

Cardiovascular effects of waterpipe smoking: a systematic review and meta-analysis

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Waterpipe smoking has developed into a major and rapidly growing global tobacco epidemic affecting more than 100 million people worldwide. This study identifies and analyzes comprehensively all available data on the cardiovascular effects of waterpipe smoking. Databases PubMed, EMBASE, Web of Science, and the Cochrane Library were searched for studies published until December 2019 assessing cardiovascular effects of waterpipe smoking. We included experimental, cohort, cross-sectional and case-control studies and excluded systematic reviews, case reports/series and qualitative studies. Studies not conducted in humans or not distinguishing waterpipe smoking from other forms of smoking were also excluded. A total of 42 studies with 46 cardiovascular parameters were eligible for analysis. The meta-analysis included 31 studies with 38,037 individuals. Results showed that one waterpipe smoking session leads to immediate increases in heart rate and blood pressure ($P < 0.001$). Compared to non-smokers, waterpipe smokers had significantly lower high-density lipoprotein levels ($P < 0.001$), higher levels of low-density lipoprotein ($P = 0.04$), triglyceride ($P < 0.001$) and fasting blood glucose ($P = 0.03$) and higher heart rate ($P = 0.04$) with a tendency to have higher blood pressure. Mean heart rate, blood pressure and lipids levels did not differ between waterpipe and cigarette smokers, except for total cholesterol, being higher among waterpipe smokers ($P < 0.001$). Current level of evidence suggests that waterpipe smoking is associated with substantial adverse effects on cardiovascular system, which seem to be similar to those of cigarette smoking. Longitudinal studies are required to scrutinize the magnitude of these effects.

Keywords

Waterpipe; smoking; cardiovascular disease; cardiovascular risk factors

1. Introduction

Waterpipe smoking (WPS) has developed into a major and rapidly growing global tobacco epidemic worldwide (Maziak et al., 2015). Several factors have hindered recognition of the harmful effects of WPS especially the flavored smoke and the fashionable aspect. In addition, the water gives the impression that it clears most of harmful substances in the smoke. A single WPS session lasts 30-90 minutes of uninterrupted smoking, producing a large volume of smoke which contains up to 80 times more of toxicants than those which found in the smoke of a single cigarette and carried through the water in the bubbles, so the assumption of users that the smoke is "filtered" by the water is incorrect (El-Zaatari et al., 2015; Shihadeh, 2003). Potential adverse cardiovascular effects of WPS have been reported in several scattered studies with varied results based on different estimation criteria. However, the overall clinical effect of WPS on the cardiovascular system is not clear yet. The few available systematic reviews on this topic were not specifically focused on cardiovascular outcomes or synthesis of the results were not performed, being of limited validity (El-Zaatari et al., 2015; Marshall et al., 2018; Rezk-Hanna and Benowitz, 2019; Waziry et al., 2018). We aimed to explore the clinical cardiovascular effects of WPS quantitatively and qualitatively and to compare them with those of cigarette smoking (CS) by combining all available related data in order to provide a better understanding of the relationship between WPS and cardiovascular disease (CVD) risk.

2. Methods

2.1 Study protocol and eligibility criteria

The analyses were conducted according to a prespecified, non-registered protocol. A systematic literature search was performed for all published original studies on adults with no limitation on the number of participants. The exposure of interest was WPS and the outcomes of interest were any cardiovascular parameters. We included experimental studies assessing the acute effects of WPS and observational studies (i.e. cohort studies, cross-sectional studies and case-control studies) that compared waterpipe smokers to

cigarette smokers or non-smokers. Systematic reviews, case reports/case series and qualitative studies were considered not appropriate for inclusion. Furthermore, studies not conducted in humans or not distinguishing WPS from other smoking forms were also excluded (Fig. 1).

2.2 Search and selection strategy

Until December 2019, two investigators (R.A., D.V.) independently searched PubMed, EMBASE, Web of Science, and the Cochrane Library using free search text terms combined with Medical Subject Heading (MeSH). The search was performed using variant terms and spellings for waterpipe used in different languages in the title or abstract, or as keywords. Eligibility assessment was performed independently by two investigators (R.A., L.K.). Disagreements were resolved by consulting a third investigator (M.B.).

2.3 Data extraction

One investigator extracted the following data from included studies and a second investigator checked the extracted data: 1) study characteristics including study design and settings and sample size; 2) characteristics of study participants including age, gender, health status, smoking status and settings; 3) data concerning outcome measurements for each cardiovascular parameter.

2.4 Risk of bias assessment

Risk of bias was assessed by two investigators independently (R.A., L.K.) using ROBINS-I (Sterne et al., 2016), a tool recommended from Cochrane Bias Methods Group for assessing the risk of bias in non-randomized interventions. In case of disagreements a third investigator (M.B.) was consulted.

2.5 Statistical analysis

Each analysis was conducted by pooling the appropriate data which could be extracted from at least three studies that we considered to be sufficiently similar in their design and comparison groups. Data from experimental studies were used to assess the acute effects of WPS. Combining data from observational studies and baseline data from multigroup experimental studies which have similar control groups were used to assess the non-acute effects of WPS by comparing waterpipe smokers to non- or cigarette smokers. Using a random-effects model, we pooled data from each study including sample size with both average value and standard deviation to estimate pooled mean difference or with prevalence rate to estimate pooled odds ratio. Results for tested parameters were presented using Forest plots along with their respective 95% confidence interval (CI). Relevant statistical heterogeneity was considered as Cochran's Q test $P < 0.05$ and $I^2 > 50\%$. As sensitivity analyses, relevant statistical heterogeneity was removed using a previously described "sequential algorithm" approach (Patsopoulos et al., 2008) based on repeating meta-analysis after dropping the outlying study that is responsible for the largest decrease in I^2 . Funnel plots for parameters reported in > 10 studies and eventual asymmetry was interpreted as the presence of publication bias. All P values were 2-sided, with $P < 0.05$ considered as significant. All statistical analyses were performed using Review Manager version 5.3 software. We presented summary and descriptive statistics of those parameters, where quantitative (meta-) analysis would not be appropriate.

3. Results

3.1 Search results

After duplicates were removed, the literature search identified 2,141 studies, of which 149 studies investigated WPS effects. We excluded literature reviews, qualitative studies, case reports/series, and studies conducted among teenagers or on animals or machines. Finally, a total of 42 studies were eligible for inclusion in the systematic review. These included 23 observational (case-control and cross-sectional cohort) studies, which compared waterpipe to non- or cigarette smokers, and 19 experimental studies, all of which were non-randomized and investigated the acute effects of WPS, mostly using one-group pretest-posttest design (Fig. 1). One or more potential longitudinal effects of regular WPS were reported in three of these identified studies (Al Suwaidi et al., 2012; Wolfram et al., 2003; Wu et al., 2013).

3.2 Study characteristics

In all experimental studies each parameter was measured at least twice; at start and end of a 15-90-minute WPS session after 12-72-hour smoking abstinence. In the observational studies, waterpipe smokers were in general those who reported regular WPS, mostly twice a week at least. Time since the last WPS session before measurements was rarely reported. Most the included participants were healthy male adults especially in the experimental and case-control studies, except for 7 studies which conducted on patients with coronary heart disease (CHD) (Table. 1). Generally, the search yielded 46 cardiovascular parameters.

3.3 Statistical analysis and study quality

Meta-analysis was conducted on 13 parameters including a total of 31 studies with 38037 participants. Most of this analysis showed a significant heterogeneity, which we considered by pooling the data using a random effects model. Based on ROBINS-I criteria we judged 29 studies with moderate and only 2 studies with serious risk of bias. According to the funnel plots there were no signs of publication bias.

3.4 Study outcomes

3.4.1 Acute effects of waterpipe

3.4.1.1 Hemodynamic parameters

3.4.1.1.1 Heart rate and blood pressure

To assess the acute effect of WPS on each of heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP), meta-analysis was conducted for each of these parameters including 18, 14 and 13 experimental studies with 1814, 1460 and 1386 participants; respectively. Results showed that one WPS session led to acute increases in mean HR by 10.14 beat/min (95% CI: 8.41 to 11.88; $P < 0.001$), SBP by 7.70 mmHg (95% CI: 5.13 to 10.27; $P < 0.001$) and DBP by 4.86 mmHg (95% CI: 2.94 to 6.78; $P < 0.001$) (Fig. 2). After removing statistical heterogeneity in sensitivity analyses, the acute effect of WPS on these three hemodynamic parameters remained significant.

3.4.1.1.2 Autonomic regulation

Potential WPS effects on cardiac autonomic regulation were investigated in three experimental studies (Al-Kubati et al., 2006; Cobb et al., 2012; Nelson et al., 2016), revealing markedly impaired HR/BP variation and baroreflex sensitivity after one WPS session ($P < 0.05$). This effect was independent of nicotine content when tobacco-free-WPS was used (Cobb et al., 2012).

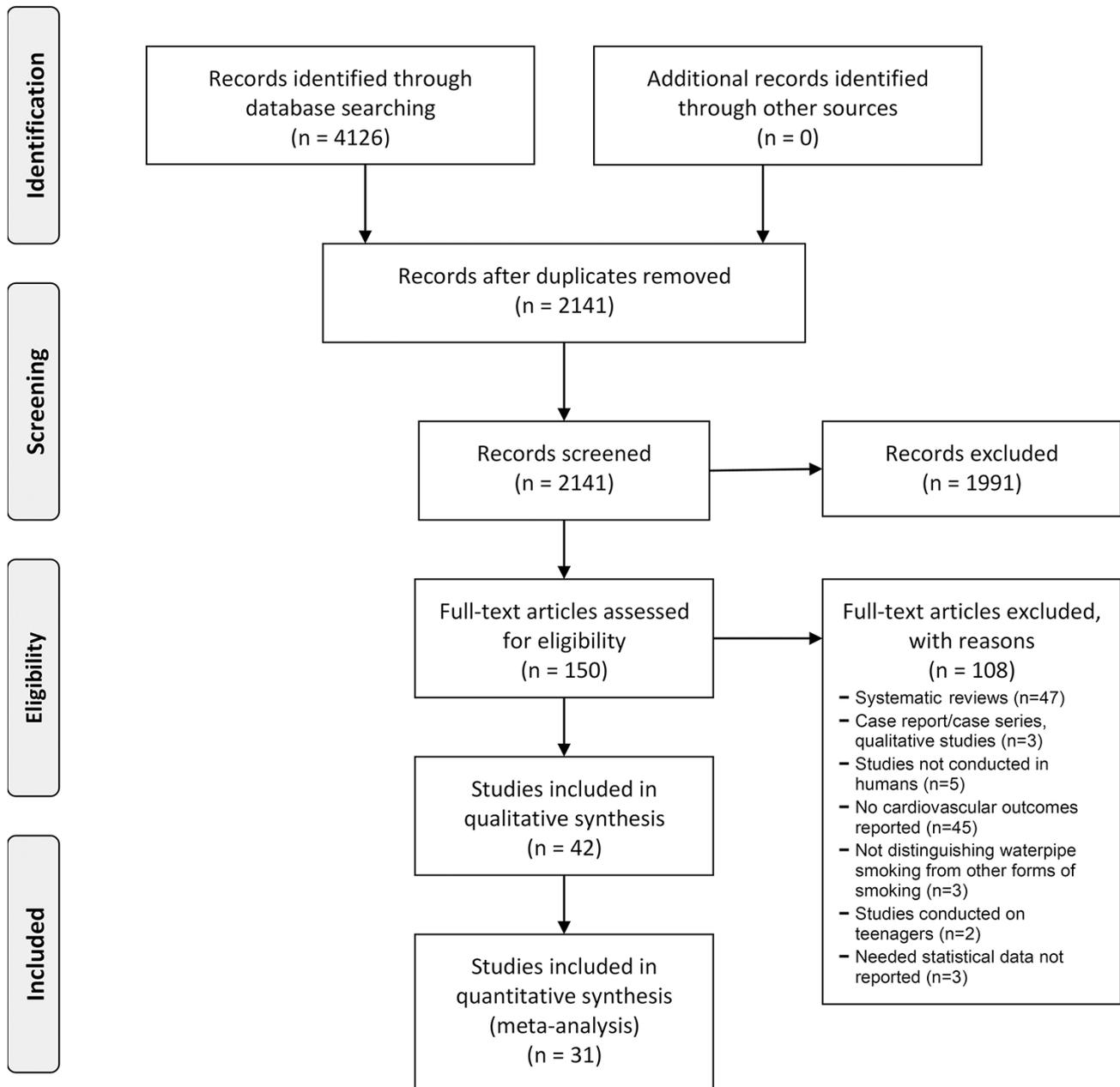


Fig. 1. PRISMA Flow diagram showing the process of the sytematic search and study selection including eligibility against the inclusion and exclusion criteria. The number of studies is the bottom of the flowchart represents that of the selected studies that were considered eligible for inclusion in this meta-analysis.

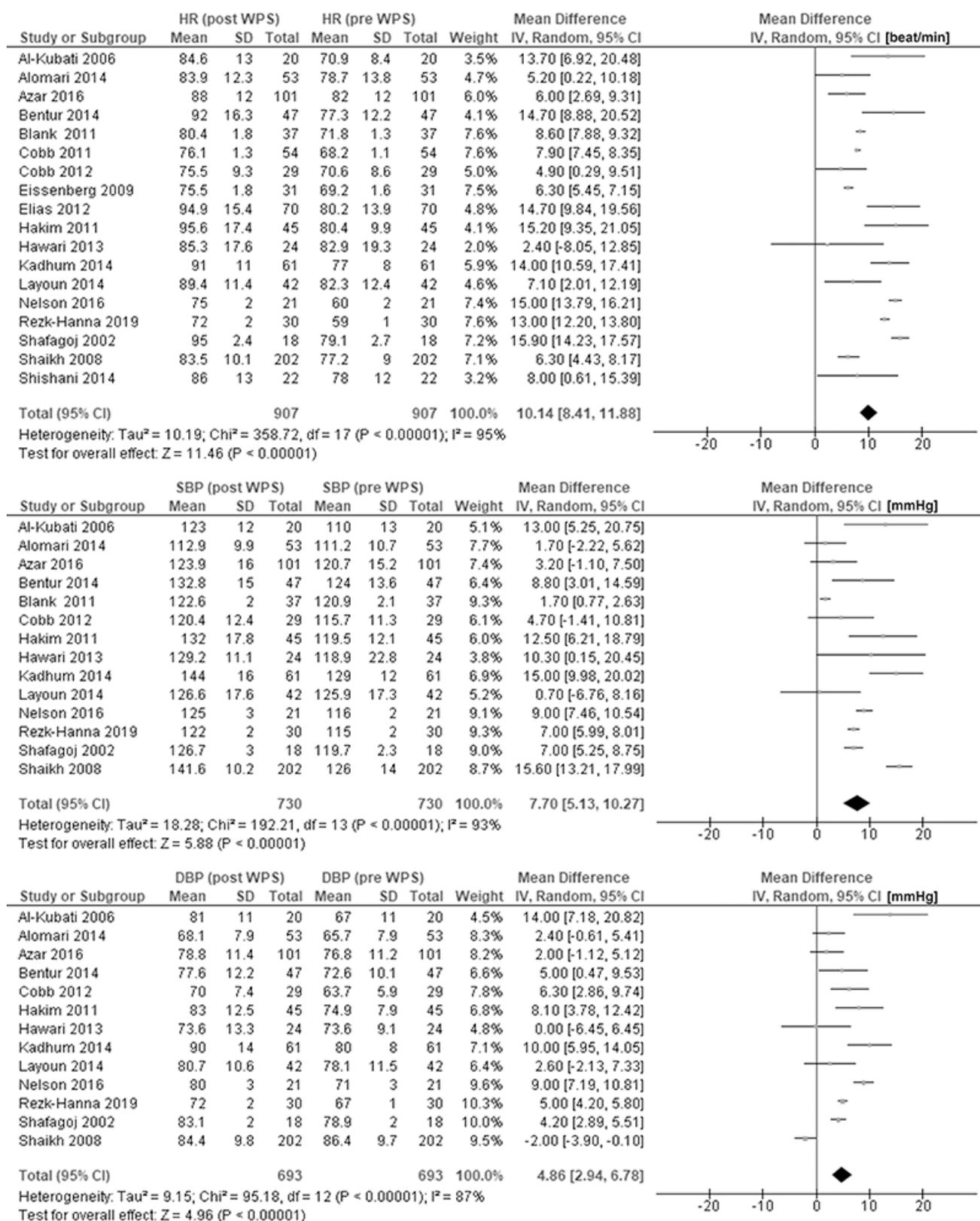


Fig. 2. Forest plots demonstrating individual (squares) and pooled (rhombus) acute changes (mean difference) in heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP), with corresponding 95% confidence intervals (horizontal lines), obtained after one waterpipe smoking session. WPS: Waterpipe smoking

Table 1. Study Characteristics.

Study	Study design	Sampling	Participants	N		Age, years Mean ± SD (range)	Total	WPS		CS	NS	Pre-session abstinence	WPS session, min.	Smoking setting	Tobacco used
				Male	Female			Exclusive	Frequency						
Experimental studies															
Al-Kubati et al., 2006	One-Group Pretest-Posttest	Convenience sampling	Healthy subjects	20	20	27.2 ± 6.4 (20-40)	20	n.s.	n.s.	-	-	12 h	45	Laboratory	5 g moassal
Alomari et al., 2014	One-Group Pretest-Posttest	Convenience sampling	Healthy subjects	53	34	22.7 ± 4.8 (18-35)	53	n.s.	≥ 3 WP/week	-	-	n.s.	30	A well-ventilated room	10 g flavoured tobacco
Azar et al., 2016	Three-Group Pretest-Posttest	Convenience sampling	Healthy subjects	194	112	35.6 (> 18)	101	n.s.	n.s.	-	42	12 h	15	Restaurants	n.s.
Bentur et al., 2014	Two-Group Pretest-Posttest	Convenience sampling	Healthy subjects	62	33	24.9 ± 6.2 (≥ 18)	47	n.s.	n.s.	-	-	24 h	30	Indoor environment	10 g moassal
Blank et al., 2011	One-Group Pretest-Posttest, Two-condition crossover	Convenience sampling	Healthy subjects	37	29	20.5 ± 2.1 (18-50)	37	≤ 5 cig/month	2-5 WP/month	-	-	Overnight	45	Laboratory	10 g flavoured tobacco
Cobb et al., 2011	One-Group Pretest-Posttest, Two-condition crossover	Convenience sampling	Healthy subjects	54	36	21.2 ± 2.3 (18-50)	54	≥ 5 cig/day	≥ 2 WP/month	54	-	12 h	43.3 (CS 6.1)	Laboratory	n.s.
Cobb et al., 2012	One-Group Pretest-Posttest, Two-condition crossover	Convenience sampling	Healthy subjects	32	16	21.6 ± 2.7 (18-50)	32	≤ 5 cig/month	≥ 4 WP/month	32	-	12 h	45	Laboratory	10 g flavoured tobacco
Eissenberg and Shihadeh, 2009	One-Group Pretest-Posttest, Two-condition crossover	Voluntary response sampling	Healthy subjects	31	21	21.4 ± 2.3 (18-50)	31	≥ 1 cig/week	≥ 1 WP/month	31	-	≥ 12 h	45 (CS 5)	Laboratory	15 g flavoured tobacco
Elias et al., 2012	Two-Group Pretest-Posttest	Convenience sampling	Healthy subjects	100	n.s.	29.5 ± 10.4 (18-60)	70	70	weekly WPS, (6.9 ± 3.7)	-	30	n.s.	30	n.s.	n.s.
Hakim et al., 2011	One-Group Pretest-Posttest	Convenience sampling	Healthy subjects	45	30	32.3 ± 23.4 (18.3-65.1)	45	37	Regularly	-	-	24 h	30	An outdoor environment.	10 g moassal
Hawari et al., 2013	One-Group Pretest-Posttest	Convenience sampling	Healthy subjects	24	24	20.4 (18-25)	24	n.s.	4 (0.5-14) WP/week	-	-	≥ 48 h	45	Laboratory	n.s.
Kadhun et al., 2014	One-Group Pretest-Posttest	Convenience sampling	Healthy subjects	61	49	(18-25)	61	61	n.s.	-	-	≥ 24 h	45-90	Cafes	n.s.
Layoun et al., 2014	Three-Group Pretest-Posttest	Convenience sampling	n.s.	132	87	33.4 (≥ 18)	42	42	≥ 1WP/week	48	42	n.s.	45	Restaurants	20 g moassal
Nelson et al., 2016	One-Group Pretest-Posttest	Convenience sampling	Healthy subjects	28	20	27 ± 5 (17-39)	28	28	> 12 times in the past year	-	-	72 h	30 (102 ± 60)	Laboratory	n.s.
Rezk-Hanna et al., 2019	Two-Group Pretest-Posttest	Voluntary response sampling	Healthy subjects	55	10	26 ± 1 (18-34)	40	40	≥ 12 times in the past year	15	-	Overnight	96 ± 40 (60-120)	Laboratory	n.s.
Shafagoj and Mohammed, 2002	One-Group Pretest-Posttest	Convenience sampling	Healthy subjects	18	18	27 ± 8 (20-45)	18	18	≥ 3 times/week	-	-	84 h	45	Laboratory	20 g moassal

Table 1. Study Characteristics.

Study	Study design	Sampling	Participants	N		Age, years Mean ± SD (range)		WPS		Frequency	CS	NS	Pre-session abstinence	WPS session, min.	Smoking setting	Tobacco used
				Male	Total	Exclusive										
Shaikh et al., 2008	One-Group Pretest-Posttest	Cluster sampling	Healthy subjects	202	202	33.2 (> 17)		202	202	n.s.	-	-	20 min	30-45	Café	n.s.
Shishani et al., 2014	One-Group Pretest-Posttest Two-condition crossover	Voluntary response sampling	Healthy subjects	22	n.s.	23 ± 3.1 (18-30)		22	22	≥ 10 times in the past year, and ≤ 2 times/week in the past 3 months	-	-	24 h	45-60	Outdoor laboratory	n.s.
Wolfram et al., 2003	One-Group Pretest-Posttest	Convenience sampling	Healthy subjects	7	7	≥ 18		7	7	occasionally	-	-	3 months	55 (45-70)	Laboratory	15 g of tobacco
Case-control studies																
Al-Amri et al., 2019	Case-control hospital-based	Convenience sampling	Cases are myocardial infarction, controls from dermatology and surgery departments	296	203	47.8 ± 14.6 (≥ 18)		35	35	Daily	89	261	n.s.	-	-	n.s.
Al-Numair et al., 2007	Case-control	Convenience sampling	Healthy subjects	200	200	(19-50)		100	100	Daily	-	100	n.s.	-	-	ma'ssel
Chami et al., 2019	Case-control community-based	Convenience and voluntary response sampling	Healthy subjects	345	233	53.7 ± 9.1 (≥ 35)		175	98%	Daily	-	170	n.s.	-	-	n.s.
Chwyeed, 2018	Case-control	Randomly selection	Healthy subjects	75	75	(30-60)		20	20	n.s.	20	35	n.s.	-	-	n.s.
Diab et al., 2015	Case-control	Convenience sampling	Healthy subjects	77	77	35.1 ± 1.05 (≤ 60)		30	30	Daily	30	17	n.s.	-	-	n.s.
Ghasemi et al., 2010	Case-control community-based	Convenience sampling	Healthy subjects	54	54	33.3 ± 2.94		27	27	Daily	-	27	n.s.	-	-	mostly of moassal
Hashem Sezavar et al., 2004	Case-control community-based	Convenience sampling	n.s.	450	450	(20-75)		150	150	Daily	150	150	n.s.	-	-	n.s.
Jabbour et al., 2003	Case-control hospital-based	Convenience sampling	Cases are CHD patients, controls recruited from 3 hospitals	525	n.s.	n.s.		49	n.s.	> 4/week	-	299	n.s.	-	-	n.s.
Koubaa et al., 2015a	Case-control community-based	Convenience sampling	Healthy subjects	43	43	43.6 ± 2.2		14	14	≥ 5 WP-year	15	14	n.s.	-	-	10 and 25 g

Table 1. Study Characteristics.

Study	Study design	Sampling	Participants	N	Male	Age, years Mean ± SD (range)	Total	WPS		CS	NS	Pre-session abstinence	WPS session, min.	Smoking setting	Tobacco used
								Exclusive	Frequency						
Koubaa et al., 2015b	Case-control community-based	Convenience sampling	Healthy subjects	43	43	43.6 ± 2.2	14	14	≥ 5 WP-year	15	14	n.s.	-	-	10 and 25 g
Muddathir et al., 2018	Case-control	Convenience sampling	Healthy subjects	120	80	29.2 (18-51)	40	40	Daily	40	40	n.s.	-	-	n.s.
Selim et al., 2013a	Case-control community-based	Convenience sampling	Healthy subjects	70	63	28.7 (25-35)	30	30	Daily	30	10	n.s.	-	-	n.s.
Cross-sectional/cohort studies															
Al Suwaidi et al., 2012	Cross-sectional prospective hospital-based cohort	Convenience sampling	ACS patients	7930	6253	59.6	130	130	Regular	3605	3742	-	-	-	n.s.
Al-Safi et al., 2009	Cross-sectional population-based	Stratified cluster random sampling	Healthy subjects	14310	7400	31.4 (≥ 18)	2272	1132	≥ 1 WP/week	2691	9347	n.s.	-	-	n.s.
Islami et al., 2013	Cross-sectional prospective population-based cohort	Systematic clustering random sampling	Cases: participants with heart disease history, Controls: participants with no heart disease history	50045	21234	(40-75)	525	n.s.	Ever	-	49489	n.s.	-	-	n.s.
Khan et al., 2020	Cross-sectional community-based	Voluntary response sampling	Healthy subjects	73	41	39.8 (21-65)	12	12	Daily	26	25	n.s.	-	-	n.s.
Platt et al., 2017	Cross-sectional hospital-based	Convenience sampling	Coronary angiography patients	57	27	25.4	33	33	≥ 1 WP/month	-	24	n.s.	-	-	n.s.
Saffar	Cross-sectional hospital-based	Convenience sampling	Coronary angiography patients	7705	5188	61.2 ± 11.4	574	574	Regularly	2625	4506	n.s.	-	-	n.s.
Soflaei et al., 2018	Cross-sectional population-based	Stratified cluster random sampling	-	9690	n.s.	(35-65)	1067	1067	n.s.	864	6742	n.s.	-	-	n.s.
Selim et al., 2013b	Cross-sectional hospital-based	Convenience sampling	Coronary angiography patients	287	n.s.	n.s.	63	63	Regularly	100	109	n.s.	-	-	n.s.
Shafique et al., 2012	Cross-sectional population-based cohort	Voluntary response sampling	Healthy subjects	2032	1039	(30-75)	325	325	≥ 1 WP/week	-	1707	n.s.	-	-	n.s.
Sibai et al., 2014	Cross-sectional hospital-based	Convenience sampling	Coronary angiography patients	1754	n.s.	(≥ 40)	235	n.s.	Ever ≥ 1 WP-year	544	975	n.s.	-	-	n.s.
Ward et al., 2015	Cross-sectional population-based	Stratified cluster random sampling	-	2536	1220	25-65	286	n.s.	Regularly	-	2134	n.s.	-	-	n.s.
Wu et al., 2013	Cross-sectional prospective population-based cohort	Convenience sampling	n.s.	20033	1971	(18-75)	n.s.	n.s.	Ever regularly	n.s.	n.s.	n.s.	-	-	n.s.

WP: Waterpipe, WPS: Waterpipe smoking, CS: Cigarette smoking, ACS: Acute coronary syndrome, CHD: Coronary heart disease. n.s.: Not specified.

3.4.1.2 Oxidative status and vascular function

3.4.1.2.1 Oxidative status

Immediate effects of WPS on endothelial function was investigated through oxidative stress in one study evaluated the acute effect of WPS on the oxidative status (Wolfram et al., 2003), showing a significant increase in mean malondialdehyde from 3.6 ± 0.4 to 4.3 ± 0.3 pg/ml ($P = 0.001$), 11-dehydro-thromboxane-B2 (11-DH-TXB2) from 24.9 ± 1.9 to 29.8 ± 2.7 pg/ml ($P < 0.001$), and 8-Epi-Prostaglandin-F2Alpha (8-epi-PGF2a) from 19.4 ± 2.4 to 20.6 ± 2.6 pg/ml ($P = 0.03$) after one WPS session.

3.4.1.2.2 Vascular function

To investigate the potential acute effect of WPS on vascular function, different clinical methods were used in three experimental (Alomari et al., 2014; Bentur et al., 2014; Rezk-Hanna et al., 2019) and two case-control (Diab et al., 2015; Selim et al., 2013a) studies. One WPS session led to a significantly acute reduction in arterial blood flow by -8.8% ($P = 0.035$) and increase in arterial vascular resistance by 16% ($P = 0.003$) using strain-gauge plethysmography (Alomari et al., 2014), while no acute changes were observed in arterial pulse wave amplitude using "EndoPat" device (Bentur et al., 2014). However, an acute reduction in flow-mediated dilatation (FMD) by 28% was observed after one WPS session ($P < 0.001$) in a recent study, where the effect of charcoal combustion was removed when the waterpipe-tobacco-product was heated electrically (Rezk-Hanna et al., 2019).

3.4.2 Non-acute effects of waterpipe smoking

3.4.2.1 Hemodynamic parameters

3.4.2.1.1 Heart rate and blood pressure

Meta-analysis was conducted using data from 10 studies with 14909 participants for HR, 12 studies with 17386 participants for SBP and DBP and 5 studies with 5742 participants for having hypertension. Results showed an increased mean HR by 2.12 (95% CI: 0.11 to 4.13; $P = 0.04$) with a tendency to have higher blood pressure (BP) among waterpipe smokers compared to non-smokers (Fig. 3). No significant association between WPS and any of these hemodynamic parameters was observed in meta-analysis after eliminating the statistical heterogeneity in sensitivity analyses. However, a large population-based cross-sectional study with 14310 participants (Al-Safi et al., 2009) showed a significant correlation between hemodynamic status and frequency of WPS. Compared to non-smokers, waterpipe smokers of 1-2 sessions/week had higher mean HR by < 1 beat/min ($P < 0.01$), SBP by 1 mmHg ($P < 0.002$) and DBP by 1 mmHg ($P < 0.009$); and those who smoked > 4 sessions/week had even higher HR by 3 beat/min, SBP by 7 mmHg and DBP by 4 mmHg ($P < 0.001$ for all comparisons).

3.4.2.2 Lipo- and apolipoproteins

3.4.2.2.1 Lipoproteins

The potential correlation of WPS with serum lipid levels was investigated by conducting the meta-analysis for each of total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglyceride and having dyslipidemia including 5, 6, 7, 6, and 5 observational studies with 12120, 12320, 14352, 14007 and 13206 participants; respectively. Results demonstrated increased mean LDL-cholesterol by 8.77

mg/dl (95% CI: 0.55 to 17.0; $P = 0.04$) and triglyceride by 30.6 mg/dl (95% CI: 14.4 to 46.7; $P < 0.001$) and decreased HDL-cholesterol by -3.39 mg/dl (95% CI: -5.13 to -1.65 ; $P < 0.001$) in waterpipe smokers compared to non-smokers (Fig. 4). The correlation between WPS and increased triglyceride and decreased HDL-cholesterol remained significant after removing statistical heterogeneity in sensitivity analyses.

3.4.2.2.2 Apolipoproteins

One case-control study (Al-Numair et al., 2007) compared apolipoproteins (Apo) between waterpipe smokers and non-smokers, revealing decreased mean Apo-A1 (46 ± 1.10 vs. 42 ± 1.92 mmol/l; $P < 0.05$) and increased mean Apo-B (2.02 ± 0.61 vs. 2.38 ± 0.40 ; $P < 0.05$) among waterpipe smokers.

3.4.2.3 Coagulation factors

3.4.2.3.1 Fibrinogen

Three case-control studies investigated the association between WPS and fibrinogen (Hashem Sezavar et al., 2004; Khan et al., 2020; Muddathir et al., 2018), where significantly increased levels of fibrinogen by about 15-25% were observed among waterpipe smokers compared to non-smokers ($P < 0.01$) in two of them (Hashem Sezavar et al., 2004; Muddathir et al., 2018).

3.4.2.3.2 Factor-VII and VIII

Factor-VII and VIII were investigated in one study (Muddathir et al., 2018), showing higher levels by about 25% and 50%, respectively, in waterpipe smokers than in non-smokers, especially in those who smoked waterpipe for more than 3 years ($P < 0.01$).

3.4.2.3.3 Other coagulation factors

No significant long-term effect has been reported on Serpine1/Plasminogen activator inhibitor-1 (Khan et al., 2020).

3.4.2.4 Oxidative status, inflammation, and vascular function

3.4.2.4.1 Oxidative status and inflammation

One study investigated the longitudinal effect of WPS on the oxidative status (Wolfram et al., 2003). Blood levels of malondialdehyde, 11-DH-TXB2 and 8-epi-PGF2a continued to rise over two weeks of daily WPS and remained significantly elevated even before the initiation of a new WPS session.

Two (Al-Numair et al., 2007; Koubaa et al., 2015a) of three studies (Al-Numair et al., 2007; Khan et al., 2020; Koubaa et al., 2015a) observed significantly increased levels of malondialdehyde among waterpipe smokers compared to non-smokers. These two studies also showed significantly reduced levels of total antioxidant capacity (TAC) among waterpipe smokers compared to non-smokers ($P < 0.05$). No significant differences were found regarding plasma myeloperoxidase and Intercellular Adhesion Molecule-1. However, urinary levels of 8-isoprostanes and myeloperoxidase were significantly higher in waterpipe smokers than in non-smokers (Khan et al., 2020; Koubaa et al., 2015a).

In one study, Nitric oxide (NO) metabolites were measured in waterpipe smokers (Ghasemi et al., 2010) demonstrating higher levels than in non-smokers (34.3 vs. 22.5 micromol/l; $P < 0.01$). No difference was observed regarding C-reactive protein (CRP) in three studies (Diab et al., 2015; Khan et al., 2020; Saffar Soflaei et al., 2018).

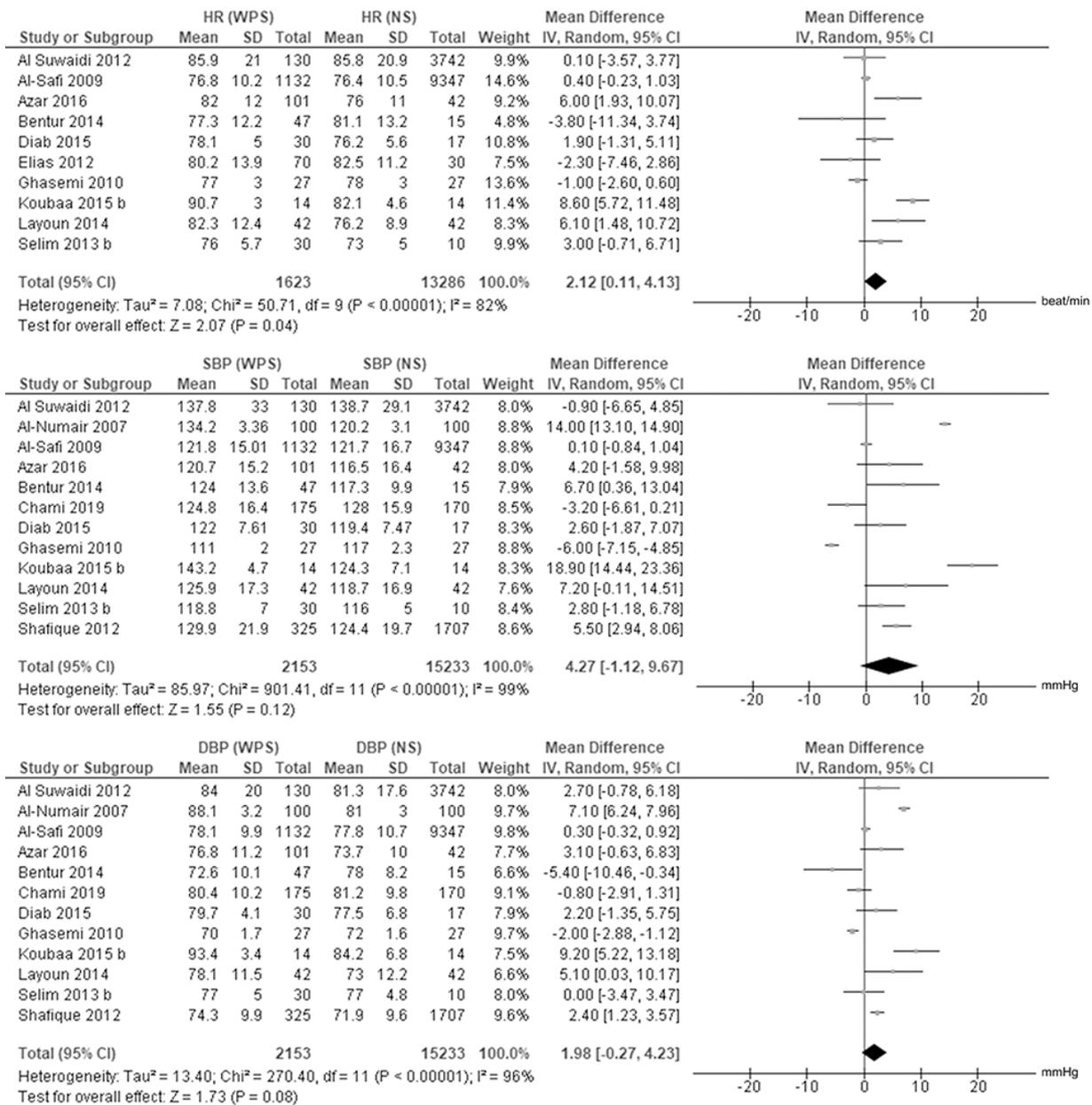


Fig. 3. Forest plots demonstrating individual (squares) and pooled (rhombus) mean differences in heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP), with corresponding 95% confidence intervals (horizontal lines), obtained in waterpipe smokers compared to non-smokers. WPS: Waterpipe smoking. NS: Non-smoking.

3.4.2.2.2 Vascular function

Two case-control studies evaluated the potential non-acute effect of regular WPS on FMD, where lower FMD values by about 30-60% were observed in waterpipe smokers than in non-smokers ($P < 0.05$) (Diab et al., 2015; Selim et al., 2013a), with a negative correlation between FMD and both smoking duration in years ($P < 0.001$) and number of daily sessions ($P < 0.001$) (Selim et al., 2013a).

3.4.2.5 Fasting blood glucose

Our meta-analysis showed that waterpipe smokers had a higher mean fasting blood glucose (FBG) of 4.66 mg/dl (95% CI: 0.53 to 8.80; $P = 0.03$) than non-smokers did, with no association between

WPS and having diabetes mellitus (DM). After removing the statistical heterogeneity in sensitivity analyses, a significant correlation was revealed between WPS and both of DM (OR = 1.35; 95% CI: 1.16 to 1.57; $P < 0.001$) and mean FBG.

3.4.2.6 Body mass index

No difference was observed between waterpipe smokers and non-smokers regarding body mass index (BMI) in our meta-analysis. However, two population-based cross-sectional studies observed a significant association between obesity and each of regular waterpipe smokers (OR = 1.44; 95% CI: 1.26 to 1.65; $P < 0.001$) (Saffar Soflaei et al., 2018) and daily waterpipe smokers (OR = 2.87; 95% CI: 1.06 to 7.76; $P = 0.038$) (Ward et al.,

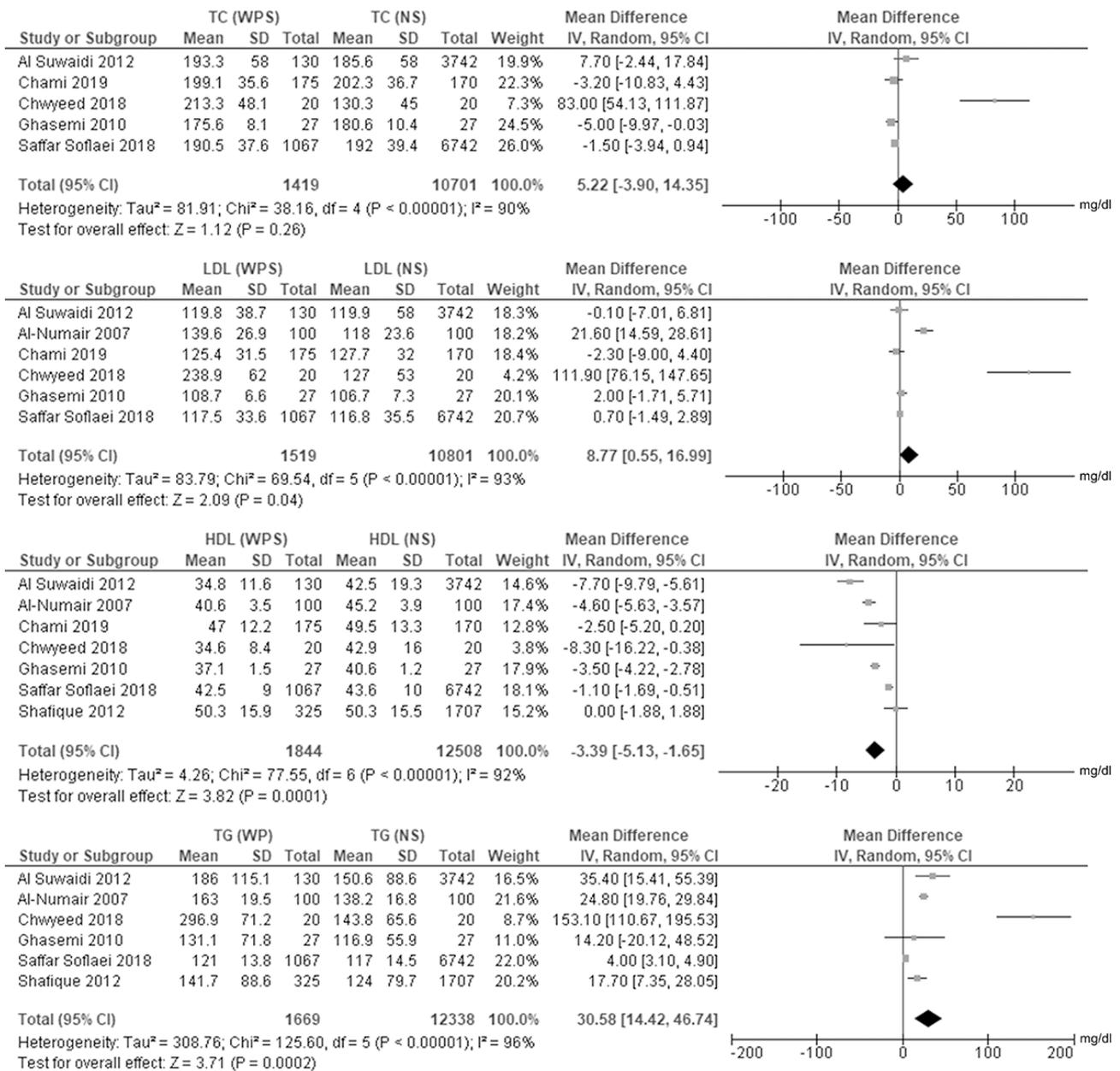


Fig. 4. Forest plots demonstrating individual (squares) and pooled (rhombus) mean differences in blood levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL) and triglyceride (TG), with corresponding 95% confidence intervals (horizontal lines), obtained in waterpipe smokers compared to non-smokers. WPS: Waterpipe smoking. NS: Non-smoking.

2015), but no significant correlation was observed in a hospital based cross-sectional study (Selim et al., 2013b).

3.4.2.7 Metabolic syndrome and 10-year CHD risk

Two population-based studies (Saffar Soflaei et al., 2018; Shafique et al., 2012) assessed the potential correlation of WPS with metabolic syndrome (MS). Waterpipe smokers were more likely to have MS compared to non-smokers (OR = 1.29; 95% CI: 1.12 to 1.48; P < 0.001; and OR = 3.21; 95% CI: 2.38 to 4.33; P < 0.01).

One case-control study (Chami et al., 2019) evaluated the 10-year CHD risk in waterpipe smokers, showing higher mean risk

score in waterpipe smokers than in non-smokers (7.12 ± 7.18 vs. 4.05 ± 4.48 ; P < 0.001).

3.4.2.8 Coronary artery calcium

Coronary Artery Calcium (CAC) score was measured among waterpipe smokers in one case-control study (Chami et al., 2019). Waterpipe smokers had higher mean CAC score than non-smokers did (90.6 ± 400.3 vs. 52.8 ± 218.6 AUs; P = 0.02).

3.4.2.9 Cardiovascular disease

3.4.2.9.1 Incidence of cardiovascular disease

A significant correlation between WPS and the incidence of CVD was reported in four out of seven differently designed stud-

ies (Al-Amri et al., 2019; Al Suwaidi et al., 2012; Chami et al., 2019; Islami et al., 2013; Jabbour et al., 2003; Platt et al., 2017; Saffar Soflaei et al., 2018). In a large population-based cohort study with 50045 participants (Islami et al., 2013) heart disease correlated to the consumption of > 180 waterpipe-year (OR: 3.75; 95% CI: 1.52 to 9.22). A recent hospital-based case-control study showed that myocardial infarction (MI) was independently associated with WPS (OR = 10.3; 95% CI: 2.22 to 47.29) (Al-Amri et al., 2019). Similarly, WPS significantly associated with having MI in a cross-sectional hospital-based on 7705 patients referred for cardiac catheterization (OR = 1.3; 95% CI: 1.04 to 1.68; $P = 0.021$) (Platt et al., 2017) and with having ST-elevation MI (STEMI) in another cross-sectional hospital-based on 7930 patients admitted with acute coronary syndrome (ACS) (Al Suwaidi et al., 2012).

3.4.2.9.2 Severity of coronary artery disease

Two cross-sectional studies assessed the correlation between WPS and the severity of coronary artery disease (CAD). Compared to non-smokers, waterpipe smokers had a higher mean Duke Jeopardy score (DJS) of anatomical extension of CAD ($P < 0.05$), with a positive correlation between DJS and the duration of smoking in years ($r = 0.574$, $P < 0.001$) (Selim et al., 2013b). Waterpipe smokers with > 40 waterpipe-years were more likely to have severe coronary stenosis (OR = 2.94; 95% CI: 1.04-8.33) with a higher Duke CAD prognostic index ($\beta = 7.835$, $P = 0.027$) than non-smokers did (Sibai et al., 2014).

3.4.2.9.3 Outcomes of cardiovascular disease

The relationship between WPS and CVD outcomes was investigated in two cross-sectional studies (Al Suwaidi et al., 2012; Wu et al., 2013). Among patients with ACS, waterpipe smokers were more likely to develop arrhythmias at presentation (OR = 2.0; 95% CI: 1.08 to 3.69; $P = 0.026$) and in-hospital complications (OR = 2.7; CI 95%: 1.85 to 3.88, $P < 0.001$), especially recurrent myocardial ischemia (OR = 2.08; 95% CI: 1.40 to 3.10; $P < 0.001$), than non-smokers did. No significant differences were observed regarding Killip classification or mortality rate (Al Suwaidi et al., 2012). However, in a large prospective population-based cohort study with 20033 participants, WPS for > 5 times/day significantly correlated with increased risk of death from ischemic heart disease (HR = 1.96; 95% CI: 1.05 to 3.63; $P = 0.04$) (Wu et al., 2013).

3.4.3 Waterpipe compared with cigarette smoking

3.4.3.1 Heart rate and blood pressure

Meta-analysis including data from seven observational studies with 7842 participants showed no differences between waterpipe and cigarette smokers regarding HR, SBP or DBP (Fig. 5). After removing the statistical heterogeneity in sensitivity analyses, significantly increased mean HR by 3.21 (95% CI: 2.31 to 4.11; $P < 0.001$), SBP by 2.82 (95% CI: 1.15 to, 4.49; $P = 0.001$) and DBP by 2.38 (95% CI: 0.98 to 3.79; $P < 0.001$) were revealed. One of two studies (Al Suwaidi et al., 2012; Selim et al., 2013b) observed higher hypertension rates (53.1% vs. 39.2%; $P = 0.001$) (Al Suwaidi et al., 2012) in waterpipe than in cigarette smokers.

3.4.3.2 Lipoproteins

Pooled data from three observational studies with 5721 participants showed higher mean total cholesterol of 6.80 mg/dl (95% CI: 3.23 to 10.38; $P < 0.001$) in waterpipe than in cigarette smokers. No differences were found regarding levels of LDL-cholesterol, HDL-cholesterol or triglyceride or having dyslipidemia (Fig. 6). However, a significant correlation between WPS and triglyceride level was revealed after removing the statistical heterogeneity in sensitivity analyses.

3.4.3.3 Body mass index and diabetes mellitus

Meta-analysis showed no differences regarding mean BMI and prevalence of DM between waterpipe and cigarette smokers. However, one of two studies (Saffar Soflaei et al., 2018; Selim et al., 2013b) reported a higher obesity rate (OR = 4.19; 95% CI: 3.33 to 5.28; $P < 0.001$) in waterpipe than in cigarette smokers (Saffar Soflaei et al., 2018).

3.4.3.4 Oxidative status, inflammation, and vascular function

Meta-analysis showed no difference regarding FMD between waterpipe and cigarette smokers. Furthermore, the three studies that compared CRP levels (Diab et al., 2015; Khan et al., 2020; Saffar Soflaei et al., 2018) and the two studies that compared levels of malondialdehyde and TAC (Khan et al., 2020; Koubaa et al., 2015a) observed no differences between waterpipe and cigarette smokers.

3.4.3.5 Coagulation factors

In two of the three case-control studies (Hashem Sezavar et al., 2004; Khan et al., 2020; Muddathir et al., 2018), waterpipe smokers had significantly higher levels of fibrinogen than cigarette smokers did ($P < 0.05$) (Hashem Sezavar et al., 2004; Muddathir et al., 2018). The one study which investigated the levels of factor-VII and VIII (Muddathir et al., 2018) found no significant difference between waterpipe and cigarette smokers.

3.4.3.6 Cardiovascular Disease

Different aspects of CVD were compared between waterpipe and cigarette smokers in three studies (Al Suwaidi et al., 2012; Saffar Soflaei et al., 2018; Selim et al., 2013b). No differences were observed regarding CVD incidence (Al Suwaidi et al., 2012; Saffar Soflaei et al., 2018). However, higher mean DJS was also observed in waterpipe than in cigarette smokers in a cross-sectional study conducted on CAD patients ($P < 0.05$) (Selim et al., 2013b). In another study on ACS patients, waterpipe smokers were more likely to have arrhythmia at presentation (OR = 1.79; 95% CI: 1.26 to 2.54; $P = 0.001$), in-hospital cardiovascular complications (OR = 3.37; 95% CI: 2.33 to 4.89; $P < 0.001$), especially recurrent ischemia (OR=2.25; 95% CI: 1.51 to 3.35; $P < 0.001$), higher mortality rate (OR = 1.8; 95% CI: 1.06 to 3.09; $P < 0.05$) and killip classification of > 1 (OR = 1.7; 95% CI: 1.14 to 2.45; $P < 0.01$) than cigarette smokers did (Al Suwaidi et al., 2012).

4. Discussion

The main findings of our analyses are: i) WPS leads to an acute increase in HR, SBP and DBP; ii) waterpipe smokers have increased HR, higher triglyceride and LDL-Cholesterol and lower

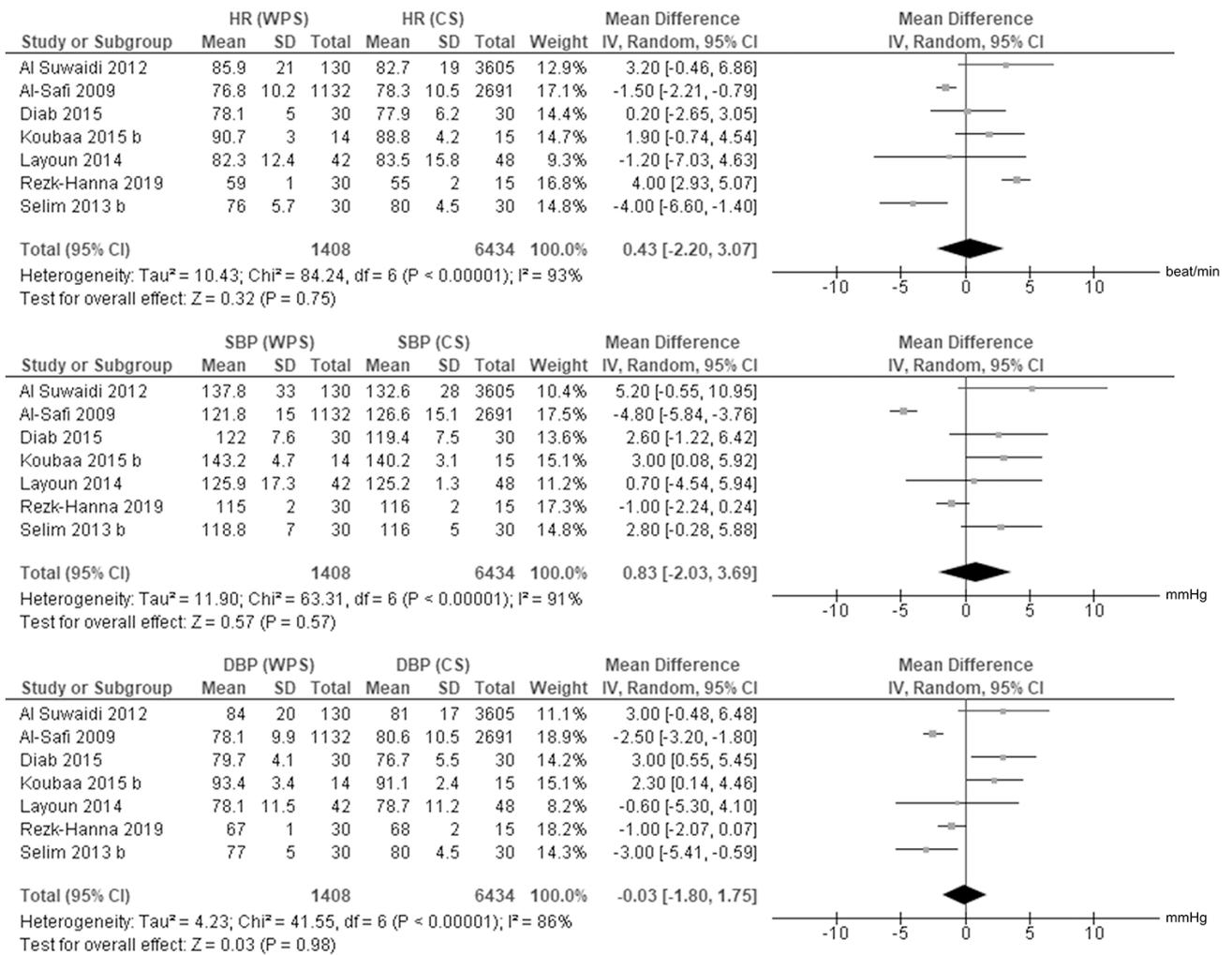


Fig. 5. Forest plots demonstrating individual (squares) and pooled (rhombus) mean differences in heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP), with corresponding 95% confidence intervals (horizontal lines), obtained in waterpipe smokers compared to cigarette smokers. WPS: Waterpipe smoking. CS: Cigarette smoking.

HDL-Cholesterol levels compared to non-smokers; iii) the cardiometabolic profile in waterpipe smokers is not less worse than in cigarette smokers.

It is well known that increased HR and BP, the two most widely used hemodynamic parameters in assessment of cardiovascular system, negatively affect cardiovascular outcome. (Ettedah et al., 2016; Nikolovska Vukadinović et al., 2017). According to our results one WPS session causes acute increase in HR by about 11 beats/minute, SBP by 7 mmHg and DBP by 5 mmHg. This itself may lead to increased oxygen demand of the heart, augment shear stress of the blood vessel, which in some cases may provoke ACS, thereby increasing morbidity and mortality. Based on available data, it is not known how long these acute hemodynamic effects of WPS might last. The answer to this question needs more studies with serial measurements of these parameters. As waterpipe is mostly consumed regularly for several times a week, it could be expected that accumulation of these acute adverse effects negatively impacts prognosis over time. However, our results show that waterpipe smokers had slightly increased HR in comparison with

non-smokers for about 2 beats/minute, while SBP and DBP tend to be higher among waterpipe smokers but without reaching the statistical significance. These results differ somewhat unexpectedly from those observed with the acute effects of WPS, which could be partially explained through large heterogeneity across the studies. Furthermore, frequency and duration of WPS sessions and years of smoking were not adjusted across the studies, which might affect the results. A significant positive correlation was previously observed between the number of weekly use of waterpipe and each of SBP, SBP and HR (Al-Safi et al., 2009). The acute hemodynamic changes revealed in our analyses may be attributed to some extent to nicotine exposure, which augments the sympathetic nervous system activity, leading to increases in HR, myocardial contractility and cardiac output (Salahuddin et al., 2012). Such an effect has been reported in the three cross-over design studies (Blank et al., 2011; Cobb et al., 2012; Shishani et al., 2014) comparing flavor-matched tobacco- with tobacco-free-WPS. However, an acute cardiac autonomic dysregulation was observed after a WPS session independently of nicotine content (Cobb et al., 2012). In

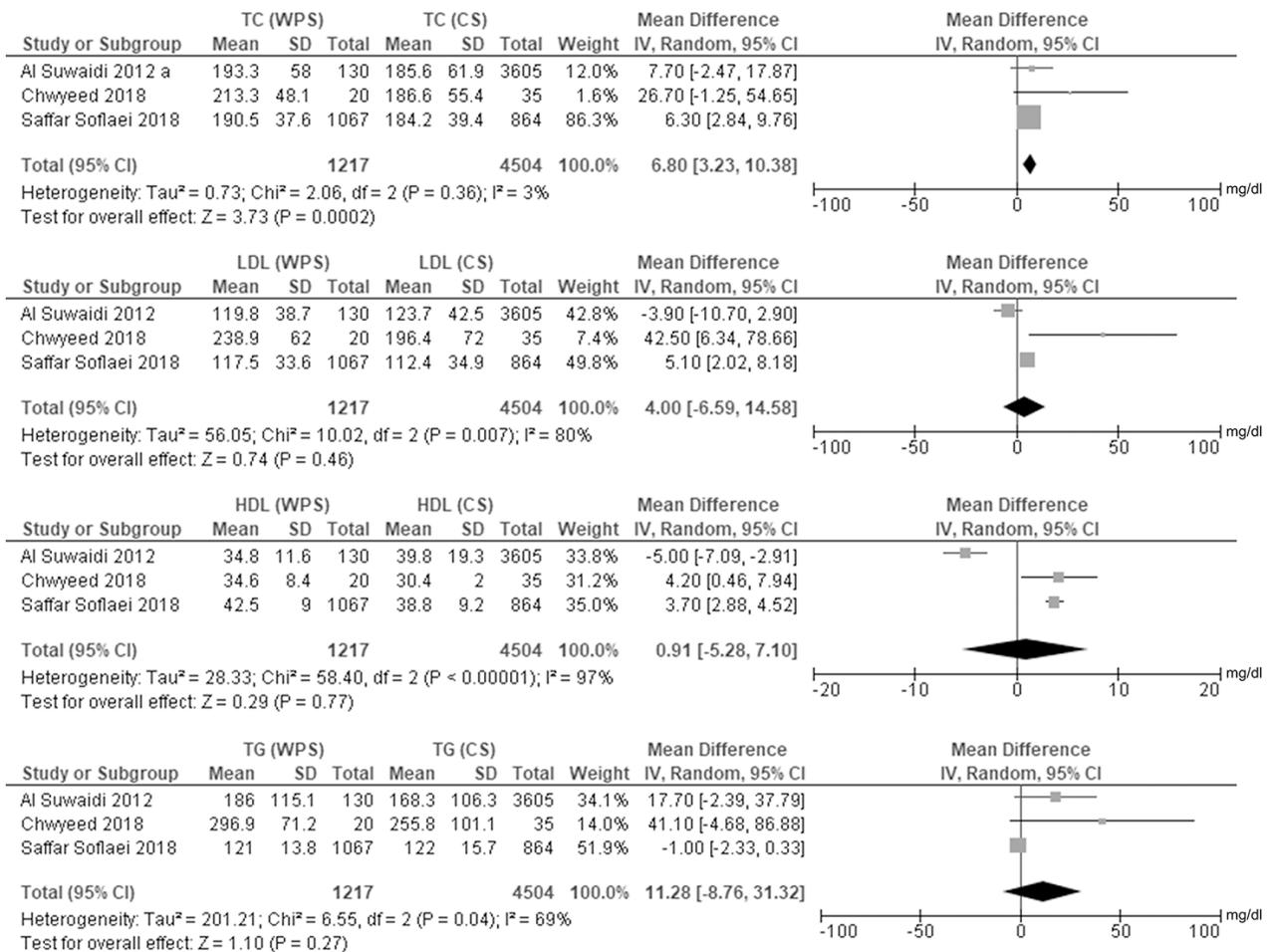


Fig. 6. Forest plots demonstrating individual (squares) and pooled (rhombus) mean differences in blood levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL) and triglyceride (TG), with corresponding 95% confidence intervals (horizontal lines), obtained in waterpipe smokers compared to cigarette smokers. WPS: Waterpipe smoking. CS: Cigarette smoking.

addition, the high levels of exposed CO during WPS (Eissenberg and Shihadeh, 2009) can lead to decreased oxygen supply to tissues including the heart due to the formation of CO-Hb (Benowitz, 2003). In turn, it has been well established that hypoxia is a potent stimulator of several autonomic mechanisms leading to increases in resting HR, BP and cardiac output (Vigo et al., 2010). These findings contradict harm reduction claims of so-called "herbal" waterpipe-products and correspond to outcomes of non-clinical studies on such products using a human-mimic waterpipe-machine (Hammal et al., 2015). Owing to the lack of data from longitudinal studies, it is not possible to determine to what extent WPS can be hemodynamically harmful at the long-term.

Pooling data from available studies revealed a significant correlation between WPS and increased triglyceride and LDL-cholesterol and decreased HDL-cholesterol, which are recognized as CVD risk factors that promote atherosclerosis (Pedro-Botet et al., 2020). As is well known for CS, the mechanisms responsible are not clearly elucidated. However, the triglyceride/high-density lipoprotein abnormalities have recently been suggested to be related to insulin resistance. (Ambrose and Barua, 2004). This can be supported with our results that showed a significant increase in

FBG in waterpipe smokers compared to non-smokers.

The association between CS and increased activity of coagulation factors and thrombotic risk has been previously reported (Eliasson, 1995). Likewise, WPS also correlates with increased levels of fibrinogen and factors VII and VIII (Hashem Sezavar et al., 2004; Khan et al., 2020; Muddathir et al., 2018), which may increase thrombogenicity, thus increasing the risk for cardiovascular events. The harmful effects of WPS are reflected by the increased CAC score (Chami et al., 2019) and the acute (Alomari et al., 2014; Rezk-Hanna et al., 2019; Wolfram et al., 2003) and long-term (Al-Numair et al., 2007; Diab et al., 2015; Ghasemi et al., 2010; Koubaa et al., 2015a; Selim et al., 2013a) endothelial dysfunction, which were established among waterpipe smokers, providing clinical evidence for the potential contribution of WPS to vascular disease. Our findings on WPS effects on cardiovascular system explain and support results of studies which reported a significant correlation between WPS and each of incidence (Al-Amri et al., 2019; Islami et al., 2013; Jabbour et al., 2003; Platt et al., 2017), worse clinical outcomes (Al Suwaidi et al., 2012) and estimated prognoses (Selim et al., 2013b; Sibai et al., 2014) of CVD.

As cardiovascular effects of CS are well known (Ambrose and

Barua, 2004; Leone, 2003; Mons et al., 2015), the comparison between WPS and CS is of a great importance. Unfortunately, fewer studies could be included for this comparison. The lack of studies reporting the rate of cardiovascular and cerebrovascular events in waterpipe vs cigarette smokers may be the main limitation. However, based on our results, the non-acute effects of WPS on the vast majority of cardiovascular parameters of interest seem similar to those produced by CS. The few available studies showed no clear difference in the CVD incidence between WPS and CS (Al Suwaidi et al., 2012; Saffar Soflaei et al., 2018). Furthermore, CVD complications (Al Suwaidi et al., 2012) and mortality (Al Suwaidi et al., 2012) tend to be of higher rates in waterpipe than in cigarette smokers. This might be explained due to prolonged WPS and, therefore, cumulatively higher amounts of inhaled toxic substances and consequently adverse effects on the cardiovascular system (Sibai et al., 2014).

5. Strengths and limitations

A limitation of these analyses is the high heterogeneity of the available data. This can be attributed to the geographic diversity of the analyzed studies, the multiple study protocols, as well as different frequency and session duration of WPS. Furthermore, some parameters were reported in only few studies, which limits the explanatory power of this analysis. Therefore, some results should be interpreted with caution. As long-term follow-up studies on cardiovascular effects of WPS are scarce, chronic effect of WPS has been estimated in our analyses using data from available case-control and cross-sectional cohort studies that compared waterpipe smokers to non-smokers. Of note, the observed effects could be explained solely due to WPS, as limited number of waterpipe smokers may occasionally have also smoked cigarettes. Although the comparison between WPS and CS may be the most important part of systematic review, only few studies are available for this comparison, with the main limitation is the lack of studies reporting the rate of cardiovascular and cerebrovascular events. On the other hand, some waterpipe smokers could be ex-cigarette smokers. The time spent smoking cigarette are likely impacting, observed outcomes. Such information is missed in most observational studies. Thus, a meta-regression considering time from quitting of cigarette smoking in waterpipe smokers is not possible. This applies to the other results showed a worst cardiometabolic profile of waterpipe smokers compared to non-smokers, as many studies did not consider all potential confounders in the comparisons. To the best of our knowledge, our study provides the most comprehensive image of the potential cardiovascular effects of WPS based on scientific evidence and reflects the current magnitude of research efforts performed so far regarding this issue.

6. Conclusions

There is still a widespread believe that WPS is harmless and not real smoking. This wide-ranged systematic review and meta-analysis outlines the spectrum of acute and long-term cardiovascular effects of waterpipe smoking. Despite all the stated limitations, current level of evidence suggests that WPS is associated with substantial adverse effects on cardiovascular system, which seem to be similar to what reported for cigarette smoking. Further research is required especially longitudinal studies evaluating the

long-term consequences of both waterpipe smoking and cessation to scrutinize the magnitude of these effects and to provide a strong evidence for a causal relationship.

Authors' contributions

Concept and design: RA and MB. Literature search for eligible studies: RA, DV, and LK. Data extraction and quality assessment: RA and LK. Data analysis and interpretation: RA, MB and DV. Writing of original draft: RA. Review and editing of article: all authors. Critical revision of article: RA, MB and DV. Approval of article: all authors.

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Conflict of interest

Authors do not have any conflict of interest related to this study.

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