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The effects of waterpipe tobacco smoking on health outcomes: an updated systematic review and meta-analysis

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Abstract

Rationale: A systematic review conducted in 2008 found significant associations between waterpipe tobacco smoking and lung cancer, respiratory disease, periodontal disease and low birth weight. Since then, a number of relevant studies have been published.

Objectives: The objective of this study was to update the systematic review on the effects of waterpipe tobacco smoking on health outcomes.

Methods: In May 2015 we electronically searched the following databases with no date restrictions: MEDLINE, EMBASE and ISI the Web of Science using a detailed search strategy with no language restrictions. We also screened references lists of included studies. We also screened the references lists of the included studies. We included cohort, case-control and cross-sectional studies, and excluded case reports, conference abstracts, editorials and reviews. We excluded studies not conducted in humans, assessing physiological outcomes, not distinguishing waterpipe tobacco smoking from other forms of smoking, and not reporting association measures. We assessed risk of bias for each included study and conducted meta-analyses for each of the outcomes of interest.

Results: We identified 50 eligible studies. We found that waterpipe tobacco smoking was significantly associated with respiratory diseases (COPD odds ratio (OR)= 3.18, 95% CI= 1.25, 8.08; Bronchitis odds ratio (OR)= 2.37, 95% CI= 1.49, 3.77; Passive water-pipe smoking and wheezes odds ratio (OR)= 1.97, 95% CI= 1.28, 3.04), oral cancer (OR=4.17, 95% CI =2.53,6.89), lung cancer (OR=2.12, 95% CI =1.32,3.42), low birth weight (OR=2.39, 95% CI =1.32,4.32), metabolic syndrome (OR 1.63-1.95; 95% CI 1.25,2.45), cardiovascular disease (OR = 1.67, 95% CI= 1.25,2.24) and mental health (OR 1.30-2.4 95% CI 1.20,2.80). Waterpipe tobacco smoking was not significantly associated with esophageal cancer (OR=4.14, 95%

CI=0.93,18.46), worse quality of life scores (Standardized Mean Difference (SMD)=-0.16, 95% CI = -0.66, 0.34) gastric carcinoma (OR=2.16, 95% CI =0.72,6.47), bladder cancer (OR=1.25, 95%CI 0.99,1.57), prostate cancer (OR=7.00, 95 % CI 0.90,56.90), hepatitis C infection (OR=0.98 95% 0.80,1.21), periodontal disease (OR=3.00,5.00), gastro-esophageal reflux disease (OR=1.25, 95% CI =1.01,1.56), nasopharyngeal carcinoma (OR=0.49,95% CI 0.20,1.23), bladder cancer (OR=1.25, 95% CI =0.99,1.57), infertility (OR = 2.50, 95% CI 1.00-6.30), and mortality (OR=1.15, 95% CI 0.93,1.43).

Conclusions: There is accumulating evidence about the association of waterpipe tobacco smoking with a growing number of health outcomes.

MeSH: Quality of life, road traffic crashes, cardiovascular diseases, Cancer, Oral dysplasia, Mental health, Metabolic syndrome, Reflux disease, Pregnancy outcomes, respiratory disease, Esophageal Neoplasms, Infant, Low Birth Weight, Lung Neoplasms, hepatitis C, tobacco, waterpipe.

Key messages

- Waterpipe tobacco smoking is likely associated with oral cancer, and lung cancer
- It is also likely associated with respiratory diseases, low birth weight, metabolic syndrome, cardiovascular disease and mental health.
- Waterpipe tobacco smoking is likely not associated with esophageal cancer, gastric carcinoma, bladder cancer, or prostate cancer
- It is also likely not associated with hepatitis C infection, periodontal disease, gastro-esophageal reflux disease, infertility, or mortality.

Background

The past decade has witnessed a steady increase in waterpipe tobacco smoking especially among the younger age groups ([1, 2]). A systematic review found that school and university students have the highest prevalence of waterpipe tobacco smoking across countries ([3]). In the Global Adult Tobacco Survey ([4, 5]) conducted in 13 low and middle-income countries the prevalence of waterpipe use among men was highest in Vietnam (13%) and Egypt (6.2%). Among women, waterpipe use was highest in Russia (3.2%) and Ukraine (1.1%). Even though the Middle Eastern youth are affected the most by the waterpipe smoking epidemic, over the past two decades many studies have reported increase in waterpipe use among youth in North America and Europe ([6, 7 8 9])

We systematically reviewed the literature in 2008, we found significant associations between waterpipe tobacco smoking and a number of health outcomes([10]). For example, waterpipe tobacco smoking was associated with increased odds of lung cancer (OR=2.12), and respiratory disease (OR=2.30). We also found evidence suggesting clinically significant association with periodontal disease (OR=3-5) and low birth weight (OR=2.12).

The available evidence at that time did not allow ruling out or confirming an association between waterpipe tobacco smoking and bladder cancer, nasopharyngeal cancer, esophageal cancer, oral dysplasia and infertility. Since then, newly published studies have addressed some of these outcomes (e.g., esophageal carcinoma) ([11, 12]) as well as additional outcomes (e.g., quality of life, cardiovascular diseases, gastro-esophageal reflux disease (GERD)) ([13-17]). Therefore, the objective of this study was to update our systematic review of the medical literature for the effects of waterpipe tobacco smoking on health outcomes.

Methods

Eligibility criteria

We included observational studies (i.e., cohort studies, case-control studies and cross-sectional studies). The exposure of interest was waterpipe tobacco smoking and the outcomes of interest were any health outcomes.

We excluded case reports, case series, outbreak investigations, and abstracts. We also excluded studies assessing waterpipe use for non-tobacco smoking purposes (e.g. marijuana smoking and other recreational drug use); not distinguishing waterpipe tobacco smoking from other forms of smoking; assessing physiological (e.g. forced expiratory volume in 1 second (FEV1)) or other surrogate outcomes (e.g., artery occlusion); and not reporting any measure of association.

Search Strategy

In May 2015, we updated the literature search originally conducted in June 2008. We used the OVID interface to electronically search MEDLINE (1950 onwards) and EMBASE (1980 onwards). We also searched the ISI Web of Science. Appendix 1 presents our detailed search strategy. We designed the search strategy based on extensive internet search for waterpipe synonyms and based on the search strategy used by Akl et al ([10]). The strategy consisted of the synonyms for waterpipe (e.g., 13 synonyms in the Medline strategy) but did not include any study design filter and was not restricted to any language. Two medical librarians reviewed and provided input on the search strategy. Additional search strategies included: (1) a review of the

reference lists of included studies, (2) the use of the 'Related citations' feature in PubMed, and (3) an ongoing surveillance of the literature in place while updating the manuscript

Selection process

Teams of two reviewers independently screened the title and abstract of identified citations for potential eligibility. We acquired the full texts of citations judged as potentially eligible by at least one of two reviewers. Next, two reviewers used a standardized and pilot tested form to independently screen each full text for eligibility. Disagreements were resolved by discussion or by consulting a third reviewer.

Data abstraction

Teams of two reviewers used a standardized and pilot tested form to independently abstract data. Disagreements were resolved by discussion or by consulting a third reviewer. Data abstracted from individual studies included information about study design, population, exposure, outcomes, methodological features, results, and funding.

Risk of bias assessment

We have assessed the risk of bias of all the included studies based on the following four commonly used criteria: selection bias, information bias, confounding and completeness of data. The risk of bias was rated as “high” in studies that failed three or more of these criteria, “moderate” in studies that failed one or two criteria, and “low” in studies that failed none of them. To assess selection bias we reviewed sampling of participants, their recruitment, and their representativeness. We have assessed Information bias for measurement of exposure and outcome with regards to using validated tools with adequate evidence of validation provided.

Confounding assessment was based on whether authors reported controlling for relevant confounders with adequate details (e.g., in the design phase through matching and/or in the analysis through adjustment). Completeness of data was based on whether authors provided information about missing data and participation rate (Appendix 4)

Data analysis

Agreement between the reviewers was calculated using Cohen's kappa statistic. We conducted meta-analyses for the outcomes for which at least two studies reported effect estimates of their association with waterpipe tobacco smoking. When a study reported more than one relevant effect estimate, we selected the one that adjusted for the maximum number of confounders, particularly for other forms of tobacco smoking.

For continuous outcomes using different scales, we calculated the standardized mean difference (SMD) for each study and then pooled across eligible studies using the inverse variance method. For dichotomous outcomes, we used the reported ORs to calculate the ln(ORs) and standard errors. We then pooled the ln(ORs) across eligible studies using the inverse variance method. We used fixed-effects models when pooling only two studies, and used the random-effects model in all other cases. We measured heterogeneity across studies using the I^2 statistic. We considered heterogeneity to be high when I^2 was greater than 50%. We used Review Manager software Version 5.0.2 for all analyses.

Results

Search results

Appendix 1 shows the study flow. Out of 360 full texts assessed, we excluded 301, with reasons for exclusion provided in Appendix 1. Of the 50 included studies, 24 were identified by the original search, and 26 were identified by the update. Agreement between reviewers for study eligibility was excellent (kappa= 0.94 and 0.80 for the two teams).

The included studies assessed the associations between waterpipe tobacco smoking and the following outcomes: respiratory diseases (n=9), quality of life (n=2), esophageal cancer (n=3), gastric carcinoma (n=3), oral cancer (n=3), bladder cancer (n=2), nasopharyngeal cancer (n=1), lung cancer (n=6), prostate cancer (n=1), colorectal cancer (n=1), pregnancy outcomes (n=3), periodontal disease (n=6), hepatitis C infection (n=3), infertility (n=1), metabolic syndrome (n=1), gastro-esophageal reflux disease (GERD) (n=1), cardiovascular diseases (n=2), mental health (n=1) and mortality outcomes (n=1)

Methodological features

Risk of bias assessment

Out of the 50 included studies only eight studies were assessed to have selection bias and/or reporting insufficient information about the sampling techniques and 16 studies have reported the participation rate. There was no agreement across studies on a standardized way to measure exposure to waterpipe tobacco smoking and this was the main reason for heterogeneity in the meta-analysis. There was agreement across studies on the need to adjust for potential confounders as age, gender, education and other forms of tobacco use.

Evidence synthesis

Table 1. Summary of studies published on health outcomes of waterpipe tobacco smoking between 1990- 2015¶

ID	Study	Design	Participants(N)	*Outcome*	Reported OR(95% CI)
			Respiratory diseases		
1	Tamim 2003([18])	Cross-sectional	143	*Wheezes/Passive*	2.30 (1.10,5.10)
2	Mohammed 2013([5])	Cross-sectional	788	*COPD*	2.60 (0.60,11.50)
3	Mohammed 2008([19])	Cross-sectional	77	*COPD*	N/A
4	Tageldine 2012([20])	Cross-sectional	61,551	*COPD*	1.42 (1.12,1.80)
5	Salameh 2012([21])	Case-control	211 cases 527 controls	*Bronchitis*	6.40 (2.55,16.11)
6	Waked 2011([22])	Cross-sectional	425	*COPD*	2.53 (1.83,3.50)
7	Waked 2009([23])	Cross-sectional	1,268,315	*Bronchitis*	1.95(0.96,8.08)
8	Mohammed 2014([24])	Cross-sectional	2,734	*Wheezes/Passive*	2.05 (1.01,4.17)
9	She 2014([25])	Cross-sectional	1,238	*COPD*	10.61 (6.89,16.34)
			Quality of Life		
10	Tavafian 2009([13])	Cross-sectional	1,675	*Quality of life*	Physical 2.15 (1.56,2.96) Mental 1.88 (1.36,2.60)
11	Joseph 2012([26])	Cross-sectional	2,201	*Quality of life*	N/A
			Cancers		
12	Malik 2010([27])	Case-control	135 cases 195 controls	*Oesophageal*	21.44 (11.63,39.54)
13	Dar 2012([11])	Case-control	702 cases 1,663 controls	*Oesophageal*	1.85 (1.41,2.44)
14	Nasroallahzadeh 2008([12])	Case-control	300 cases 571 controls	*Oesophageal*	1.69 (0.76,3.77)
15	Hosseini 2009([28])	Case-control	300 cases 571 controls	*Prostate*	7.00 (0.90 , 56.9)
16	Sadjadi 2014([29])	Cohort	928	*Gastric*	3.44 (1.66,7.11)
17	Shakeri 2013([30])	Case-control	309 cases 613 controls	*Gastric*	1.10(0.30,3.30)
18	Karajibani 2014([31])	Case-control	50 cases 46 controls	*Gastric*	N/A
19	Zheng 2012([32])	Case-control	1,886 cases 2,716 controls	*Bladder*	Urothelial carcinoma: 1.30 (1.00,1.80)

					SCC: 1.20 (0.80,1.70)
20	Bedwani 1997([33])	Case-control	151 cases 157 controls	*Bladder*	0.80 (0.20,4.00)
21	Qiao 1989([34])	Case-control	107 cases 107 controls	*Lung*	1.90 (0.40,9.40)
22	Lubin 1990([35])	Case-control	74 cases 74 controls	*Lung*	3.60
23	Lubin 1992([36])	Case-control	427 cases 1,011 controls	*Lung*	1.80 (0.80,4.20)
24	Hsairi 1993([37])	Case-control	110 cases 110 controls	*Lung*	3.00 (1.20,7.6)
25	Gupta 2001([38])	Case-control	265 cases 525 controls	*Lung*	1.94 (0.85,4.44)
26	Hazelton 2001([39])	Cohort	1,289 WP only 2,306 WP/cigarettes 8,416 non-smokers	*Lung*	RR 4.39 (3.82,5.04)
27	Feng 2009([40])	Case-control	636 cases 615 controls	*Nasopharyngeal*	0.49 (0.20,1.23)
28	Ali 2007([41])	Cross-sectional	33	*Oral*	8.33 (0.78,9.47)
29	Dangi 2012([42])	Cross-sectional	761	*Oral*	4.42 (2.32,8.41)
30	Schmidt-Westhausen 2014([43])	Cross-sectional	162	*Oral*	4.35 (1.73, 10.93)
31	Nikbakht 2015([44])	Cross-sectional	120	*Colorectal*	N/A
			Pregnancy outcomes		
32	Nuwayhid 1998([45])	Retrospective cohort	895	*Low birth weight*	2.17 (0.74,6.33)
33	Aghamolaei 2007([46])	Case-control	60 cases 60 controls	*IUGR*	3.50 (1.1,12.6)
34	Tamim 2008([47])	Retrospective cohort	1,391	*Low birth weight*	1.20 (0.60,2.20)
35	Eftekhar 2007([48])	Case-control	60 cases 60 controls	*IUGR*	3.50(1.10,12.60)
			Periodontal disease		
36	Natto 2005([49, 50])†	Cross-sectional	355	*Periodontal disease*	3.50 (1.6,7.6)
37	Natto 2004([51])	Cross-sectional	244	*Periodontal disease*	N/A
38	Baljoon 2005([52])	Cross-sectional	262	*Periodontal disease*	2.90 (1.20,7.00)
39	Al-Belasy 2004([53])	Cohort	100	*Dry socket*	RR 3.00 (*P value* 0.001)

			Infectious diseases		
40	Habib 2001([54])	Cross-sectional	1827	*HCV*	1.10 (0.7,1.5)
41	Medhat 2002([55])	Cross-sectional	2717	*HCV*	0.90 (0.4, 2.0)
42	El-Sadawy 2004([56])	Cross-sectional	782	*HCV*	1.02 (0.64,1.62)
			Infertility		
43	Inhorn 1994([57])	Case-control	45	*Infertility*	2.50 (1.0,6.3)
			Digestive/GIT diseases		
44	Shafique 2012([58])	Cross-sectional	30-75	*Metabolic syndrome*	Hypertriglycemia 1.63(1.25,2.10) Hypergylcemia 1.82 (1.37,2.41) Hypertension 1.95 (1.52,2.45)
45	Islami 2014([17])†	Cross-sectional	75	*GERD*	1.34 (1.02,1.75)
			Cardiovascular disease		
46	Al-Suwaidi 2012([14])	Cohort	7,939	*ACS*	N/A
47	Islami 2012([16])†	Cross-sectional	75	*CVD*	3.75 (1.52,9.22)
			Mental health		
48	Primack 2013([59])	Cross-sectional	100,891	*Mental health*	1.40 (1.30, 1.50)
			Mortality		
49	Wu 2013([15])	Cohort	11,746	*Mortality*	HR 1.15 (0.93, 1.43)

¶ excluding studies that did not fulfil the eligibility criteria; † Indicates two studies from the same population, thus grand total = 50 studies

Respiratory diseases

Nine studies evaluated the association between waterpipe tobacco smoking and respiratory disease. Five studies assessed the association between waterpipe tobacco smoking and chronic obstructive pulmonary disease (COPD) (4 cross-sectional studies and one case-control) (Appendix 4. Table 1) ([5, 19-23]). The pooled odds ratios for the association of waterpipe tobacco smoking and COPD was OR= 3.18, (95% CI= 1.25, 8.08(I^2= 95%). Two studies assessed the association between waterpipe tobacco smoking and bronchitis (2 cross-sectional studies) (Appendix 4. Table 1) ([23, 25]). The pooled odds ratios for the association of waterpipe tobacco smoking and bronchitis was OR= 2.37, (95% CI= 1.49, 3.77).

Two cross sectional studies ([18, 24]) evaluated the association between passive waterpipe tobacco smoking and respiratory illness (defined as nasal congestion and wheezing) (Appendix 4 – Table 1). The pooled odds ratio for the association of passive waterpipe tobacco smoking and respiratory illness was 1.97 (95% CI= 1.28, 3.04).

Quality of life

Two cross-sectional studies evaluated the association between waterpipe tobacco smoking and quality of life ([13, 26]) (appendix 4. Table 2). One found that waterpipe smokers have a poorer respiratory quality of life using the Clinical COPD Questionnaire (CCQ) and the MRC dyspnea scale ([26]). Another found that waterpipe smokers have a higher risk for poorer health-related quality of life with regards to physical function, role physical, bodily pain, general health, mental health, vitality and social function on the Short Form Health Survey (SF-36) ([13]). They also found a higher risk on the Mental Component Score (MCS) and Physical Component Score

(PCS). The pooled standardized mean difference (SMD) was -0.16 (95% CI =-0.66, 0.34; I^2=93%).

Cancer outcomes

1-Esophageal cancer

Three case-control studies evaluated the association between waterpipe tobacco smoking and esophageal cancer: one from Iran and two from Kashmir (Appendix 4.Table 3). ([11, 12, 27]) .The pooled odds ratios for the association of waterpipe tobacco smoking with esophageal cancer was OR= 4.14 (95% CI= 0.93, 18.46). The level of statistical heterogeneity was high (I^2=96%).

2- Gastric carcinoma

Two case-control and one prospective cohort studies evaluated the association between waterpipe tobacco smoking and gastric carcinoma (Appendix 4. Table 3). ([29-31]). Both studies were from Iran. The pooled odds ratio for the association of waterpipe tobacco smoking with gastric carcinoma was OR= 2.16 (95% CI= 0.72, 6.47). The level of statistical heterogeneity was high (I^2= 61%). One case-control study reported only means so was not included in the meta-analysis ([31]). It reported higher frequency of waterpipe smoking among those with gastric carcinoma (mean=3 ±1.6 compared to healthy controls mean=2 ±1.1; P value=0.4).

3-Oral cancer

Three cross-sectional studies evaluated the association between waterpipe tobacco smoking and oral cancer: one from Yemen and one from India ([41-43]). The pooled odds ratio for the association of waterpipe tobacco smoking with oral cancer was OR= 4.17 (95% CI= 2.53, 6.89). (Appendix 4. Table 3).

4-Bladder cancer

Two case-control studies evaluated the association between waterpipe tobacco smoking and bladder cancer, both of which were conducted in Egypt ([32, 33]) (Appendix 4. Table 3). The pooled odds ratios for the association of waterpipe tobacco smoking with bladder cancer was OR= 1.25 (95% CI= 0.99, 1.57).

5- Nasopharyngeal cancer

One case-control study evaluated the association between waterpipe tobacco smoking and nasopharyngeal cancer in Tunisia, Morocco and Iran ([40]) (Appendix 4. Table 3). The OR for the association of waterpipe tobacco smoking with nasopharyngeal cancer was 0.49 (95% CI= 0.20, 1.23).

6- Lung cancer

Five of six eligible studies were case-control studies measuring lung cancer diagnosis, ([34, 36, 38, 60, 61]) and one was a retrospective cohort study measuring lung cancer mortality ([39]) (Appendix 4. Table 3). One was conducted in Northern India, one was conducted in Tunisia, while four reported data from the same population in China. While nowadays waterpipe tobacco is processed, flavored and indirectly heated by the charcoal, in most of the included studies (those conducted in China and India) tobacco is typically unprocessed and burned directly by charcoal.

The pooled OR for the association of waterpipe tobacco smoking with lung cancer diagnosis was 2.12 (95% CI= 1.32, 3.42; I^2=0%) (Appendix 4.Table 3). The calculated crude RR for the association with lung cancer mortality was 4.39 (3.82-5.04). A sensitivity analysis restricted to one study with no major methodological limitations produced an OR of 3.00 (95% CI= 1.20, 7.60) ([60]).

7- Prostate cancer

One case control study assessed the association between waterpipe tobacco smoking and prostate cancer([28]). A sample of 137 male participants from Northern Iran who were histologically confirmed with prostate cancer were included in the study. The OR for the association between waterpipe tobacco smoking and prostate cancer was 7.00 (95 % CI= 0.90, 56.90).

8-Colorectal cancer

One cross-sectional study assessed the association between waterpipe smoking and colorectal cancer([44]). A sample of 120 participants who were recorded on the cancer registry center of Babol and then contacted to fill in a survey about demographics and risk factors including waterpipe use. Among waterpipe smokers 22.70% of men and 15.80% of women were diagnosed with colorectal-cancer (Appendix 4.Table 3).

Pregnancy outcomes

Two retrospective cohort studies and two case-control studies evaluated the association between waterpipe tobacco smoking and pregnancy outcomes ([45-48]) (Appendix 4. Table 4). One study

also reported Apgar score, pulmonary problems, malformations and perinatal complications([46])

The pooled OR for the association of waterpipe tobacco smoking with low birth weight was 2.39 (95% CI= 1.32, 4.32; I^2=0%). The reported OR for the association of waterpipe tobacco smoking with newborn pulmonary problems was OR=3.65 (95% CI= 1.52, 8.75). The associations were not significant for Apgar scores at 1 minute and 5 minutes, malformations or perinatal complications.

Periodontal disease

Of the five studies that evaluated the association between waterpipe tobacco smoking and periodontal disease ([49-53]), four were cross sectional studies conducted in the same (or in a subgroup of the same) group of participants ([49-52]) (Appendix 4. Table 5). These four studies assessed periodontal disease using different measures (periodontal bone height loss, plaque index and gingivitis, deepening of the sulci or pockets, vertical periodontal bone loss). We did not pool data from the four related studies as they were derived from the same participants. Their results were consistently showed a significant association of waterpipe tobacco smoking with periodontal disease (OR ranging 3.00-5.00).

The fifth study was a cohort study with seven days follow-up after surgical removal of mandibular third molars and evaluated the outcome of dry socket ([53]). The reported RR for the association of waterpipe tobacco smoking with dry socket was 3.70 (p=0.001). Dry socket, or alveolar osteitis, is the most common complication following tooth extractions. It is caused by the dislodgement of the blood clot at the site of the tooth extraction, exposing underlying bone and nerves and causing increasing pain.

Infectious disease

Three cross-sectional studies evaluated the association between waterpipe tobacco smoking and hepatitis C ([54-56]). The three studies were conducted in Egypt and included male participants exposed to group waterpipe tobacco smoking (Appendix 4. Table 6). The pooled OR for the association of group waterpipe smoking with hepatitis C was 0.98 (95% CI= 0.80, 1.21).There were no eligible studies assessing the association between waterpipe tobacco smoking and the transmission of tuberculosis. The two reports that we found of outbreak investigations suggested an association between tuberculosis and sharing tobacco waterpipe and marijuana waterpipe ([62, 63]).

Infertility

One case-control study evaluated the association between waterpipe smoking and male factor infertility (based on semen analysis) ([57]) (Appendix4. Table 7). The reported OR for the association of waterpipe tobacco smoking with male factor infertility was OR = 2.50 (95% CI= 1.00, 6.30).

Metabolic syndrome

One cross-sectional study evaluated the association between waterpipe tobacco smoking and metabolic syndrome ([58]). Waterpipe smokers were significantly more likely to have hypertriglyceridemia (OR 1.63, 95% CI= 1.25, 2.10), hyper-glycaemia (OR 1.82, 95% CI= 1.37, 2.41), hypertension (OR 1.95, 95% CI= 1.51, 2.51) and abdominal obesity (OR 1.93, 95% CI= 1.52, 2.45. (Appendix 4. Table 8).

Gastro esophageal reflux disease

One cross-sectional study evaluated the association between waterpipe tobacco smoking and gastro esophageal reflux disease (GERD) ([17]). The reported odds ratio for the association of waterpipe tobacco smoking with having any gastro-esophageal reflux disease symptom was 1.25 (95% CI= 1.01, 1.56) (Appendix 4, Table 8).

Cardiovascular disease

Two cross-sectional studies evaluated the association between waterpipe tobacco smoking and cardiovascular disease ([14, 16]). In one study the reported odds ratio for the association between waterpipe tobacco smoking and heart disease was 1.67 (95% CI= 1.25, 2.24). The other study was based on data obtained from a population based cohort study conducted in the Golestan province in Iran and included individuals between 40-75 years old. The reported OR for the association between waterpipe tobacco smoking and heart disease was 3.75 (95% CI= 1.55, 9.22) (Appendix 4. Table 8)

Mental Health

One cross-sectional study conducted among institutions participating in the national college health assessment of the American college health association, evaluated the association between waterpipe tobacco smoking and mental health ([59]). All mental health diagnoses were significantly associated with increased rates of waterpipe tobacco smoking with ORs ranging from 1.30 to 2.40 (Appendix 4. Table 8).

Mortality outcomes

One cohort study associated waterpipe tobacco smoking with mortality outcomes ([15]). The first study by Fen Wu et al, found that waterpipe tobacco smoking was significantly associated with increased risk of mortality from all cause (HR=1.15 and 95% CI 0.93, 1.43), cancer (HR= 1.30 and 95% CI= 0.78, 2.18) and ischemic heart disease (HR=1.20 and 95% CI= 0.87, 1.67). (Appendix 4. Table 8).

Discussion

We systematically reviewed the medical literature for the effects of waterpipe tobacco smoking on health outcomes. We found that waterpipe tobacco smoking was associated with respiratory diseases (COPD, bronchitis and wheezes due to exposure to passive water-pipe smoking),oral cancer, lung cancer, low birth weight, metabolic syndrome, cardiovascular disease and mental health. The existing evidence suggested no association with esophageal cancer, gastric carcinoma, bladder cancer, prostate cancer, hepatitis C infection, periodontal disease, gastro-esophageal reflux disease, nasopharyngeal carcinoma, bladder cancer, infertility, and mortality.

Cigarette smoking is known to be a major cause of respiratory diseases through promoting lung function loss and decreasing lung function rates ([64-66]). In a similar manner, Waterpipe smoking was associated with significant reduction in FEV-1 and FVC by 4.04% and 1.38% respectively compared to non waterpipe smokers ([67]). This suggests an obstructive mechanism as was similarly reported by Chaouchi et al who have shown that chronic use of waterpipe with one or more smoking sessions per day can lead to COPD([68]) . This result is also in agreement with the reported estimates that tobacco smoking increases the risks of death from lung cancer or COPD

by 20 folds([6]). Another mechanism for the effect of waterpipe smoking on respiratory outcomes was found to be through the damage that it causes to the lung parenchyma and the associated inflammation to the airways ([69, 70]).

Tobacco was found to be a source of 69 carcinogens thus has been widely associated with increasing the risk of developing cancers and malignancies ([6, 71]). Thus, strong associations have been established between cigarette smoking and different cancers particularly in the lungs and the digestive system ([65, 66, 72-75]). These results can also be extended to include waterpipe smoking as has been reported by a study of 56 chronic Pakistani waterpipe smokers that found markedly increased levels of carcinoembryonic antigen (CEA) as compared to non-smokers ($p < 0.0001$)([76]). CEA is known to be elevated in lung, pancreatic, uterus and breast cancers as well as in cases of chronic inflammation. Other studies also reported increased risk of carcinogenesis among waterpipe smokers due to genotoxic and clastogenic components in the waterpipe smoke such as tar and polycyclic aromatic hydrocarbons ([69, 77]). This likely explains the association between waterpipe tobacco smoking and cancers outside the lung such as prostate cancer, an association previously shown between cigarette smoking and prostate cancer([78, 79]) There is also evidence that smoking induces hormonal changes in men that could affect the risk of prostate cancer([80]).

The effects of tobacco on atherosclerosis have been attributed to various mechanisms that promote atherosclerosis and endothelial dysfunction([6, 81]). Cigarette smoking has been associated with cardiovascular disease through promoting atherosclerosis and being highly dose related ([81-83]). Similarly, a comparative double blinded study done on 37 waterpipe smokers who reported smoking waterpipe 2-5times/month showed increased mean (±SEM) plasma nicotine concentration (3.6 ± 0.7 ng/ml) and heart rate (8.6 ± 1.4 bpm) as compared to placebo

(0.1 ± 0.0 ng/ml; 1.3 ± 0.9 bpm), indicating that the effects of waterpipe smoking on cardiovascular outcomes are mediated by its nicotine content[84]. Some studies also attributed the deleterious effects of watetpipe smoking on cardiovascular disease to in vivo oxidation injury and systemic inflammation that increases the likelihood of atherosclerosis and arrhythmia ([85-87],[2])

Strengths and limitations

To our knowledge, no systematic reviews have been conducted on the association between waterpipe smoking and health outcomes since our earlier review in 2010. Further strengths of the review include adhering to the Cochrane Collaboration methodology, which is considered the gold standard for systematically reviewing literature, using a sensitive search strategy, and conducting screening and data extraction independently and in duplicate.

The confidence in the effects estimates in this systematic review is affected by a number of limitations. Indeed, five out of 11 meta-analyses suffered from high degree of heterogeneity namely (esophageal carcinoma, gastric carcinoma, low birth weight, COPD and quality of life). Also, Appendix 4 shows the methodological limitations of the included studies. Most of the studies used non-validated tools for measurement of waterpipe tobacco exposure, which is a major limitation given that the practice of waterpipe tobacco smoking can vary widely according to the quantity of tobacco used, the frequency and the length of the session.

We were not able to conduct meta-analyses for all outcomes. One reason was the high level of heterogeneity as was the case for the quality of life outcome. Another reason was that we could not pool several outcomes several outcomes derived from the same study, as was the case for the metabolic syndrome, nasopharyngeal carcinoma, gastro esophageal reflux disease, mental health, and mortality outcomes.

Additional research implications of our findings include the need for more research on this topic using validated tools for measurement of both the exposure and the outcome of interest. There is also a need to investigate the effect of second hand exposure due to the amount of smoke generated by a waterpipe.

Our findings have both clinical and public health implications. Our findings reinforce the message that all forms of combustible message are unsafe, and clinicians should be clear about delivering this unified message to patients. Given the available evidence, public health agents and policy makers need not to wait for more evidence to enact and implement laws, and develop public health programs to reduce waterpipe tobacco use, particularly among youth. This is particularly relevant given the emerging evidence that waterpipe tobacco smoking may predict cigarette initiation and thus serve as a gateway to cigarette smoking ([88]).

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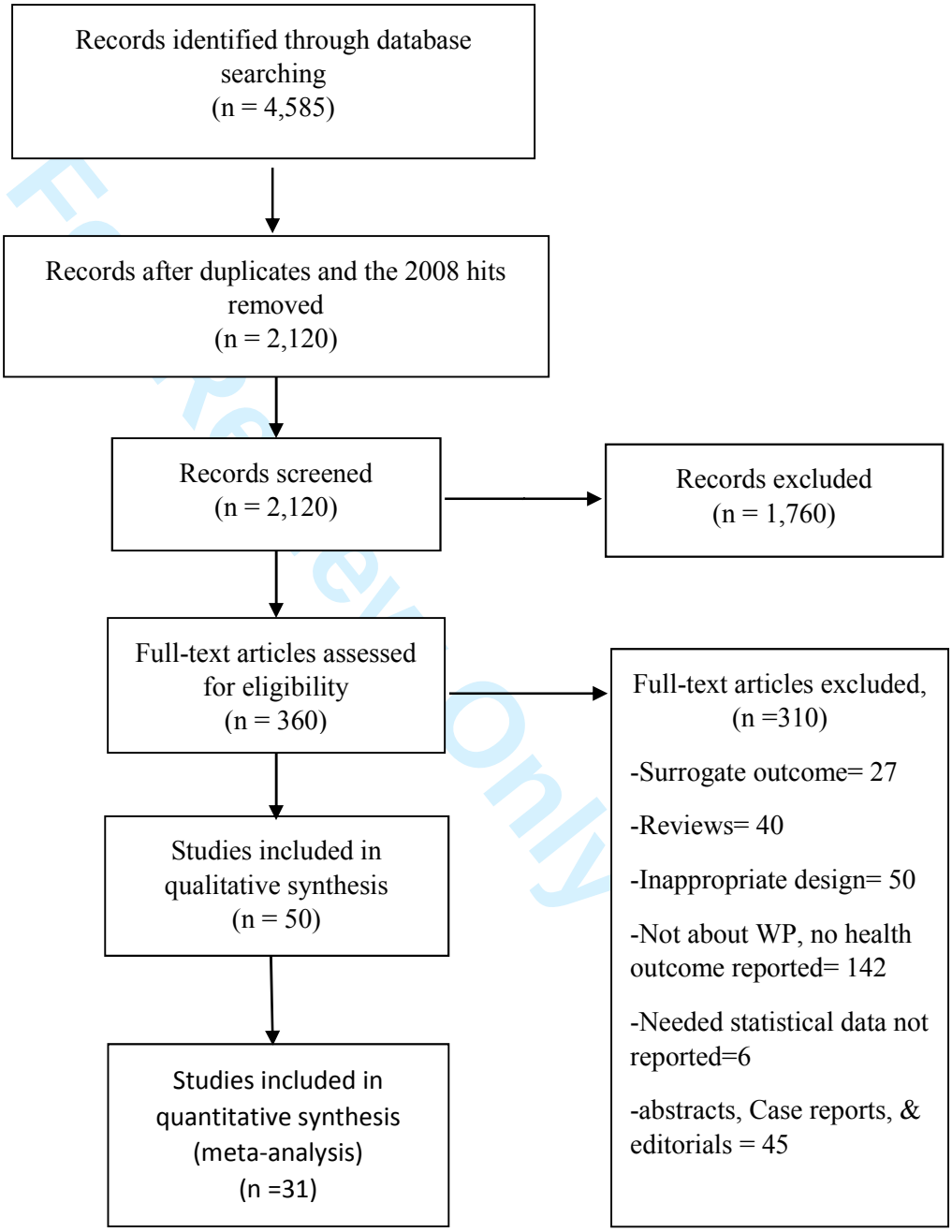
Appendix 1: PRISMA flow chart

PRISMA Flow Diagram-Effects of WP on health outcomes-Update 2015



Appendix 2: Electronic search strategy

MEDLINE (1950 onward)

Waterpipe*.mp.

"water pipe*".mp.

shisha*.mp.

sheesha*.mp.

hooka*.mp.

huqqa*.mp.

guza*.mp.

goza*.mp.

narghil*.mp.

nargil*.mp.

arghil*.mp

argil*.mp

(hubbl* adj3 bubbl*).mp.

or/1-13

EMBASE (1988 onward)

Waterpipe*.mp.

“water pipe*”.mp.

shisha*.mp.

sheesha*.mp.

hooka*.mp.

huqqa*.mp.

guza*.mp.

goza*.mp.

narghil*.mp.

nargil*.mp.

arghil*.mp

argil*.mp

(hubbl* adj3 bubbl*).mp.

or/1-13

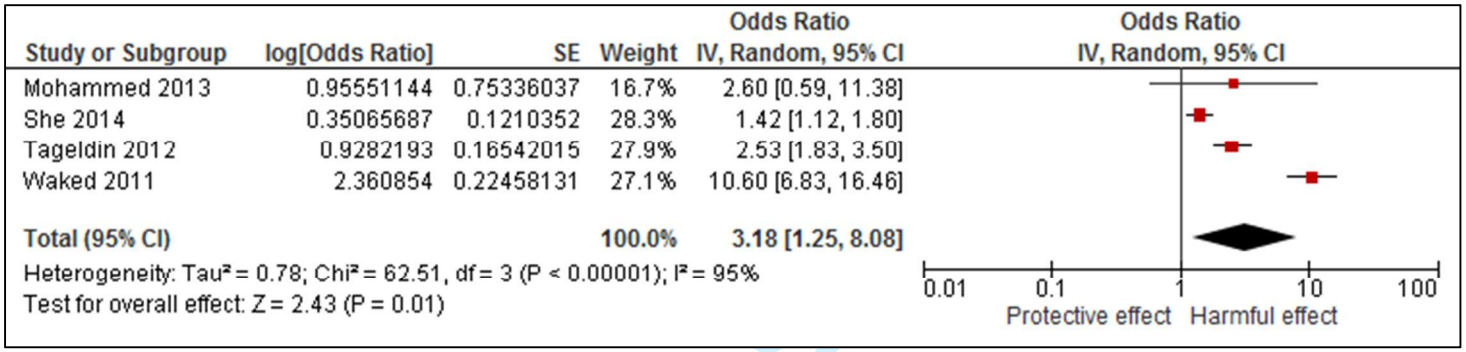
ISI the Web of Science

(waterpipe* OR "water pipe*" OR shisha* OR sheesha* OR hooka* OR huqqa* OR guza* OR goza* OR narghil* OR nargil* OR argil* OR arghil* OR (hubbl* SAME bubbl*)) AND (smoking OR smoke OR health OR disease OR cancer* OR malignan* OR lung* OR pulmonary OR heart OR cardiac OR vascular OR stroke) (in Title or Topic)

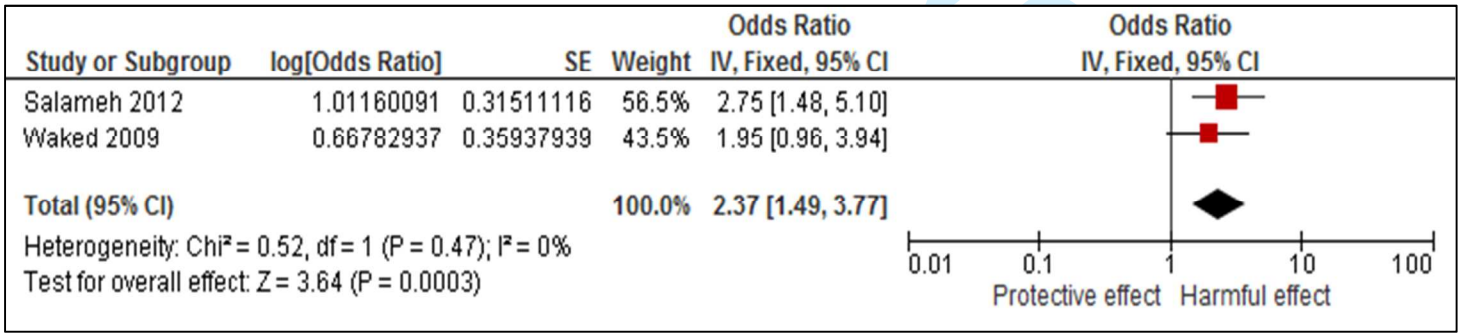
Appendix 3: Meta-analyses

Figure 2: Association between waterpipe tobacco smoking and **respiratory diseases (a, b &c)**

a- Association between waterpipe tobacco smoking and **COPD**



b- Association between waterpipe tobacco smoking and **bronchitis**



c- Association between waterpipe tobacco **passive smoking and wheezes**

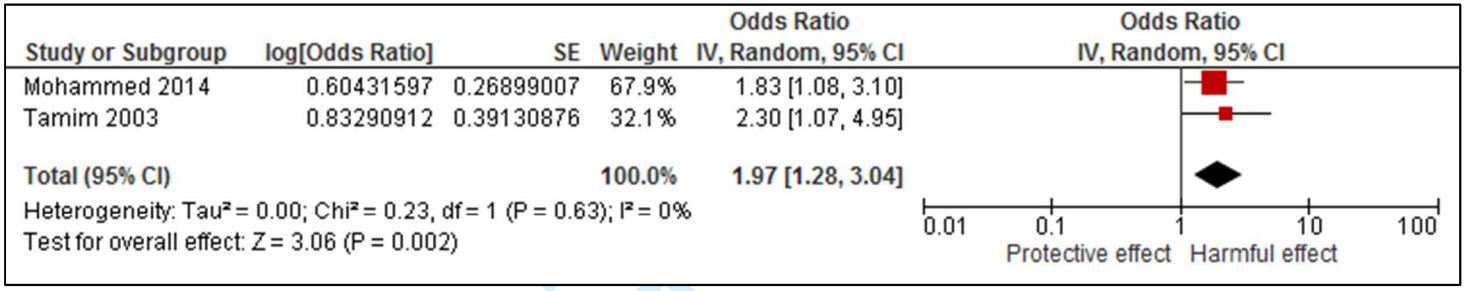


Figure 3: Association between waterpipe tobacco smoking and **Quality of life**

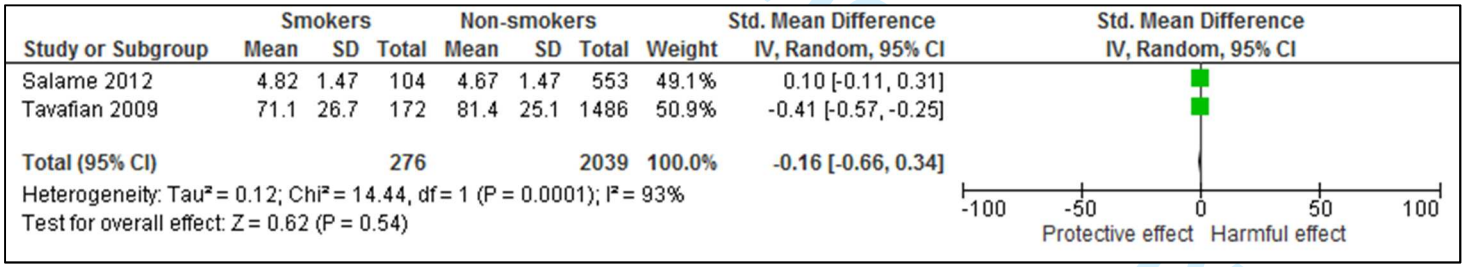


Figure 4: Association between waterpipe tobacco smoking and **esophageal cancer**

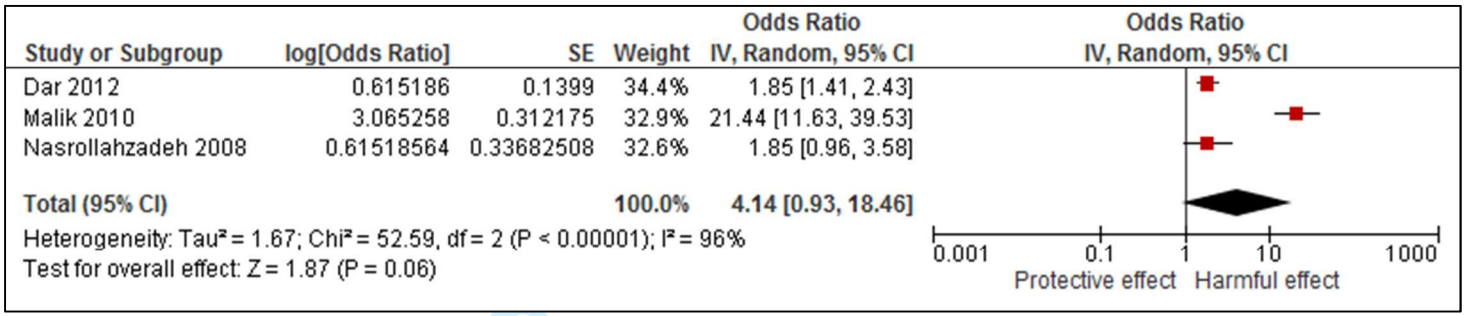


Figure 5: Association between waterpipe tobacco smoking and **Gastric cancer**

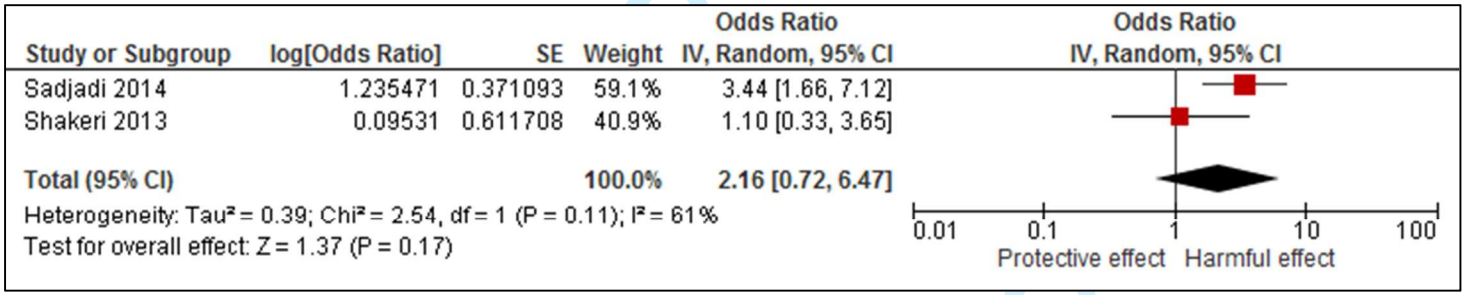


Figure 6: Association between waterpipe tobacco smoking and **oral cancer**

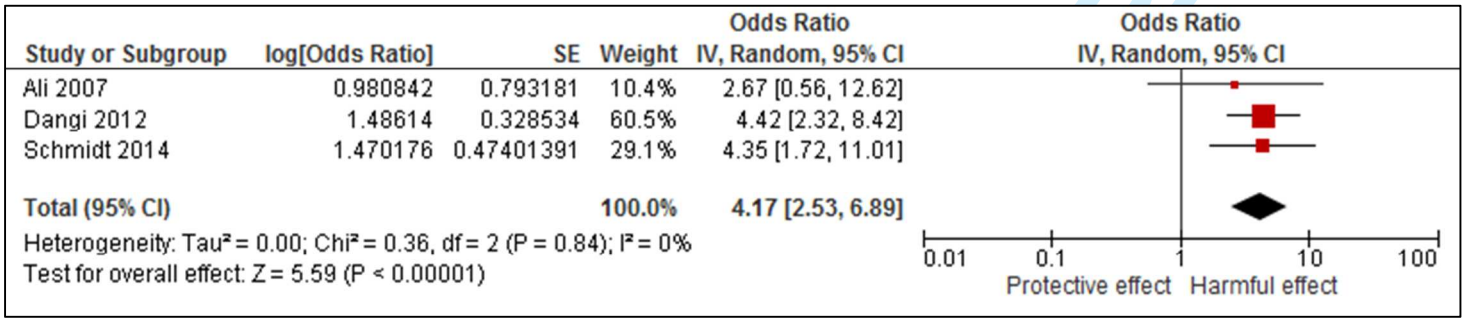


Figure 7: Association between waterpipe tobacco smoking and **Bladder cancer**

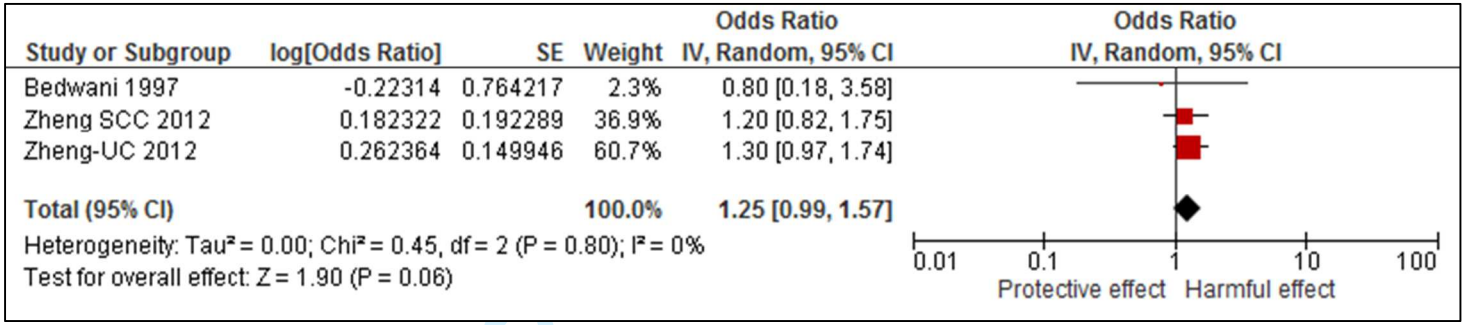


Figure 8: Association between waterpipe tobacco smoking and **lung cancer**

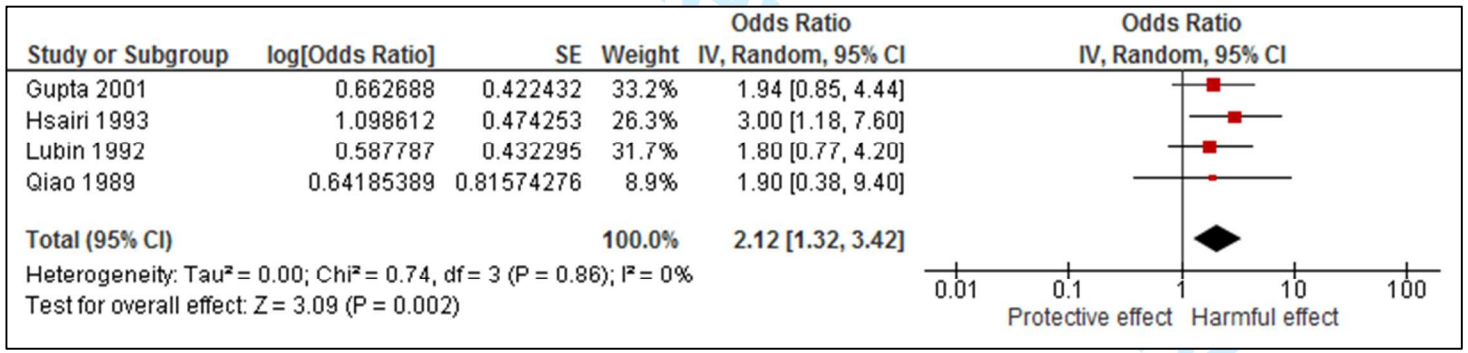


Figure 9: Association between waterpipe tobacco smoking and **low-birth weight**

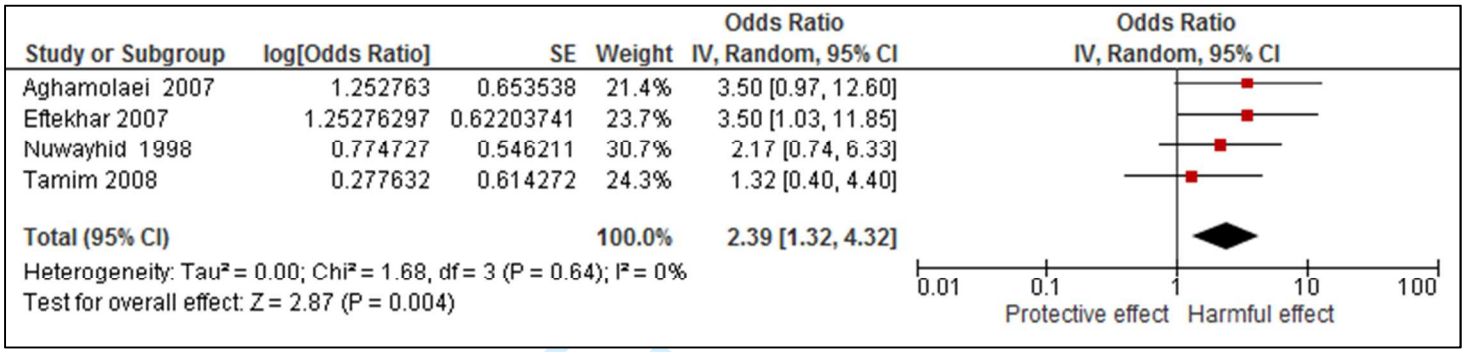
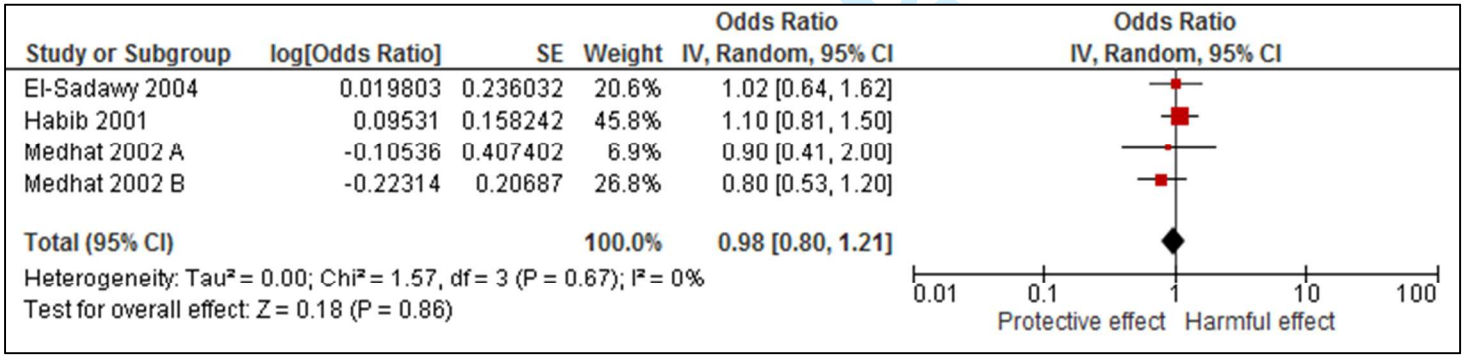


Figure 10: Association between waterpipe tobacco smoking and **hepatitis C infection**



Appendix 4: Included studies

Table 1 : respiratory disease

ID	Study design Funding	Study setting and population	Exposure	Outcome	Methodological features	Results
1	**Tamim 2003 ([1])** • Study design: Cross-sectional study • Funding: not reported	• Setting and period: students in the 2nd and 3rd intermediate classes from 5 primary schools in Greater Beirut area, in April 2000 • Population: 625 students with mean age 13 years (range 10-15). 143 students (85 males) reported respiratory tract symptoms, 482 students (237 males) reported no symptoms.	• Type: Second hand exposure to cigarettes and waterpipe. • Measurement tool: questionnaire, standardization not reported	• Health outcome: Respiratory illness throughout the year (not seasonal) including nasal congestion or wheezing • Measurement tool: questionnaire assessing clinical condition throughout the year • Blinding of outcome adjudicator: not reported	• Selection bias: sample representative of populations of the 5 primary schools • Information bias: objective outcome measurement: no, standardized exposure measurement: no • Confounding: no matching or adjustment in the analysis reported • Participation rate: not reported	• OR compared to no exposure at home 2.3 (1.1-5.1) (waterpipe only exposure)
2	**Mohammad 2013 ([2])** • Study design: Cross-sectional • Funding: not reported	• Setting and period: A questionnaire was given to 788 randomly selected females during 1 week in the fiscal year 2009–2010 in 22 primary care centers in six of the fourteen different regions of Syria. Inclusion criteria were age 6 years, presenting for any medical complaint	• Type: Waterpipe and cigarette smoking (active vs passive) • Measurement tool: Standardized questionnaire	• Health outcome: COPD • Measurement tool: GARD spirometry form + lung-function measurements	• Selection bias: "Female patients 6 years of age or older were randomly recruited from 22 centers in six of the 14 different regions of Syria" • Information bias: valid outcome measurement: yes, valid exposure measurement: yes • Confounding: Unclear • Participation rate:	• OR of waterpipe smokers compared to non-smokers 2.6 (0.6-11.5)

					Not reported	
3	**Mohammad 2008([3])** • Study design: Cross sectional • Funding: Not reported	• Setting and Period: A survey was performed during the first semester of 1994 among 77 female narguileh smokers, and was completed in the first semester of 1995 for 77 cigarette smokers and 100 nonsmoker controls. All these women were older than 14 (range 14–70) and were recruited from the general population by a field survey. For a woman to be eligible, they were required to have no comorbidity, no respiratory symptoms related to factors other than smoking, and no exposure to other known risk factors in her daily life	•Type: Cigarette smoking, waterpipe smoking and non-smoking •Measurement tool: Locally-designed and pilot-tested questionnaire •Exposure levels of included subjects: Women were categorized up to their cumulative duration of smoking by 5 years for time and to the cumulative quantity smoked by 50 kilos for quantity. We obtained 10 pairs of subgroups for time and 8 pairs of subgroups for quantity. Duration of smoking was directly obtained from the questionnaire, while a quantitative evaluation of smoking was indirectly calculated according to the type of smoking: For narguileh smokers, we used the following formula: Q = S.q (g).T (days)/1000	• Health outcome: Chronic Respiratory symptoms • Measurement tool: questionnaire + flow-volume loop was performed with all women	• Selection bias: the survey was performed during the first semester of 1994 among 77 female narguileh smokers, and was completed in the first semester of 1995 for 77 cigarette smokers and 100 nonsmoker controls. All these women were older than 14 (range 14–70) and were recruited from the general population by a field survey • Information bias: valid outcome measurement: yes (questionnaire + OPD tests), valid exposure measurement: yes • Confounding: Unclear • Participation rate: 100/254 were seen in the OPD only	• No odds ratios reported
4	**Tageldin 2012 ([4])** • Study design: Cross-sectional • Funding:	• Setting and period: Eleven countries: Algeria, Egypt, Jordan, Lebanon, Morocco, Pakistan, Saudi Arabia, Syria, Tunisia,	• Type: Previous daily waterpipe smoking • Measurement tool:	• Health outcome: Symptomatic COPD	• Selection bias: Representative sample from eleven countries.	• OR of previous daily waterpipe smokers

	GlaxoSmithKline Laboratories,	Turkey and UAE, between June 2010 and December 2011.	Questionnaire/(Self-reported		• Information bias: Validation of the exposure measurement tool is unclear • Confounding: Adjusted for multiple factors including cigarette smoking • Participation rate: Not reported	compared to non-previous daily waterpipe smokers: Chronic bronchitis AOR 1.42 (1.12-1.80)
5	**Salameh 2012 ([5])** • Study design: Case-control • Funding: None mentioned	• Setting and period: Two tertiary care hospitals in Beirut between July 2009 and June 2010	• Type: Waterpipe smoking • Measurement tool: Self-reported-questionnaire	• Health outcome:Chronic bronchitis • Measurement tool: Diagnosed by chest physician and responded positively to the question "Have you had a productive morning cough for more than 3 months a year for more than 2 years?"	• Selection bias: Newly diagnosed cases with chronic bronchitis were recruited and controls recruited from outpatient clinics. • Information bias: Validation of the exposure measurement tool is unclear • Confounding: adjusted for multiple covariates including previous cigarette smoking • Participation rate: Not reported	• OR of ex-waterpipe-only smokers compared to never smokers. AOR 6.40 (2.55-16.11) • Current waterpipe-only smokers compared to never smokers AOR 1.87 (0.74-4.72) • Current waterpipe-only-dependent smokers compared to never smokers

						AOR 3.74 (1.24-7.58)
6	**Waked 2011 ([6])** • Study design: Cross-sectional • Funding: Boehringher Ingelheim Pharmaceuticals	• Setting and period: Lebanon, October 2009 and September 2010 • Participants: More than 40 years old	• Type: Current waterpipe • Measurement tool: Self-reported questionnaire: validation not reported	• Health outcome: COPD • Measurement tool: The questionnaire of the American thoracic society for evaluation of chronic pulmonary disease and the Medical research council (MRC) for evaluation of dyspnea.	• Selection bias: Multistage cluster sampling from all over Lebanon • Information bias: Validation of the exposure measurement tool is unclear • Confounding: Adjusted for multiple variables including previous cigarette smoking • Participation rate: Not reported	• OR of current waterpipe smokers compared to non-current waterpipe smokers: 2.53 (1.83-3.50)
7	**Waked 2009([7])** • Study design: Cross-sectional. • Funding: Not reported	• Settings and Period: Telephone interview of randomly selected participants from a list of active users provided by the national telephone company • Population: Lebanese, aged ≥ 16 years and being a regular WP smoker (defined as current smoking of ≥ 1 WP per week) or a non-WP smoker.	• Type : Cigarette and waterpipe • Measurement tool: Telephone interview using standardized Arabic questionnaire. • Exposure levels of included subjects: calculated by multiplying the number smoked per week by the duration of WP smoking; the product was divided into 4 cumulative exposure classes: non-smokers, 1–3 WP years, 4–28 WP	• Health outcome: Respiratory disease. • Measurement tool: Respiratory disease was assessed by a positive answer regarding physician-diagnosed chronic respiratory disease (PDRD). Chronic bronchitis was defined as having a morning productive cough for > 3 months a year for > 2 years.	• Selection bias: The selected waterpipe smokers represented Lebanese household who answered the phone and were randomly selected. • Information bias: Standardised Arabic questionnaire was used • Confounding: Adjusted for potential confounding including Age, sex.	• OR of waterpipe smokers compared to non-smokers 1.95(0.99-4.05)

			years and > 28 WP years.		BMI, education, work status, marital status, active cigarette smoking and passive smoking. • Participation rate: N/A	
8	**Mohammad 2014[8]** • Study design: Cross-sectional study • Funding: "provided by the ISAAC Data Center (University of Auckland, Auckland, New Zealand) and Tishreen University, Lattakia, Syria"	• Setting and period: In 3 centers with children coming from 24 randomly selected schools in Tartous, Syria, between March 2001 and November 2002 • Participants: - Inclusion criteria: children who are 6-7 years old from the selected schools - Excluded: 266 of the 3000 students that were randomly selected were excluded but without stating the reasons of exclusion - Included: 2734 students, age group 6-7 yo with a mean of 6.6 years, 49% of which were females, and they had a mean BMI of 15.6 kg/m^2	• Type: Passive waterpipe and/or cigarette smoke exposure • Measurement tool: Questionnaire that was validated by ISAAC screening committee and filled by the parents of the exposed children after face-to-face meetings with the research staff to explain the process to them Exposure levels of included subjects: Could not be assessed; "we did not track the quantity smoked, as there is no standardized validated method for quantifying narghile smoking"	• Health Outcome: Wheezing, nocturnal coughs, and rhinoconjunctivitis • Measurement tool: Validated questionnaire by ISAAC with separate modules for symptoms of asthma, rhinoconjuntivitis, and eczema	• Selection bias: Low Risk; Random selection of schools and the children in them • Information bias: The questionnaires were validated for specificity and sensitivity with the use of standard ISAAC definitions • Confounding: adjusted for concomitant smoking of cigarettes and waterpipes • Participation rate: 2734/3000	• OR (95% CI); p-value: Ever Wheezing: -For father smoking: 1.374 (0.952-1.982); p=0.088 -For mother smoking: 1.749 (1.194-2.560); p=0.004 -For both smoking: 1.829 (1.08-3.1); p=0.023
9	**She 2014[9]** • Study design: Cross-sectional study • Funding: "supported	•Setting and period: Multicenter population based study from 10 Chinese towns (Dahe, Dongshan, Housuo, Fuchun, Zhongan, Yingshang, Zhuyuan, Laochang, Shibalianshan,	• Type: Water-pipe smoking versus never smoking (men); The study also looked at passive waterpipe smoking versus never passive smoking	• Health Outcome: Prevalence of COPD • Measurement tool: "Lung function (ie, FEV 1, FVC, and FEV 1 /FVC) was examined	• Selection bias: Population based study • Information bias: Validation of the tool used for	• Mean +/- SD: In men: Chinese Water-pipe smokers: 115 +/- 56.1

primarily by the National Key Scientific and Technology Support Program, Collaborative Innovation of Clinical Research for Chronic Obstructive Pulmonary Disease and Lung Cancer [2013BAI09B09] . Dr She was supported by the National Natural Science Foundation for Young Scholars of China [81200051]; the Research Fund for the Doctoral Program of Higher Education of China [20110071120060]; the Science Foundation for Young Scholars in Zhongshan Hospital [2012ZSQN04]; and the Scientific Project for Fudan University [20520133474]"	and Huangnihe) covering a wide geographic area in Fuyuan County, Yunnan Province, China between October 15, 2011 and January 12, 2013 • Participants: - Inclusion criteria: randomly sampled residents ≥ 40 years of age from the designated towns . - Included: 1238 individuals, 205 of which were active water-pipe smokers (mean age: 55.1 years), 219 passive water-pipe smokers (mean age: 53.9 years), 198 never smokers (mean age: 56.7 years), and 203 never passive smokers (mean age: 55.4 years). The rest were active or passive cigarette smokers	for women. • Measurement tool: Standard questionnaire by trained personnel • Exposure levels of included subjects: Reported for cigarette smokers as "dose of cigarette smoke" but not reported for water-pipe smokers	by spirometry (CHEST HI-801; CHEST M.I., Inc); According to the diagnostic criteria of the GOLD (Global Initiative for Chronic Obstructive Lung Disease), subjects with a post-bronchodilator FEV 1 /FVC < 70% were assigned as having COPD.""	measurement of exposure is unclear • Confounding: adjusted for CO, BMI, hypertension, and cleanliness of water used in Chinese water-pipes, as confounders in the development of COPD • Participation rate: not reported	with COPD Vs Never smokers: 31 +/- 15.7 with COPD • OR (95% CI); p-value: In men: Chinese Water-pipe smokers: 10.61 (6.89-16.34); p < 0.001

Table 2 : Quality of life

10	**Tavafian 2009 ([10])** • Study design: Cross-sectional • Funding: Hormozgan University of Medical Sciences	• Setting and period Bandar Abbas, Iran, June-July 2007 • Participants: - Excluded: N=not reported <15 years old, language barrier - Included: N=1675, 50.4% female, mean age (SD) 42.1 (16.5), 56.7% have 6-12 years of education, 36.8% employed, 70.6% married	• Type: Current waterpipe smoking • Measurement tool: Self-reported questionnaire: validation not reported • Measurement time points: N/A Exposure levels of included subjects: N/A	• Health outcome: Health Related Quality of Life: Physical Component Summary and Mental Component Summary • Measurement tool: Self-reported questionnaire (Short Form Health Survey 36; SF-36): previously reported validated tool • Blinding of data collector: not reported • Blinding of outcome adjudicator: not reported	• Selection bias: Multistage random sampling • Information bias: Unclear definition of current waterpipe smokers • Confounding: adjusted for gender, age, years of education, employment status and marital status. In second model, adjusted for cigarette smoking status instead of age. • Participation rate: N/A	• OR of current WP smokers, compared non-current WP smokers: Model 1: • Physical Component Summary 2.15 (1.56-2.96) • Mental Component Summary 1.88 (1.36-2.60) • Additional results: AORs adjusted for gender, age, years of education, employment status, marital status Model 2: • Physical Component Summary 2.27 (1.56-3.11) • Mental Component Summary 1.65 (1.24-2.71) • Additional results: AORs adjusted for gender, years of education, employment status, marital status and cigarette smoking
11	**Joseph 2012 ([11])** • Study design: Cross sectional • Funding: Not reported	• Settings and period: study was carried out between October 2009 and September 2010, using a multistage cluster sample (n = 2201) across Lebanon.	• Type: Waterpipe smoking • Measurement tool: Mean number of weekly waterpipe multiplied by duration of smoking.	• Health outcome: Respiratory quality of life • Tool: Clinical COPD questionnaire (hecked for construct validity and reliability)	• Selection bias: multistage cluster sample all over Lebanon. • Information bias: Data collected after referral from pulmonogist. Confounding: adjusted for cigarette smoking status, age, sex,	• OR of current waterpipe smokers compared to non-smokers. Mean=1.99 (standard deviation=1.57) and P value < 0.001

				residency, education, work status and marital status Participation rate: 90%		

Table 3 : cancer

12	**Malik 2010 ([12])** • Study design: Case-control • Funding: Indian Council of Medical Research (ICMR), New Delhi	• Setting and period: Kashmir Valley, India, May 2006-August 2008 • Cases: N=135, not clear if incident • Controls: N= 195, cases:control ratio 1:1.4	• Type: Waterpipe smoking • Measurement tool: self-reported face-to-face interview	• Health outcome: Oesophageal cancer • Measurement tool: Histopathologically confirmed diagnosis	• Selection bias: Cases were untreated and histopathologically confirmed • Information bias: Definition of current waterpipe smoker is unclear • Confounding: adjusted for age and gender • Participation rate:N/A	• OR of waterpipe smokers compared to non-waterpipe smokers 21.44 (11.63-39.54) • Adjusted for age and gender
13	**Dar 2012 ([13])** • Study design: Case-control • Funding: Indian Council of Medical Research (ICMR), New Delhi.	• Setting and period: Kashmir Valley, India, September 2008 – January	• Type: Ever waterpipe smoking • Measurement tool: self-reported face-to-face interview • Measurement time points: N/A Exposure levels of included subjects: reported in	• Health outcome: Oesophageal squamous cell carcinoma • Measurement tool: Histologically confirmed diagnosis	• Selection bias: Cases were histologically confirmed • Information bias: Validation of exposure measurement tool is unclear	• OR of waterpipe smokers compared to never waterpipe smokers 1.85 (1.41-2.44)

		2012 • Cases: N=702, incident • Controls: N= 1663, cases:control ratio 1:2.4	categories	• Blinding of data collector: not reported • Blinding of outcome adjudicator: not reported • Incidence: N/A	• Confounding: adjusted for age, ethnicity, religion, rural residence, education level, daily fruit and fresh vegetable intake, ever use of bidi, cannabis, gutka and alcohol, and cumulative use of cigarette, and nass • Participation rate:	
14	**Nasrollahzadeh (2008)** [14] • Study design: case-control study • Funding: Digestive Disease Research Center : Tehran University of Medical Sciences (DDRC/TUMS); and National Cancer Institute at National Institute of	• Setting and period: Atrak Clinic in Gonbad City, eastern Golestan Province of Iran, Dec 2003 to Jun 2007 • Cases: 300 esophageal squamous cell carcinoma cases, 50% males, mean age 64.5 years Controls: 571 controls, two population based matched control subjects per case for 90% of cases	• Type: Waterpipe smoking • Measurement tool: self-developed questionnaire, tested for reliability and validity, cumulative consumption calculated as waterpipe-years and categorized into never users, ≤ 32 waterpipe-years, > 32 waterpipe-years • Exposure levels of included subjects: median of 32 waterpipe-years	• Health outcome: Esophageal squamous cell carcinoma diagnosis • Measurement tool: Histopathologically confirmed • Blinding of outcome adjudicator: not reported •	• Selection bias: series of incident cases (70% of incident cases registered with local cancer registry were referred to the Atrak Clinic), controls were selected from the same study base as cases • Information bias: objective outcome evaluation: yes; standardized exposure measurement: yes.	OR compared to no smoking: • 1.85 (0.95-3.58) (waterpipe smoking) • 1.69 (0.76-3.77) (<u>waterpipe only</u> smoking) • Test for trend significant for intensity (p=0.03) but not for duration, total amount, or age started)

	Health				• Confounding: matching for age, sex, residence; adjustment for education, ethnicity, other types of tobacco use, total intake of fruit and vegetables • Participation rate: not reported	•
15	**Hosseini 2009 ([15])** • Study Design : Case Control • Funding: Not reported.	• Settings and Period: this study was conducted in Mazandaran province in Northern Iran between 2005 and 2008. •Cases: A total of 137 male histologically confirmed prostate cancers whose addresses were taken from Mazandaran cancer registry were defined as the case series. •Controls: 137 controls were from the same neighborhood as each case. In selecting controls, the male neighbor closest in age to the case was recruited.	• Type: Waterpipe smoking • Measurement tool: Questionnaires by trained interviewers. • Exposure levels of included subjects: not reported.	• Health outcome: Prostate cancer. • Measurement tool: histologically confirmed prostate cancer cases from Mazandaran cancer registry.	•Selection bias: Representative sample •Information bias: Validation of the tool used for measurement of exposure is unclear •Confounding: Adjusted for age and place of residence •Participation rate: N/A	• OR of waterpipe smokers compared to non-smokers 7.0 (0.9 – 56.9)
16	**Sadjadi 2014 ([16])** • Study design : Prospective Cohort • Funding : Not reported	• Settings and Period: • Population based follow up study took place in Ardabil province, North West Iran. • 928 participants were included based on a H. Pylori positive test in either histology or rapid urease test.	• Type: Waterpipe smoking • Measurement tool: Validated questionnaires. • Exposure levels of included subjects: 10 years	• Health outcome: Gastric Cancer • Measurement tool : Histology of specimen collected on endoscopy or surgery.	• Selection bias: Representative sample • Information bias: Only cases with confirmed H.Pylori included • Confounding: adjusted for age and all variables	• OR of waterpipe smokers compared to non-smokers 3.44, 95% CI (1.66–7.11), P

					Alternative means as radiology reports, physician reports and death reports were used as an alternative if Histo-pathological assessment wasn't available.	included in the multivariable analysis as: Cigarette smoking, opium use, Salt intake and Fruit intake. • Participation rate:N/A	value- 0.001
17	**Shakeri 2013([17])** • Study design : Case-control • Funding: not reported.	• Settings and Period: In Gonbad city, the largest city in Golestan province in the period from December 2004 to December 2011. -Cases: Cases who were suspected of having upper gastrointestinal (GI) tract diseases, were referred by the local physicians to the Atrack clinic where they underwent upper GI endoscopy. Only patients with confirmed Adenocarcinoma were invited to participate. A total of 309 cases of gastric adenocarcinoma (118 non-cardia, 161 cardia and 30 mixed-location adeno-carcinomas) were enrolled. -Controls: a total of 613 cases matched for age, sex and neighbor-hood were selected. Controls were selected from 50,045 healthy subjects aged 40-47 years who were enrolled	• Type: Waterpipe smoking • Measurement tool: Validated questionnaire. • Exposure levels of included subjects : Not reported.	• Health outcome: Gastric adenocarcinoma. • Measurement tool: Clinically and by GI endoscopy by expert pathologists at the Digestive Disease Research Center, Tehran University of Medical Sciences.	• Selection bias: Cases were recruited from Atrak clinic in Gonbad • Information bias: Cases confirmed with pathology reports and upper GI endoscopy • Confounding: adjusted for ethnicity, education, wealth score, total daily fruit intake and total daily intake of vegetables and tobacco use. • Participation rate:N/A	• OR of ever versus never waterpipe smokers Adjusted OR & 95% CI : 1.1(0.3–3.3)

		in the Golestan Cohort study between January 2004 and June 2008.				
18	**Karajibani 2014**[18] • Study design: Case-control study • Funding supported by the Deputy of Research	• Setting and period: In the cancer clinic of Imam Ali Hospital, Zahedan, Sistan and Baluchistan Province, southeast of Iran between December 2011 and October 2012 • Participants: - Inclusion criteria: participants were diagnosed with GC or non-GC based on the pathologicalor cytology findings - Excluded: 4 of the 50 Gastric cancer patients (3 men and 1 women) were excluded but without stating the reasons of exclusion - Included: 50 Gastric cancer patients, 33 men and 17 women, ages 60 +/- 14.5 years and 46 Healthy subjects, 30 men and 16 women, ages 59 +/- 14.1 years	• Type : waterpipe smoking • Measurement tool: self-report or by relatives.	• Health Outcome: Gastric Cancer • Measurement tool: Using the International Agency for Research on Cancer (IARC/WHO) guidelines and Pekka Lauren's system for classification of tumors while their diagnosis was based on histological methods	• Selection bias: series of hospital-based incident cases (December till October) • Information bias: Validation of the tool used for measurement of exposure is unclear (self-reported exposure or by relatives) • Confounding: adjusted for use of water purifiers in pipeline water • Participation rate: 46/50 GC patients vs 46/46 healthy controls	• Mean +/- SD: Frequency of hookah smoking: In Gastric cancer patients: 3 +/- 1.6 vs In healthy controls: 2 +/- 1.1 • (p-value = 0.4)
18	**Zheng 2012([19])** • Study design: case control. • Funding: Not reported.	• Settings and period : Three cancer centers in Cairo, Egypt. • -Cases: 1,886 newly diagnosed and histologically confirmed cases. • -Controls: 2,716 age, gender and residence matched,	• Type : Waterpipe smoking • Measurement tool: Structured questionnaire by trained interviewers. • Exposure levels of included subjects: not reported.	• Health outcome: Bladder cancer • measurement tool : pathology report and available slides prepared from the surgical or	• Selection bias: Cases selected from three referral centers in Cairo • Information bias: Validation of the tool used	• OR of of waterpipe only smokers versus non-users for urothelial Carcinoma

		population based controls. Two methods were used to recruit controls: random sampling of households and random sampling of family health records.		biopsy specimen of urinary bladder tissue were reviewed by either one of the two study pathologists, who worked together to standardize case classification, and report it as: (i)-urothelial carcinoma, (ii) SCC, (iii) adenocarcinoma, or (iv) other, including undifferentiated carcinomas. Carcinoma that metastasized to the bladder was excluded. This report includes only urothelial carcinoma and SCC cases. -Blinding of outcome adjudicator: not reported.	for measurement of exposure is unclear • Histologically confirmed diagnosis of bladder cancer • Confounding: Adjusted for potential confounders including tobacco use. • Participation rate: Cases (88%) and Controls (97%)	1.3 (1.0–1.8) And SCC: 1.2 (0.8–1.7)- WP and UC for Former Vs. Never (1.7 (0.9–3.1))
20	**Bedwani 1997** [20] • Study design: Case-control study • Funding: National Research	• Setting and period: Greater Alexandria, Egypt; study conducted, Jan 1994 to Jul 1996 • Cases: 151 male incident cases of invasive bladder cancer with median age 61	• Type: Waterpipe smoking • Measurement tool: self-developed structured questionnaire; standardization not reported; participants categorized as	• Health outcome: Bladder cancer diagnosis • Measurement tool: centrally reviewed histopathologica	• Selection bias: hospital-based cases of bladder cancer confirmed within the year preceding interview,	OR compared with never smoking: • 0.8 (0.2-4.0) (waterpipe smoking)

	Council-Applicazioni cliniche della ricerca oncologica (CNR-ACRO Project); and Italian Association for Cancer Research	years (range 31-74) admitted to a network of general and teaching hospitals. • Controls: 157 males admitted for acute, non-neoplastic, non-urinary tract, non-smoking-related conditions, median age 50 years (range 32-74) • 39 female cases and 30 female controls were excluded because "only one female case was a smoker	ever smokers and never smokers. Age at starting, duration of habit, average daily consumption extracted from history but not reported • Exposure levels of included subjects: not reported	l diagnosis • Blinding of outcome adjudicator: not reported	hospital-based controls selected from the same study base as cases. Selection related to exposure status (in the case of females and patients with non-smoking-related conditions) • Information bias: objective outcome evaluation: yes; standardized exposure measurement: no • Confounding: adjustment for age, education, type of house, history of schistosomiasis, high risk occupation, tobacco smoking • Participation rate: greater than 95% of eligible subjects participated in the interview	•
21	**Qiao 1989** [21] • Study design: case-control study	• Setting and period: Gejiu city, Yunnan Province, China, interviews conducted in 1985 • Cases: 107 lung cancer cases in males 35-80 years old	• Type: Chinese water pipes • Measurement tool: self-developed	• Health outcome: Lung cancer diagnosis • Measurement	• Selection bias: series of incident cases but unclear whether all incident cases	OR compared to never smoking: • 1.9 (0.4-9.4) (waterpipe

	• Funding: China State Science and Technology Commission; and the U.S. National Cancer Institute grant	reported to Labor Protection Institute of the Yunnan Tin Corporation (YTC) during 1967-1984 • Controls: 107 controls chosen systematically by selecting every 20th person from the list of all living past or present workers of the YTC; 1 control per case	questionnaire, no standardization reported; cumulative consumption calculated as pipe years • Exposure levels: Cases: mean pipe years = 177 (range 0-560); Controls: mean pipe years = 122 (range 0-480).	tool: detected by radiology and confirmed by histology or cytology • Blinding of outcome adjudicator: not reported	reported, controls were selected from the same study base as cases • Information bias: objective outcome evaluation: yes; standardized exposure measurement: no. Surrogates were interviewed for 10% of cases and 6% of controls • Confounding: matching for age; adjustment for age; no adjustment reported for radon • Participation rate: not reported	only smoking) Statistically significant dose response to water pipe smoking OR=3.4 (1.3-8.1) by quarter of pipe-years
22	**Lubin 1990** [22] • Study design: Case-control study • Funding: China Science and Technology Commission; and the U.S National Cancer Institute	• Setting and period: Gejiu city, Yunnan Province, China, study conducted in 1985 • Cases: 74 lung cancer cases in males with mean age 62years (range 35-80) alive at the time of the study reported to Labor Protection Institute of the YTC during 1981-1984 • Controls: 74 controls chosen from the list of all living past or present workers of the	• Type: Chinese water pipes • Measurement tool: self developed questionnaire, no standardization reported; cumulative consumption calculated as pipe years • Exposure levels of included subjects: # pipe years (cases/controls): 0 (6/16); 1-114 (18/23); 115-220	• Health outcome: Lung cancer diagnosis • Measurement tool: cases confirmed by an independent panel of pathologists, clinicians and cytologists	• Selection bias: series of incident cases but unclear whether all incident cases reported; excluded those who had died by the time of the study; controls were selected from the same study base as	OR compared to no tobacco smoking: • 3.6 (waterpipe only smoking)

		YTC; 1 control per case	(21/15); ≥220 (29/20)		cases • Information bias: objective outcome evaluation: yes; standardized exposure measurement: no; validated confounder measurement (arsenic): no • Confounding: matching for age (within 5-year age groups) • Participation rate: not reported • Data were sparse and authors were unable to adjust for important confounding factors	
23	**Lubin 1992** [23] • Study design: Case-control study • Funding: not reported	• Setting and period: Gejiu city, Yunnan Province, China • Cases: 427 male lung cancer patients, mean age 63 years (range 35-75); reported between 1984 and 1988 to the Cancer Registry of the Labor Protection Institute of YTC or to the Gejiu City Cancer Registry; 339 from Yunnan Tin Corporation and 88 from Gejiu City • Controls: 1011 male controls , 2 controls per case, mean age	• Type: Chinese waterpipe • Measurement tool: self-developed standardized structured questionnaire, no standardization reported; consumption calculated as pipe years • Exposure levels of included subjects: mean duration of pipe only smoking is 41 years	• Health outcome: Lung cancer diagnosis • Measurement tool: confirmed by independent panel of pathologists, clinicians, radiologists and cytologists • Blinding of outcome adjudicator: not	• Selection bias: series of incident cases, controls were community based and selected from the same study base as cases; • Information bias: objective outcome evaluation: yes; standardized exposure	OR compared to no smoking: • 1.8 (0.8-4.2) (<u>waterpipe only</u> smoking) • ORs for pipe users show increasing trend with increased duration of use (test for trend

		62 years (range 35-75), 770 from YTC and 241 from Gejiu city		reported	measurement: no. • Confounding: matching for age (within 5-year age groups) ; adjustment for age, number of years of work underground, source of subject, type of respondent • Participation rate: 72% for cases, 88% for controls	statistically significant)
24	**Hsairi 1993** [24] • Study design: Case-control study • Funding: not reported	• Setting and period: Ariana, Tunis, Dec 1988-May 1989 • Cases: 110 lung cancer patients; epidermoid (56%), anaplastic small cell (17%), undifferentiated (13%), adenocarcinoma (12%), anaplastic large cell (3%), • Controls: 110 residents of the same area	• Type: Waterpipe smoking • Measurement tool: self-developed tool, no standardization reported; • Exposure levels of included subjects: not reported	• Health outcome: Lung cancer diagnosis • Measurement tool: histologically confirmed in 70% of cases, "very probable" in 30% of cases based on clinical, radiological and endoscopic suspicion • Blinding of outcome adjudicator: not reported	• Selection bias: series of incident cases, controls were community based and selected from the same study base as cases; • Information bias: objective outcome evaluation: yes; standardized exposure measurement: no. • Confounding: matching for age, sex, consumption of cigarette per day; adjustment for age, sex, cigarette consumption,	OR compared to no smoking: • 3.0 (1.2-7.6)

					occupational risks • Participation rate: not reported	
25	**Gupta 2001** [25] • Study design: Case-control study • Funding: International Agency for Research on Cancer, Lyon France; and the International cancer related technology transfer fellowship award	• Setting and period: Northern India; recruitment, Jan 1995 - Jun 1997 • Cases: 265 incident cases of lung cancer • Controls: 525 visitors and attendants of the patients; 2 controls per case • Participants were 85% males, of different religions, ages ranging from<50 to over 70 living in rural or urban areas.	• Type: Waterpipe smoking • Measurement tool: self-developed tool, no standardization reported; cumulative consumption calculated as pack-year equivalent of cigarettes (1 waterpipe=4 cigarettes) stratified in 4 groups (0-9; 10-19; 20-29; 30+) • Exposure levels of included subjects: incompletely reported	• Health outcome: Lung cancer diagnosis • Measurement tool: detected by radiology and confirmed by histology or cytology • Blinding of outcome adjudicator: not reported	• Selection bias: series of hospital based incident cases, community-based controls selected from the same study base as cases • Information bias: objective outcome evaluation: yes; standardized exposure measurement: no • Confounding: matching for age and sex; adjustment for age, and education. No adjustment for any confounding factor including other forms of tobacco consumption • Participation rate: not reported • Missing data: 54.3 % for exposure	OR compared to no smoking: • 1.94 (0.85-4.44) in men • Numbers for women were too small to derive stable risk estimates

26	**Hazelton 2001** [26] • Study design: Retrospective cohort study • Funding: National Institute of Health	• Setting and period: Gejiu city, Yunnan Province, China, 12 years follow up (1976-1988) • Exposed: 1289 male waterpipe only smokers and 2306 male waterpipe and cigarette smokers • Non-exposed: 8416 males	• Type: Chinese water pipe • Measurement tool: not reported, calculated as cumulative exposure and categorized into quartiles of liang/month year • Measurement time points: every 5 years • Exposure levels of included subjects: cumulative dose quartiles: 0 (n=8,416), 0.16-4.44 (n=877), 4.44-6.25 (n=888), 6.25-9.21 (n=906), 9.21-82.19 (n=924)	• Health outcome: Lung cancer mortality • Measurement tool: not reported • Blinding of outcome adjudicator: not reported • Incidence: 7%	• Selection bias: smokers were representative of the study base, non-smokers selected from the same community as smokers • Information bias: unlikely for mortality outcome; standardized exposure measurement: no • Confounding: no adjustment (no adjusted RR reported; crude RR calculated from reported data) • Participation rate: not reported • 8% lost to follow up	• RR compared to no smoking 4.39 (3.82-5.04)
27	**Feng 2009** [27] • Study design: Case-control study • Funding: Association for International Cancer Research	• Setting and period: 5 hospitals in Algeria, Morocco, and Tunisia, Jan 2002 to Mar 2005 • Cases: 636 incident cases of nasopharyngeal cancer • Controls: 615 controls (patients hospitalized for non-cancer diseases (61%) and friends and family of non-cancer patients (39%)	• Type: Waterpipe smoking • Measurement tool: interviews, self-developed questionnaire, no standardization reported; participants categorized as ever smokers and never smokers. Ages of starting, and quitting daily consumption extracted from	• Health outcome: Nasopharyngeal carcinoma • Measurement tool: cases identified by clinician in the Oncology and radiotherapy departments • Blinding of outcome	• Selection bias: series of hospital-based incident cases (2001-2004), controls were hospital-based or friends and family of cases, and recruited from the same study base as cases.	OR compared ever waterpipe smoking to never smoking: 0.49 (0.20-1.23)

			history but not reported • Exposure levels of included subjects: not reported	adjudicator: not reported	• Information bias: objective outcome measurement: yes, standardized exposure measurement: no • Confounding: matching for hospital, age, sex, household type (urban/rural); adjustment for age • Participation rate: >90%	
28	**Ali 2007** [28] • Study design: Cross-sectional study • Funding: not reported	• Setting and period: Yemen; period not reported • Population: Yemeni volunteers (27 men and 6 women) all chewers of al qat, mean age 38.5 yrs (range 22-58), all of them free from any systematic diseases. 11 waterpipe smokers, 11 cigarette smokers, 11 non-smokers.	• Type: Waterpipe smoking • Measurement tool: interviews, standardization not reported, subjects categorized as heavy cigarette smokers (>20/day), non-smokers, and waterpipe smokers • Exposure levels of included subjects: not reported	• Health outcome: Dysplasia of oral mucosa diagnosis • Measurement tool: histo-pathological examination of buccal mucosa biopsies • Blinding of outcome adjudicator: not reported	• Selection bias: volunteer recruitment into the study • Information bias: objective outcome measurement: yes, standardized exposure measurement: no; • Confounding: no matching or adjustment in the analysis reported • Participation rate: not reported	OR compared to no smoking: • 8.33 (0.78-9.47) (waterpipe smoking). Results are restricted to the chewing side; no events in either group on non-chewing side. OR calculated from reported numbers.
29	**Dangi 2012** [29] • Study design: Cross	• Settings and Period: The study was carried out in three villages of Haryana	• Type: Waterpipe smoking • Measurement tool : Questionnaires	• Health outcome: Oral Cancer • Measurement	• Selection bias: an interpreter was recruited from the local village who	OR of water pipe smokers compared to non- smokers :

sectional • Funding: not reported	during the months of July and August 2009. • Participants: A total of 761 patients of age group 45-95 years participated in the study.		tool : Any lesion which was red, painless, and firm, indurated and had a history of being unresolved for more than 14 days in the mouth was considered a suspicious lesion. - Subjects with these lesions were referred to the local dentist for further follow-up, including the biopsy and diagnosis of OC. - Blinding of outcome adjudicator: not reported.	convinced the villagers about the benefits of screening and motivated them to participate in the study. • Information bias: Subjects with suspected lesions were referred to the local dentist for further follow-up, including the biopsy and diagnosis of OC • Confounding: adjusted for gender, age, education level and religion • Participation rate: 97.5%	4.42 (2.32-8.41) P value = 0.000*

30	**Schmidt-Westhausen 2014**[30] • Study design: Cross-sectional study • Funding: not reported	• Setting and period: At the dental clinics of Al-Thawra Health Institute in Sana'a City, Yemen, during the period 2006–2008 • Participants: -Inclusion criteria: Adult, Yemeni, and healthy Women, aged 20–65 years, who have been habitual qat chewers on one side of their mouths for at least 5 years. - Included: 162 adult and healthy Yemeni women with a mean age of 38.25 years and ranging from 20-65 yo, with 53 of them being qat non-chewers and the remaining 109 being qat-chewers	• Type: waterpipe smoking compared to Qat chewing • Measurement tool: Clinical examination sheet and a structured interview questionnaire; relying on self-reported exposure by the women Exposure levels of included subjects: Reported for water-pipe smokers as duration in years and frequency per day.	• Health Outcome: Oral mucosal white lesions (leukoplakia) • Measurement tool: Clinical examination • Blinding of outcome adjudicator: High risk; the outcome adjudicators knew on which side the participants chewed qat.	• Selection bias: patients were recruited from a dental clinic and thus exposure and disease were assessed simultaneously •Information bias: Validation of the tool used for measurement of exposure is unclear •Confounding: adjusted for hookah and/or cigarette smoking as a confounder in the appearance of leukoplakias •Participation rate: not reported	• OR (95% CI); p-value: Among water-pipe smokers: 4.351 (1.732, 10.932); p = 0.002
31	**Nikbakht 2015**[31] • Study design: Cross-sectional study • Funding: Not reported	• Setting and period: Cancer cases as recoded by the cancer Registry Center of Babol, Iran, during a 6-year period (2007-2012) • Participants: - Inclusion criteria: Subjects with the codes of	• Type: Waterpipe and/or cigarette smoke exposure • Measurement tool: Questionnaires filled by trained interviewers after explaining the objectives of the study to the participants	• Health Outcome: Colorectal Cancer • Measurement tool: From the cancer Registry center of Babol	• Selection bias: Census sampling bias ie series of hospital-registered cases between 2007 and 2012 • Information	• Prevalence of hookah smoking: -In men: 17/75 (22.7%) -In women: 2/45 (4.4%)

		interest [C18 (colon), C19 (rectosigmoid junction), C20 (rectum), and C21 (anus and anal canal)], being alive, residing within Babol, and diagnosed within the study period." - Excluded: 117 of the 237 subjects eligible were excluded: 96 because of death, 5 because of immigration, 3 because of non-cooperation, and 13 because of incorrect phone and home addresses - Included: 120 Colorectal cancer patients residing in Babol, 62.5% of which were males and 37.5% females with 70% of the participants below the age of 50 years			bias: Validation of the tool used for measurement of exposure is unclear • Confounding: adjusted for positive family histories for cancer in general and colorectal cancer in particular, and for consumption of alcohol, opium, and cigarette smoking • Participation rate: 120/237 (88%)	-Overall: 19/120 (15.8%)

Table 4 : Pregnancy outcomes

32	**Nuwayhid 1998** [32] • Study design: Retrospective cohort study • Funding: Hariri Foundation; and University Research Board at the American	• Setting and period: hospitals in Lebanon; 1993 and 1995 • Participants: pregnant women delivering in hospitals. 106 waterpipe smokers (mean age 27.6 years), 277 cigarette smokers	• Type of exposure: Waterpipe smoking • Measurement tool: interviews, standardization not reported;	• Health outcome: Low birth weight, Apgar score<7 (1 & 5 min), pulmonary problems, malformations	• Selection bias: unclear whether sample is representative (data collection in a few number of hospitals) • Information bias:	OR for waterpipe smoking compared to no smoking • low birth weight = 2.17 (0.74-6.33) • low birth weight = 2.36 (0.52-10.73) (<1/day) • low birth weight = 2.07

University of Beirut	(mean age 29.1), and 512 nonsmokers (mean age 28.5)	categorized into <1 vs. ≥1 per day; and started smoking during 1st vs. 2nd or 3rd trimester • Measurement time points: not reported • Exposure levels of included subjects: <1 per day (n=38); ≥1 per day (n=67) per day; 1st trimester (n=78); 2nd or 3rd trimester (n=25)	, perinatal complications • Measurement tool: medical records; low birth weight defined as a birth weight <2500 g • Blinding of outcome adjudicator: not reported	objective outcome measurement: yes but based on medical records, standardized exposure measurement: no • Confounding: adjustment for age, hospital location, gestational age, exposure to passive smoking, and previous low birth weight • Participation rate: not reported • <10% missing data	(0.54-7.94) (≥1/day) • low birth weight = 2.93 (0.97-8.83) (waterpipe smoking started in 1st trimester) • Test for trend for low birth weight not significant for intensity (p<0.18) • Apgar score<7 at 1 min =1.73 (0.73-4.14) • Apgar score<7 at 5 min =3.39 (0.54-21.42) • Pulmonary problems =3.65 (1.52-8.75) • Malformations =2.01 (0.59-6.88) • Perinatal complications=1.67 (0.82-3.41) OR for cigarette smoking compared to no smoking • low birth weight = 2.00 (0.96-4.20) • low birth weight = 2.25 (1.04-4.86) (waterpipe smoking started in 1st trimester) • Apgar score<7 at 1 min =1.59 (0.82-3.07) • Apgar score<7 at 5 min =2.62 (0.56-12.29) • Pulmonary problems =1.76 (0.80-3.87) • Malformations =1.36

						(0.49-3.80) Perinatal complications=1.50(0.87-2.57)
33	**Aghamolaei 2007** [33] • Study design: case-control study • Funding: not reported	• Setting and period: Shariati Hospital of Bandar Abbas, South of Iran; period not reported • Cases: 60 Intra-uterine growth retardation infants • Controls: 60 normal birth infants • Included subjects: all term infants with gestational age 37-42 weeks; 29 male and 31 female in each group. "None of included mothers smoked and used alcohol during pregnancy and none of them had diabetes"	• Type: Waterpipe smoking by mother • Measurement tool: structured questionnaire administered to mothers, standardization not reported • Exposure levels of included subjects: not reported	• Health outcome: Intra uterine growth retardation (IUGR) • Definition: term infants with a birth weight <2500 g • Measurement tool: birth weight determined up to 10 min of delivery using a digital baby scale • Blinding of outcome adjudicator: not reported	• Selection bias: series of incident cases of IUGR in maternity wards, controls selected from the same study base as the cases • Information bias: objective outcome measurement: yes, standardized exposure measurement: no • Confounding: explored 18 potential risk factors and adjusted for maternal work, hypertension, antenatal care • Participation rate: not reported	• OR for waterpipe smoking during pregnancy compared to no waterpipe smoking during pregnancy =3.5(1.1-12.6)
34	**Tamim 2008** [34] • Study design: retrospective cohort study • Funding: Lebanese National Council for Scientific Research; the Medical	• Setting and period: 6 major hospitals in greater Beirut, Lebanon, Aug 2000 to Aug 2003 • Population: 378 singleton newborns to women exclusive waterpipe smokers, 929 singleton	• Type: Waterpipe • Measurement tool: interviews, questionnaire pilot tested; waterpipe	• Health outcome: Low birth weight • Measurement tool: data collection from obstetric and nursery charts, low	• Selection bias: sample representative of populations of six major hospitals in Greater Beirut • Information bias: objective outcome measurement:	OR for waterpipe only smoking compared to no smoking • low birth weight = 1.32 (0.39-4.40) (OR pooled for ≤1day and >1day) • low birth weight = 0.7 (0.3-1.6) (≤1day)

	Practice Plan; and the University Research Board at the American University of Beirut	newborns to women exclusive cigarette smokers, 84 singleton newborns to women smoking both types of tobacco, 7201 singleton newborns to women nonsmokers	smokers categorized into ≤1 vs. > 1 per day; categorized into <1 vs. ≥1 per day; and started smoking during 1st vs. 2nd or 3rd trimester • Measurement time points: not reported • Exposure levels of included subjects: ≤1 per day (n=233); > 1 per day (n=145); 1st trimester (n=309); 2nd or 3rd trimester (n=69)	birth weight defined as ≤2500 g • Blinding of outcome adjudicator: not reported	yes but based on medical records , standardized exposure measurement: no (pilot tested only) • Confounding: adjustment for maternal/paternal education, mother working status, mother's age, parity, diabetes, bleeding, pregnancy hypertensive disorders, gestational age, and passive smoking • Participation rate: not reported	• low birth weight = 2.4 (1.2-5.0) (>1day) • low birth weight = 1.2 (0.6-2.2) (waterpipe smoking started in 1st trimester)
35	**Eftekhar 2007**[35]	• Setting and period: Bandar Abbas, Iran 60 cases and 60 controls	• Type: Waterpipe • Measurement tool: questionnaire	• Health outcome: Intrauterine growth retardation	• Information bias: Data collected using on standardized questionnaire	OR : 3.5(1.1-12.6)

Table 5 : Periodontal disease

36	**Natto 2005** [36] • Study design: cross sectional study • Funding: Ministry of Health in Saudi Arabia;	• Setting and period: Jeddah, Saudi Arabia, period not reported • Participants: 355 volunteers, 28% females, mean age 36.9 years (range 17-60), having 20	• Type: Waterpipe smoking • Measurement tool:	• Health outcome: Periodontal disease measured as periodontal	• Selection bias: volunteers recruited by newspaper announcements • Information bias:	OR compared to no smoking • 3.5(1.6-7.6) (waterpipe only smoking)

	and Saudi Arabian Cultural Bureau Office in Bonn	teeth and not pregnant	standardized questionnaire administered in interviews, standardization not reported; calculated as run-years (product of waterpipe runs per day with years of smoking; a run is the completion of the waterpipe smoking until the tobacco is burnt); heavy exposure was defined as ≥ 40 run-years • Exposure levels of included subject: mean exposure of 56.8 run years for water pipe smokers	bone height loss • Measurement tool: digital panoramic radiographs. Bone loss defined as bone height ≤ 70%. Mean bone height per individual is the ratio of the periodontal bone height to the root length • Blinding of outcome adjudicator: yes	objective outcome measurement: yes, standardized exposure measurement: no • Confounding: adjustment for age only • Participation rate: not reported	• 1.0 (0.3-3.1) (light waterpipe only smoking) • 7.5 (3.0-18.3) (heavy waterpipe only smoking) • The association between waterpipe smoking and bone height remained statistically significant after controlling for "education as a surrogate for socioeconomic standard and other variables" • Differences between light and heavy exposures were statistically significant (p<0.001)
37	**Natto 2004** [37] • Study design: cross-sectional study • Funding: not reported	• Setting and period: Western part of Saudi Arabia, period not reported • Participants: 244 volunteers , 34% females, mean age 37.4 years (range 25-70), having 20 teeth and not pregnant	• Type: Waterpipe smoking • Measurement tool: standardized questionnaire administered in interviews, standardization not reported; calculated as run-years (product of	• Health outcome: Periodontal disease measured as plaque index and gingivitis • Measurement tool: Plaque: clinical examination, presence of visible dental	• Selection bias: 244 of the 355 volunteers participating in another study [38] volunteered for a clinical examination • Information bias: objective outcome measurement: yes, standardized exposure	• There was an overall significant association between smoking and plaque index and gingival index. No effect estimates reported.

			waterpipe runs per day with years of smoking; a run is the completion of the waterpipe smoking until the tobacco is burnt) • Exposure levels of included subject: not reported	plaque was recorded according to the criteria of Silness and Loe. • Blinding of outcome adjudicator: not reported	measurement: no • Confounding: adjustment for age, dental care habit • Participation rate: 68%	
37	**Natto 2005** [39] • Study design: cross sectional study • Funding: Ministry of Health in Saudi Arabia and Saudi Arabian Cultural Bureau Office in Bonn	• Setting and period: Jeddah, Saudi Arabia, period not reported • Population: 262 volunteers, 35% females, mean age 36.5 (range 17-60). Participants were required to have 20 teeth and not be pregnant. 51citizens with periodontal disease and : 211 citizens without periodontal disease	• Type: Waterpipe smoking • Measurement tool: standardized questionnaire administered in interviews, standardization not reported; calculated as run-years (product of waterpipe runs per day with years of smoking; a run is the completion of the waterpipe smoking until the tobacco is burnt); heavy exposure was defined as ≥ 40 run-years • Exposure levels of included	• Health outcome: Periodontal disease measured as deepening of the sulci or pockets • Measurement tool: clinical examination probing the depth of the sulci or pockets with a 2-mm graduated periodontal probe; periodontal disease defined as ≥10 sites with a probing depth ≥5mm • Blinding of outcome adjudicator: not reported	• Selection bias: 262 of the 355 volunteers participating in another study [40] volunteered for a clinical examination • Information bias: objective outcome measurement: yes, standardized exposure measurement: no • Confounding: adjustment for age only • Participation rate: 74%	OR compared to no smoking • 5.1 (2.0-13.5 (waterpipe only smoking) • 8.2 (2.9-22.9) (heavy waterpipe smoking) • 2.9 (1.7-4.8) (light waterpipe smoking)

			subject: mean exposure of 35.8 run years for water pipe smokers			
38	**Baljoon 2005** [41] • Study design: cross sectional study • Funding: Ministry of Health in Saudi Arabia; and Saudi Arabian Cultural Bureau Office in Bonn	• Setting and period: Jeddah, Saudi Arabia, period not reported • Population: 103 volunteers with vertical periodontal bone loss and 159 individuals without vertical periodontal bone loss	• Type: waterpipe, cigarettes • Measurement tool: standardized questionnaire administered in interviews, standardization not reported; calculated as run-years (product of waterpipe runs per day with years of smoking; a run is the completion of the waterpipe smoking until the tobacco is burnt); heavy exposure was defined as ≥ 40 run-years • Exposure levels of included subject: mean exposure of 56.8 run years for water pipe smokers	• Health outcome: Periodontal disease measured as vertical periodontal bone loss • Measurement tool: intra-oral radiographs; vertical periodontal bone loss defined as one-sided bone resorption of the interdental marginal bone ≥2 mm that had a typical angulation towards either the mesial or distal aspect of the root • Blinding of outcome adjudicator: yes	• Selection bias: 262 of the 355 volunteers participating in another study [42, 43] volunteered to participate in this study • Information bias: objective outcome measurement: yes, standardized exposure measurement: no • Confounding: adjustment for age only • Participation rate: 74%	OR compared to no smoking • 2.9 (1.2-7.0) (waterpipe only smoking) • 43.3 (12.1-71.6) (heavy waterpipe smoking) • 0.6 (0.3-1.4) (light waterpipe smoking)

39	**Al-Belasy 2004** [38] • Study design: cohort study with 7 days follow-up after surgical removal of mandibular third molars • Funding: not reported	• Setting and period: Mansoura Egypt , Jan 2000 – Feb 2002 • Exposed: 100 male waterpipe smokers, mean age 28.7 years (range 22 - 39),100 male cigarette smokers, mean age 28.7 years (range 20-38) • Non-exposed: 100 males nonsmokers, mean age, 27.7 years (range 20 - 37) • Included subjects were required to be healthy not taking medications at the time of the study and with unilateral high mesoangular impactions with exposed occlusal surfaces. Patients with recent antibiotic use or the medial need for antibiotic prophylaxis were excluded	• Type: Waterpipe smoking • Measurement tool: self-report, standardization not reported • Measurement time points: on day of the surgery, on the first and second post-operative days • Exposure levels of included subjects: not reported	Health outcome: Dry socket • Measurement tool: clinical diagnosis on the basis of constant radiating pain not relieved by the analgesic, accompanied by a denuded socket or necrotic clot and a fetid smell • Blinding of outcome adjudicator: not reported	• Selection bias: only healthy patients not taking medications were included, non-smokers selected from the same community as smokers • Information bias: objective outcome measurement: yes, standardized exposure measurement: no; same duration follow-up for both groups • Confounding: no matching or adjustment in the analysis reported • Participation rate: not reported	• "Waterpipe smokers had 3 times the risk of non-smokers for developing dry socket" (RR=3.7;p=0.001); trend of developing dry socket with frequency of waterpipe smoking was statistically significant (p=0.001) • Compared with non-smokers, waterpipe smokers who smoked the day of surgery or the first day after surgery had a significantly increased incidence of dry socket (day 0, p=0.001; day 1, p=0.005)

Table 6 : Infectious disease

40	**Habib 2001** [44] • Study design: cross-sectional study • Funding: Hepatitis C Prevention Project (USAID grant)	• Setting and period: Aghour El Soughra, a rural village in Nile Delta, in 1997 • Population: male village inhabitants screened for Hepatitis C. 455 tested positive for Hepatitis C and 1372 tested negative for	• Type: Group waterpep smoking (assessed in men only) • Measurement tool: questionnaire,	Health outcome: Hepatitis C infection • Measurement tool: second generation Enzyme Immunoassay (Abbott HCV	• Selection bias: sample was "systematically selected" • Information bias: objective outcome measurement: yes, standardized	• OR for group waterpipe smoking compared to non-group waterpipe smoking =1.1 (0.7-1.5) (males >=20 years old)

		Hepatitis C(study also recruited females but restricted waterpipe analysis to males)	standardization not reported • Exposure levels of included subjects: not reported	EIA 2.0). • Blinding of outcome adjudicator: not reported	exposure measurement: no • Confounding: adjustment for age, sex, marital status, education, history of invasive medical procedures, and dental procedures • Participation rate: half of households selected • 0.15% missing data • 2 subjects (waterpipe smokers) excluded for age<20 • It is not clear how female subjects were dealt with in the regression analyses	
41	**Medhat 2002** [45] • Study design: cross-sectional study • Funding: Hepatitis C Prevention Project [USAID grant]	• Setting and period: Community in Upper Egypt, period not reported. • Population: male village inhabitants screened for Hepatitis C. 308 tested positive for Hepatitis C and 2409 tested negative for Hepatitis C (study also recruited females but restricted waterpipe analysis to males)	• Type: group waterpipe smoking (assessed in men only) • Measurement tool: questionnaire, standardization not reported • Exposure levels of included subjects: not	Health outcome: Hepatitis C infection • Measurement tool: second generation Enzyme Immunoassay (Abbott HCV EIA 2.0). 514 of the 523 participants with positive anti-HCV test	• Selection bias: sample represents 62.8% of village inhabitants • Information bias: objective outcome measurement: yes, standardized exposure measurement: no • Confounding: adjustment for age, injection history, hospital or	• OR for group waterpipe smoking compared to non-group waterpipe smoking =0.9(0.4-2.0) (males <=30 years old) • OR for group waterpipe smoking compared to non-group waterpipe smoking =0.8(0.5-1.2) (males >30 years old)

			reported	results were tested for HCV RNA by a one-step reverse transcriptase-polymerase chain reaction method • Blinding of outcome adjudicator: not reported	clinical experiences, dental treatments, obstetric exposures (women>=20 yrs), sharing razors within family (males only), circumcision, shaving at community barber (men only), ear piercing(females only), tattoo, cautery • Participation rate: 6033 (53.7%) of the 11 227 village inhabitants were included in the study • It is not clear how female subjects were dealt with in the regression analyses	
42	**El-Sadawy 2004** [46] • Study design: cross-sectional study • Funding: not reported	• Setting and period: Urban and rural areas of Sharkia Governorate, Egypt; period not reported • Population: male village inhabitants screened for Hepatitis C. 217 tested positive for Hepatitis C and 565 tested negative for Hepatitis C(study also recruited females but restricted	• Type: Group waterpipe smoking (assessed in men only) • Measurement tool: specifically designed questionnaire; pilot tested before	Health outcome: Hepatitis C infection • Measurement tool: Antibody to HCV assessed by micro-particle enzyme immunoassay (MEIA) and HCV RNA	• Selection bias: used “stratified random sampling” which included systematic sampling • Information bias: objective outcome measurement: yes, however while 25.8% tested positive by MEIA	• OR for group waterpipe smoking compared to non-group waterpipe smoking =1.02 (0.64-1.62) (males)

	waterpipe analysis to males)	survey for reliability • Exposure levels of included subjects: not reported	tested by real-time PCR • Blinding of outcome adjudicator: not reported	7.66% test positive by PCR; standardized exposure measurement: no (pilot tested only) • Confounding: unclear whether reported results were adjusted for potential confounders • Participation rate not reported • missing data not reported	

Table 7: Infertility

43	**Inhorn 1994** [47] • Study design: case-control study • Funding: National Science Foundation, the Fulbright Institute for International Education, the U. S. Department of Education Fulbright-Hays Doctoral Dissertation Research Abroad Program, and the Soroptimists International Founder Region Fellowship Program	• Setting and period: infertility clinic of the University of Alexandria's Shatby Hospital, the public obstetrics/gynecology teaching hospital, rural areas of the northwestern Nile Delta region, Egypt; Oct 1988 to Dec 1989 • Cases: husbands of 40 female patients of the university infertility clinic who were diagnosed of male-factor infertility (problems of semen and sperm) • Controls: husbands of 90 fertile female patients of the university hospital • Participants: 15-45 years old, lower and lower-middle socioeconomic classes	• Type: husbands' waterpipe smoking behaviors • Measurement tool: interviews, self-developed semi-structured questionnaire, no standardization reported; participants categorized as regular smokers and never smokers. • Exposure levels of included subjects: not reported	Health outcome: Couple infertility associated with male-factor infertility • Measurement tool: medical records of semen analyses • Blinding of outcome adjudicator: not reported	• Selection bias: prevalent cases of infertility, controls were hospital-based and recruited from the same study base as cases. • Information bias: objective outcome measurement: yes, standardized exposure measurement: no (second hand information) • Confounding: matching for age group, socioeconomic class; adjustment for cigarette smoking, tea drinking, marital duration, husband's age, husband's education • Participation rate: >98%	OR compared to never smoking: 2.5 (1.0-6.3) (regular waterpipe smoking)

Table 8 : Others

44	**Shafique 2012 ([48])** • Study design: Cross sectional • Funding: Not funded	• Population and settings: Part of population based study carried in Punjab province in Faisalabad city. • Only healthy individuals between 30 and 75 were included in the study.	• Type: Waterpipe smoking • Measurement tool : Questionnaire/Self-reported	• Health outcome:Metabolic syndrome • Tool: Trained nurses, blood sample and ascertained by the international diabetics federation criteria	• Selection bias: Population based cohort • Information bias: validation of the exposure measurement tool is unclear • Confounding: Adjusted for multiple sociodemographic factors • Participation rate: N/A	• OR of Waterpipe smokers versus non smokers • Hypertriglycemia : aOR 1.63, 95% CI 1.25-2.1 • Hypergylcemia aOR 1.82, 95% CI 1.37-2.41 • Hypertension: aOR 1.95, 95% CI 1.52-2.45
45	**Farhad Islami 2014 ([49])** • Study design: Cross sectional • Funding: Tehran university of medical sciences, Cancer research UK and The intramural research program of the national cancer institute	• Population based cohort study 0f 40-75 years old individuals in eastern parts of Golestan province, Iran.	• Type: Waterpipe smoking • Measurement tool: Self-reported	• Health outcome: GERD symptoms • Measurement tool: elf-reported	• Selection bias: Sample selected by random systematic clustering • Information bias: GERD symptoms self reported • Confounding: adjusted for age, sex, ethnicity, place of residence, education, wealth score, BMI, physical activity, consumption of alcohol, opium, cigarette and nass chewing • Participation rate: N/A	• OR of Waterpipe smokers compared to non-smokers. aOR 1.34 and 95% CI 1.02-1.75

46	**Al Suwaidi 2012 ([50])** • Study design: Prospective data collection from registry • Funding: Gulf Heart Association (GHA), Sanofi Aventis and the College of Medicine Research Center at King Khalid University Hospital, King Saud University, KSA	• Settings & Period: Data extracted from the 2nd Gulf RACE registry that recruited 7939 consecutive Acute Coronary Syndrome from six adjacent Middle Eastern Gulf countries (Bahrain, KSA, Qatar, Oman, United Arab Emirates and Yemen) between October 2008 and June • 2009 from 65 hospitals	• Type: Waterpipe smoking • Measurement tool: Verbally from patient or a representative of the patient at the time of admission •	• Health Outcome: Cardiovascular disease (acute coronary syndrome) • Measurement tool: Reports from the 2nd Gulf registry of acute coronary events • Blinding of outcome adjudicator: • Not reported	• Selection bias: All prospective patients with ACS were recruited from 65 hospitals • Information bias: valid outcome measurement: yes, valid exposure measurement: no • Confounding: Did not measure confounding factors • Participation rate: • Not reported	• No odds ratios reported
47	**Farhad Islami 2012([51])** • Study design: Cross sectional • Funding: Tehran university of medical sciences, Cancer research UK and The intramural research program of the national cancer institute	• Population based cohort study 0f 40-75 years old individuals in eastern parts of Golestan province, Iran.	• Type: Waterpipe smoking • Measurement tool: Self-reported	• Health outcome: Heart disease • Measurement tool: self-reported	• Selection bias: Sample selected by random systematic clustering • Information bias: Validation of the tool used to measure the outcome is unclear • Confounding: adjusted for multiple confounders including cigarette smoking • Participation rate: N/A	• OR of Waterpipe smokers compared to non-smokers aOR 3.75 and 95%CI 1.52-9.22

48	**Primack 2013 ([52])** • Study design: Cross-sectional • Funding: National Institutes of Health, United States	• Setting and period: ~150 American universities, Autumn 2008-Spring 2009 • Participants: Included: N=100,891, 70.7% under 22 years old, 65.7% female, 70.2% non-Hispanic white, 87.3% undergraduate	• Type: current (past-30 day) waterpipe smoking • Measurement tool: Self-reported questionnaire: previously reported validated tool	• Health outcome: 1. Depression 2. Anxiety (anxiety, OCD, panic attacks, phobia) 3. Sleeping disorder (insomnia, other) 4. Eating disorder (anorexia, bulimia) 5. ADHD 6. Addictive disorder (substance abuse, substance addiction, other addiction) 7. Overall health 8. Sleep inadequacy 9. Stress • Measurement tool: Self-reported questionnaire: previously reported validated tool	• Selection bias: Convenient sample • Information bias: Self-reported mental status • Confounding: Adjusted for gender, sexual orientation, undergraduate status, race, relationship status, region, population size, and clustering by school. • Participation rate: Web-based survey : 22% and the paper survey 90%	• OR of current waterpipe smokers compared to non-current WP smokers: 1. Depression 1.4 (1.3-1.5) 2. Anxiety 1.3 (1.2-1.4) 3. Sleeping disorder 1.5 (1.4-1.7) 4. Eating disorder 1.7 (1.4-1.9) 5. ADHD 1.7 (1.5-1.8) 6. Addictive disorder 2.4 (2.0-2.8) 7. Overall health fair/poor 1.3 (1.2-1.4) 8. Sever e sleep inadequacy 1.08 (1.02-1.14) 9. Tremendous stress 1.1 (1.02-1.2)
49	**Wu 2013([53])** • Study design:Cohort study • Funding: National Institutes of Health, United States	• Setting and period: Araihazar, Bangladesh. Recruited October 2000 – May 2002 • Participants: - Inclusion criteria: married, aged 18-75, resident in study area for at least five years prior to recruitment, drinking water from the	• Type: Time years index for waterpipe smoking • Measurement tool: Standardised questionnaire • Measurement time points: 2	• Outcome1: All-cause mortality • Outcome 2: Deaths due to cancer Outcome 2: Deaths due to CVD • Measurement tool: Outcome 1: Validated verbal	• Selection bias: Population based study • Information bias: Validation of the tool used for measurement of exposure is unclear. • Confounding:	• Hazard ratios for ever waterpipe smokers compared to never waterpipe smokers: • All cause: Men 1.15 (0.93-1.43) Women: 2.51 (1.78-4.43)

local well - Excluded:<18 years or >75 years - Included: Original cohort 11,746, in 2006-2008 added a second cohort 8,287	years	autopsy form based on WHO classification and ICD-10	Adjusted for age (years), body mass index (BMI; kg/m2), and educational attainment (years),arsenic exposure, betel quid hewing, systolic blood pressure and diabetes. Participation rate: 97%	• Cancer: Men 1.30 (0.78-2.18) Women: N/A (N too small) • CVD: Men 1.20 (0.87-1.67) Women: 2.08 (0.96-4.49) Effect size: Hazard ratios for male past waterpipe smokers compared to never waterpipe smokers: • All cause 1.12 (0.90-1.41) • Cancer 1.19 (0.70-2.02) • CVD 1.22 (0.88-1.71) Effect size: Hazard ratios for male current waterpipe smokers compared to never waterpipe smokers: • All cause 1.46 (0.94-2.25) • Cancer 2.51 (1.08-5.82) • CVD 1.00 (0.46-2.18)	

Appendix 5. Risk of bias assessment instructions for comparative non-randomized studies

Selection of participants	Measurement of exposure	Measurement of outcome	Control for confounding	Completeness of data
Low risk When selection of participants was based on clear and specific eligibility criteria	**Low risk** Authors report using a validated tool with adequate evidence of validation provided	**Low risk** Authors report using a validated tool with adequate evidence of validation provided	**Low risk** Authors report controlling for relevant confounders with adequate details (e.g., in the design phase through matching and/or in the analysis through adjustment)	**Low risk** Authors provide specific figures for missing data, suggesting low rates
Unclear risk When no information provided about eligibility criteria or selection process	**Unclear risk** Authors report using a validated tool but no adequate evidence of validation provided	**Unclear risk** Authors report using a validated tool but no adequate evidence of validation provided	**Unclear risk** Authors report controlling for confounders but without adequate details	**Unclear risk** Authors report low rates of missing data but do not provide specific figures
High risk: When selection of participants was based on convenient samples.	**High risk** Authors do not report using a validated tool.	**High risk** Authors do not report using a validated tool.	**High risk** Authors do not report controlling for relevant confounders	**High risk** Authors provide no information about missing data, or report high rates of missing data

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