18-years-old and older • Average age in years (Mean ± SD) = 24.9 ± 6.2 • N = 62 • Convenience Sampling	Conduct clinical and laboratory analysis of acute effects from active and passive indoor groups of waterpipe smoking (WPS).	• Active WPS led to a significant decrease ($P < 0.01$) in the level of cytokines (IL-4, IL-5, IL-10, IL-17, and g—interferon) in the exhaled breath condensate (EBC). • WPS led to significant increase in carboxyhemoglobin level (active smokers, 2.0% ± 2.9% vs 17.6% ± 8.8%; $P < .00001$). • Specifically, six subjects (12.7%) had more than a 25% increase, and two subjects (4.2%) had more than a 40% increase in carboxyhemoglobin level. • Carboxyhemoglobin in passive WPS smokers significantly increased (0.8% ± 0.25% vs 1.2% ± 0.8%, respectively, $P = .003$) in addition to an increase in respiratory rate. • Active WPS led to a significant increase in plasma nicotine level (active smokers, 1.2 ± 4.3 ng/mL vs 18.8 ± 13.9 ng/mL; $P < .0001$).	• Small sample size. • Small number of passive smokers and active female WP smokers. • No assessment of smoking topography. • No analysis of EBC cytokines and endothelial function in passive smokers. • No determination of ambient CO and toxic smoke constituents (e.g., aldehydes, polycyclic aromatic hydrocarbons).

order to provide the necessary empirical evidence to the FDA and US regulatory bodies for use in developing and implementing a WPS policy and regulation to affect the manufacture, distribution, and marketing of WPs to protect public health and prevent the well-known morbidity and mortality associated with tobacco consumption.

Furthermore, although evidence confirming the harmful health effects of WPS across these studies is provided, additional research among US populations is needed in order to assess potential differences among behaviors and patterns of use. Differences may include specific popular products, including the tobacco itself, the coal used, or the different types of WPs and hoses; length of time of the WPS session; how often the product is used; and if multiple tobacco products are used. This type of information is needed given the remarkable increase in uptake and regular use of WPs in the US in order to add further clarity regarding the association between WPS and reported health outcomes, which can be used to assess risks and educate the public.

This systematic review also signifies the need for longitudinal studies in order to assess the health effects over time for users and compare WPS-only users with multiple tobacco product users and nonsmokers. This comparison is necessary given that a significant proportion of WP smokers are also cigarette smokers. Short-term effects on the respiratory system and transmission of diseases as well as long-term health effects including cancer and cardiovascular disease should be assessed. Differences in products potentially popular between different cultures should be reported and studied for any different associations with different health outcomes.

Several limitations should be noted from this review. The research compiled for this review did not include WPS-only users in their studies. As such, there is difficulty in assessing the true harm specific to WPS since many studies included WP smokers who also reported smoking cigarettes. Although the harmful effects of WPS are likely to remain the same, the research on frequency and strength of exposure for WPS-only users and WPS users in the US might reveal different findings or degrees of harm from studies conducted in countries where WPS has a long history of use. Having information for WPS-only users would assist in providing some of the needed evidence to inform consumers, health-care professionals, the Food and Drug Administration, and US tobacco regulatory bodies for use in developing and implementing WPS policy and regulations similar to those for cigarettes. The desired outcome of these controls is the decrease in overall tobacco use and prevention of its associated well-established health-related morbidity and mortality.

Conclusion

Evidence clearly exists that establishes a connection between WPS use and the related harmful health effects. This review illustrates the consistency in the reported literature that WPS may be as harmful as cigarette smoking in terms of multiple health physiologic indicators and tobacco-related condition outcomes. This systematic review shows that the negative health effects, categorized within cardiovascular, respiratory, oxidative stress, immunity, and cell cycle interference, are caused due to the effects of nicotine and chemical toxicant exposures. This review calls attention to the need for additional research as WPS grows in popularity and use in the US. Additional research is needed to examine both the short- and long-term health effects of WPS, which will be added to the body of evidence used to inform policy statements aimed at reducing harm among those smoking and/or exposed to the secondhand smoke of WP tobacco use.

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Author Contributions

Conducted the literature search, reviewed the articles, and prepared the original draft of the main sections: LH. Participated in the interpretation and writing the result sections: DLK. Reviewed and edited draft manuscripts, the final manuscript, and contributed to manuscript improvement: LSW. Participated in the study design, as well as reviewed and edited all versions of manuscript: TEB. Validated the literature search and assisted in editing the manuscript: AVF. Reviewed and edited the final manuscript: RG. All the authors read and approved the final manuscript.

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