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The association of waterpipe smoking with arterial stiffness and wave reflection in a community-based sample

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ABSTRACT

Purpose: The evidence linking waterpipe smoking to cardiovascular disease is limited. We evaluated the association of waterpipe smoking (WPS) with arterial stiffness and wave reflection measured by augmentation pressure (AP), augmentation index (Alx), and carotid-femoral pulse wave velocity (CFPWV), which are validated predictors of cardiovascular disease.

Materials and methods: Community-based, cross-sectional study including 205 exclusive waterpipe smokers and 199 matched never-smokers aged 35 years or older (mean age 51.7 ± 8.9 years, 36% females). Smoking and its extent were assessed using a validated questionnaire and urine cotinine levels. CFPWV, AP, Alx (AP/aortic pulse pressure) and heart rate adjusted Alx (Alx@75) were determined using tonometry and compared between smokers and non-smokers, and the association of WPS with tonometry measures was assessed using linear regression adjusting for possible confounders.

Results: Waterpipe smokers and non-smokers had similar mean age and sex distribution. Compared to non-smokers, waterpipe smokers had significantly higher adjusted AP (10.5 ± 3.9 vs. 9.4 ± 3.9 mmHg respectively; $p = 0.01$), Alx (28.1 ± 8.4 vs. 25.7 ± 8.5% respectively; $p = 0.01$) and Alx@75 (24.2 ± 8.7 vs. 21.8 ± 8.9% respectively; $p = 0.01$). Alx was significantly associated with WPS extent, measured by a number of waterpipe smoked/day ($\beta = 1.04$ /waterpipe, 95%CI:[0.50–1.58]), duration of waterpipe smoking ($\beta = 0.77$ /10-years, 95%CI:[0.16–1.38]), their products in waterpipe-years ($\beta = 0.30$ /10-waterpipe-year, 95%CI:[0.12–0.47]) and plasma cotinine ($\beta = 0.56$ /100 ng/ml, 95%CI:[0.14–0.98]), adjusting for possible confounders, and so were AP and Alx@75. CFPWV however, was not associated with waterpipe smoking.

Conclusion: In a community-based sample, exclusive WPS and its extent were associated with a dose-dependent increase in Alx and AP, accounting for other risk factors, suggesting that waterpipe smokers are at increased risk of cardiovascular disease.

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Introduction

Waterpipe smoking is a traditional way of smoking tobacco originating from the Eastern Mediterranean region that has gained popularity and has been spreading worldwide in the last two decades especially among the youth [1]. Indeed, waterpipe smoking was reported by 8.4% of college students in the US, 7.6% of secondary school students in Brent UK, 25% of Estonian boys and 16% of girls 11–15 years old and 10% of Canadian grade 9–12 students [1]. Since waterpipe smoke passes through water before inhalation, the public perceives waterpipe smoking to be less harmful than cigarette smoking. Nevertheless, nicotine absorption of daily

waterpipe smokers was estimated to be equivalent to smoking 10 cigarettes per day [2] and exhaled CO after smoking waterpipe was 9 times the level measured after smoking 1 cigarette [3].

To date, few studies evaluated the association of waterpipe smoking with heart disease [4,5]. The cardiovascular effects of smoking are often latent and its overt adverse health outcomes are delayed [4]. Since the waterpipe smoking epidemic is recent, evaluating the association of waterpipe smoking with markers of subclinical cardiovascular disease provides the advantage of recognising its potential adverse health effects in asymptomatic individuals.

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Carotid-femoral pulse wave velocity (CFPWV), and the augmentation pressure (AP) defined as the aortic systolic blood pressure attributed to the reflected pressure wave, are indices of arterial stiffness and pressure wave reflection measured non-invasively by analysing arterial pulse wave [6,7]. CFPWV and augmentation index (AIx), defined as AP/aortic pulse pressure, are validated markers of early vascular dysfunction and predictors of subclinical cardiovascular risk among asymptomatic individuals [6,7].

AIx has been shown to predict the presence [8] and severity [9] of coronary artery disease in individuals undergoing coronary angiography, and adverse cardiovascular events in patients with coronary artery disease [10] but not in all studies [11]. CFPWV has also been shown to be an independent predictor of longitudinal increases in blood pressure and hypertension onset [12] and a strong predictor of cardiovascular risk in multiple populations [10].

CFPWV and AIx were reported to increase acutely after waterpipe smoking in one study [13], but we are not aware of prior studies that evaluated the sustained impact of chronic waterpipe smoking on similar markers [4]. In this study, we evaluated the association of chronic waterpipe smoking with AP, AIx and CFPWV, markers of cardiovascular disease in a community-based sample.

Materials and methods

Study sample

This cross-sectional community-based study included 205 waterpipe smokers and 199 never-smokers recruited from the community in Beirut, Lebanon and Doha, Qatar between September 2013 and March 2017 using previously described methods [5]. Three participants who reported being non-smokers were excluded in a sensitivity analysis for having elevated plasma cotinine levels (>10 ng/ml) a byproduct of nicotine metabolism, which suggested that they likely smoke.

Waterpipe smokers were recruited from cafés that offer waterpipe, through advertisement flyers, social media, and word of mouth. Individuals 35 years or older who reported exclusive waterpipe smoking for more than 10 years were enrolled. Controls consisted of never-smokers matched for age and sex at each site recruited through the same advertisement as waterpipe smokers and from smoke-free cafés in Beirut and Doha.

Individuals with smoking-related lung disease (chronic bronchitis, emphysema, and lung cancer)

were included. Individuals who reported concurrent or previous cigarette smoking or history of pulmonary disease (asthma, bronchiectasis, and fibrosis), diabetes, and renal failure were excluded. The study was approved by the American University of Beirut Institutional Review Board (IM.HC.03) and Hamad Medical Centre Institutional Review Board (13-00054). All participants were counselled about the risks and benefits of participation and signed informed consent.

Study procedures

Waterpipe smoking assessment

Waterpipe smoking was assessed using a validated questionnaire that accounts for the variability in smoking patterns [14] and using plasma cotinine levels measured on fasting morning plasma samples using a solid phase competitive ELISA kit (BIOQUANT, Inc).

Hemodynamic assessment

Brachial blood pressure (BP) was measured three times at the left arm before performing tonometry using a standard calibrated sphygmomanometer (W.A. Baum Co. Inc.) with the patients seated, after resting for 15 min, and the results of the three measurements were averaged. Thereafter, CFPWV, AP and AIx were measured non-invasively using the Sphygmocor[®] tonometry system (AtCor medical, Sydney Australia). Peripheral arterial pressure waveforms were recorded by applying the tonometer probe (SPT-301 Millar Instruments Houston Texas, USA) over the radial artery. The corresponding central aortic pressure waveforms are derived from radial tonometry using validated built-in transformation function, and AP, AIx, are calculated from these central aortic waveforms using built-in mathematical equations [15]. Augmentation pressure (AP) is defined as the difference between the second (P2) and the first systolic aortic pulse wave peaks (P1), expressed in mmHg. AIx is calculated by dividing AP by aortic pulse pressure (PP) and expressed as a percentage. AIx is adjusted to a heart rate of 75 beats/min to obtain AIx@75. Pulse pressure was calculated as systolic – diastolic BP (DBP). PP amplification was expressed as the ratio of brachial pulse pressure/aortic pulse pressure. CFPWV was measured by applying the tonometer probe (Millar Instruments) over the carotid and femoral arteries to record the arterial pulse waves while simultaneously acquiring the electro-cardiac QRS complex using 3 ECG leads attached

to the chest wall. The distance from the suprasternal notch to the carotid and femoral pulse points was measured manually. CFPWV is calculated using built-in equations by dividing the transit distance (suprasternal notch-femoral minus suprasternal notch-carotid) by the time taken for the arterial pulse to propagate from the carotid to the femoral artery in m/s [16]. The Sphymocor software determines the arterial pulse transit time from the carotid to the femoral artery. The Sphymocor[®] system has been validated against invasive measures of arterial stiffness, is equipped with built-in quality control measures and demonstrates low intra and inter-operator variability [17]. All tonometry measurements were obtained in the supine position in the morning hours in a quiet temperature-controlled room (18–22 °C) following brachial BP measurement (after 15 min of rest). Participants were instructed not to smoke, consume caffeine or exercise for 8 h prior to the measurements.

Other covariates assessment

Participants were surveyed for demographics and presence of underlying hypertension, and personal or family history of cardiovascular disease (coronary heart disease, myocardial infarction, revascularization procedures, congestive heart failure, hypertension, peripheral and cerebrovascular vascular disease), respiratory disease (emphysema and chronic bronchitis), and malignancy using an investigator-administered questionnaire. Participants were also surveyed for intake of cardiovascular medications, hormone replacement therapy, caffeine and alcohol. Height and weight were measured with the participants in light clothes and body-mass index (BMI) was calculated. Total cholesterol, low-density lipoprotein and high-density lipoprotein (HDL) were measured on fasting morning serum samples using an enzymatic colorimetric method.

Statistical analysis

The independent (exposure) variable in the main analysis was waterpipe smoking status categorised as smoker or non-smoker. Waterpipe-year, a validated measure of lifetime smoking exposure [14], calculated by multiplying the number of waterpipes smoked per day by the duration of waterpipe smoking in years, was used as the independent continuous variable in a secondary analysis. The number of waterpipes smoked per day, duration of waterpipe smoking in years, and plasma cotinine level were used as alternative

measures of the extent of waterpipe smoking exposure and were also treated as continuous variables.

The main dependent (outcome) variables were the tonometry measures of arterial wave reflection and stiffness: AP, AIx, and CFPWV. Other hemodynamic measures including central aortic pressures and PP amplification were treated as secondary dependent variables. Mean AP, AIx, AIx@75 and CFPWV were compared between waterpipe smokers and non-smokers in adjusted and unadjusted analyses. The association of waterpipe smoking duration, waterpipe smoking intensity (waterpipes smoked per day), their product in waterpipe-years and plasma cotinine levels with the main measures of arterial wave reflection and stiffness (AP, AIx, and CFPWV) was assessed using linear regression. Regression models accounted for demographic characteristics: age, sex, study site and additionally for other risk factors: BMI, alcohol and caffeine consumption, regular exercise, systolic BP (SBP), heart rate, serum cholesterol and HDL, use of antihypertensive or lipid-lowering medication, and family history of cardiovascular disease. Interaction of waterpipe smoking and age was evaluated by including the interaction term for waterpipe smoking status \times age category (≥ 55 and < 55 years) in the regression model. Furthermore, waterpipe smokers and non-smokers were stratified by median age (≥ 55 years and < 55 years) into 4 groups: younger non-smokers, younger waterpipe-smokers, older non-smokers and older waterpipe-smokers and measures of arterial wave reflections and stiffness were compared between those 4 groups. To assess for the possible residual acute pharmacologic effect of the last nicotine intake, measures of arterial wave reflections and stiffness were also compared between waterpipe smokers with serum cotinine levels ≥ 10 and < 10 ng/ml. All analyses were performed using SPSS. *p*-Values < 0.05 were considered significant.

Results

Characteristics of the study participants are presented in Table 1 stratified by smoking status. On average, waterpipe smokers and non-smokers had similar age, sex distribution and BMI. They were also as likely to report hypertension, cardiovascular diseases and anti-hypertensive therapy. However, waterpipe smokers were more likely to report intake of lipid-lowering medications, caffeine consumption and a family history of cardiovascular disease. As expected, plasma cotinine level was significantly higher in waterpipe smokers compared to non-smokers. Almost all

Table 1. Characteristics of waterpipe smokers and non-smokers.

	Waterpipe smokers (n = 205)	Non-smokers (n = 199)	p-Value
Study site, n (%)			
Beirut, Lebanon	136 (66.3)	134 (67.3)	
Doha, Qatar	69 (33.7)	65 (32.7)	0.8
Age (years), Mean (SD)	51.5 (9.2)	52.0 (8.6)	0.6
Females, n (%)	75 (36.6)	70 (35.2)	0.7
Menopause (No. (% females))	52 (67.5)	44 (62.9)	0.5
Height (cm), mean (SD)	167.7 (10.1)	168.6 (9.2)	0.3
Weight (Kg), mean (SD)	83.9 (16.3)	82.6 (18.1)	0.4
Body-mass index, mean (SD)	29.8 (4.8)	28.8 (5.2)	0.07
Low density lipoprotein (mg/dl), mean (SD)	125.0 (31.3)	127.0 (33.1)	0.5
High density lipoprotein (mg/dl), mean (SD)	47.5 (13.5)	49.8 (13.8)	0.09
Total cholesterol, mean (SD)	199.3 (35.2)	202.4 (37.7)	0.4
Triglyceride, mean (SD)	139.2 (69.9)	129.2 (66.2)	0.1
Hypertension, n (%)	33 (16.1)	32 (16.1)	1.00
Cardiovascular disease, n (%)	6 (2.9)	7 (3.5)	0.7
Family history of cardiovascular disease, n (%)	118 (57.6)	91 (45.7)	0.02
History of malignancy, n (%)	2 (1.0)	4 (2.0)	0.4
Cured malignancy, n (%)	2 (100.0)	4 (100.0)	NA
Alcohol consumption, n (%)	14 (6.8)	9 (4.5)	0.3
Caffeine consumption, n (%)	203 (99.0)	176 (88.4)	<0.01
Caffeine (cups/day), mean (SD)	4.1 (3.2)	3.1 (1.9)	<0.01
Exercise regularly	64 (31.2)	69 (34.7)	0.46
Exercise sessions/month, mean (SD)	16.7 (8.9)	15.0 (9.5)	0.3
Cardiovascular medications, n (%)	47 (22.9)	40 (20.1)	0.5
Hypertension medications, n (%)	37 (18.0)	34 (17.1)	0.8
Lipid lowering medications, n (%)	29 (14.1)	17 (8.5)	0.08
Anti-platelets, n (%)	10 (5.0)	5 (2.6)	0.1
Angiotensin converting enzyme inhibitors/receptor blocker, n (%)	16 (8.1)	15 (7.7)	0.9
Calcium channel blockers, n (%)	9 (4.5)	10 (5.1)	0.8
Beta-blocker, n (%)	19 (9.6)	18 (9.2)	0.9
Other cardiac medications ^a , n (%)	4 (2.0)	5 (2.5)	0.7
Other hypertension medications ^b , n (%)	8 (3.9)	4 (2.0)	0.4
Plasma cotinine level (ng/ml), Mean (SD)	130.2 (296.5)	0.79 (2.19)	<0.001
Framingham risk score, mean (SD)	17.2 (15.0)	10.0 (7.6)	<0.001
Framingham risk without smoking, mean (SD)	10.1 (10.0)	10.0 (7.6)	0.87
Second-hand smoking, n (%)		92 (46.2)	
Age started waterpipe smoking (years), mean (SD)	26.0 (7.5)		
Waterpipe smoking duration (years), mean (SD)	25.4 (11.2)		
Daily waterpipe smoking, n (%)	200 (97.6)		
Number of waterpipes smoked per day, n (%)			
1 waterpipe/day	84 (41.0)		
2 waterpipes/day	59 (28.8)		
>2 waterpipes/day	62 (30.2)		
Average number of waterpipes smoked daily, mean (SD)	2.2 (1.6)		
Waterpipe-year, mean (SD)	58.6 (57.9)		
Type of waterpipe tobacco smoked, n (%)			
Flavored (maasal)	113 (55.1)		
Unflavored (ajami /tambak /gidou/ salloum)	85 (41.5)		
Both	7 (3.4)		

^aWarfarin (n = 2), amiodarone (n = 1) and unspecified (n = 5).

^bHydrochlorothiazide (n = 2) and unspecified (n = 10).

Bold p-values are <0.05.

waterpipe smokers reported smoking daily, on average 2.2 ± 1.6 waterpipes per day over an average of 25.4 ± 11.2 years for an average of 58.6 ± 57.9 waterpipe-years. While 46.2% of non-smokers reported regular exposure to second-hand smoke. None of the waterpipe smokers reported concurrent or previous cigarettes or other forms of tobacco smoking.

The average hemodynamic and tonometry measures among waterpipe smokers and non-smokers are presented unadjusted in Table 2 and the main parameters CFPWV, AP and AIx are presented adjusted for potential confounders in Figure 1. Unadjusted average

brachial SBP and brachial-aortic PP amplification were lower in waterpipe smokers compared with non-smokers, while differences in unadjusted mean brachial DBP, heart rate and aortic SBP, DBP and PP between waterpipe smokers and non-smokers were not significant. AP was significantly higher in waterpipe smokers compared to non-smokers after adjusting for potential confounders (10.5 ± 3.9 vs. 9.4 ± 3.9 mmHg, respectively $p = 0.01$, Figure 1) although the difference was not significant in the unadjusted analysis. AIx was significantly higher in waterpipe smokers versus non-smokers both in

Table 2. Peripheral and central hemodynamic measures among waterpipe smokers and non-smokers.

	Unadjusted mean (95% confidence interval)		<i>p</i> -Value
	Waterpipe smokers (<i>N</i> = 205)	Non-smokers (<i>N</i> = 199)	
Heart rate, bpm	66.5 (65.3–67.8)	68.2 (66.9–69.5)	0.08
Brachial systolic blood pressure, mmHg	124.3 (121.9–126.6)	127.7 (125.3–130.1)	0.04
Brachial diastolic blood pressure, mmHg	80.4 (79.02–81.8)	81.6 (80.2–83.02)	0.2
Aortic systolic blood pressure, mmHg	116.6 (114.4–118.8)	118.5 (116.2–120.7)	0.2
Aortic diastolic blood pressure, mmHg	81.4 (79.98–82.8)	82.5 (81.0–83.9)	0.3
Aortic pulse pressure, mmHg	35.2 (33.6–36.7)	36.0 (34.4–37.5)	0.5
Brachial-aortic pulse pressure amplification, %	126.7 (124.9–128.6)	130.3 (128.4–132.2)	0.01
Augmentation pressure (AP), mmHg	10.4 (9.6–11.1)	9.6 (8.8–10.4)	0.2
Augmentation index (AIx: AP/PP), %	28.3 (26.9–29.7)	25.7 (24.3–27.1)	0.01
Augmentation index adjusted for heart rate (AIx@75: AP/PP), %	24.1 (22.8–25.5)	22.1 (20.7–23.5)	0.04
Carotid femoral pulse wave velocity (CF-PWV), m/s	8.7 (8.4–9.0)	8.8 (8.5–9.2)	0.5

Bold *p*-values are <0.05.

adjusted analyses (28.1 ± 8.4 vs. $25.7 \pm 8.5\%$ respectively; $p = 0.01$ Figure 1) and unadjusted analyses (Table 2) and so was AIx@75 (adjusted means: 24.2 ± 8.7 vs. $21.8 \pm 8.9\%$ respectively; $p = 0.01$ Figure 1). However, there was no significant difference in CFPWV, between waterpipe smokers and non-smokers in adjusted (8.7 ± 2.0 vs. 8.8 ± 2.8 m/s, $p = 0.6$) and in unadjusted analyses.

Associations of tonometry measures with the presence and extent of waterpipe smoking, in models that adjust for demographic and other risk factors, are presented in Table 3. Waterpipe smoking was associated with higher AP and higher AIx adjusting for possible confounders. However, there was no significant association between waterpipe smoking and CFPWV. The extent of waterpipe smoking exposure estimated by the number of waterpipes smoked per day or by waterpipe smoking duration was associated with higher AP and AIx after adjustment for other risk factors (Table 3). Lifetime waterpipe smoking exposure estimated by the product of the number of waterpipes smoked per day and waterpipe smoking duration in waterpipe-years was also significantly associated with higher AP and AIx. Finally, plasma cotinine level, an objective measure of waterpipe smoking intensity, was also associated with AP and AIx after adjusting for other risk factors (Table 3). Conversely, CFPWV was not associated with any measure of waterpipe smoking extent (Table 3).

Augmentation pressure and index incrementally increased across age groups and with waterpipe smoking within the age group (Figure 2), with a significant

age group \times waterpipe smoking interaction term in regression models ($p < 0.001$) indicating an additive interaction of age and waterpipe smoking. Finally, tonometry parameters were similar in waterpipe smokers with low plasma cotinine (<10 ng/ml) and waterpipe smoker with high plasma cotinine levels (≥ 10 ng/ml) (results not shown).

Discussion

This study demonstrates that in middle-aged asymptomatic individuals recruited from the community, waterpipe smoking is associated with a dose-dependent increase in AIx and AP while accounting for relevant confounders. The increase in those measures of wave reflection in waterpipe smokers was additive to the age-related increase in those measures. However, waterpipe smoking was not associated with CFPWV.

AP is the absolute pressure wave reflection contribution to the systolic aortic BP, while AIx is this magnitude of pressure wave reflection expressed as a percentage of the aortic PP. Thus AIx, estimates the percentage of aortic PP attributed to the reflected pressure wave. AIx is associated with the risk of cardiovascular disease [7], predicts the presence and severity of coronary artery disease [8,9] and predicts adverse cardiovascular events in patients with coronary artery disease [10]. Therefore, finding an association between waterpipe smoking and increased AIx in a community-based sample of asymptomatic individuals is important and suggests that waterpipe

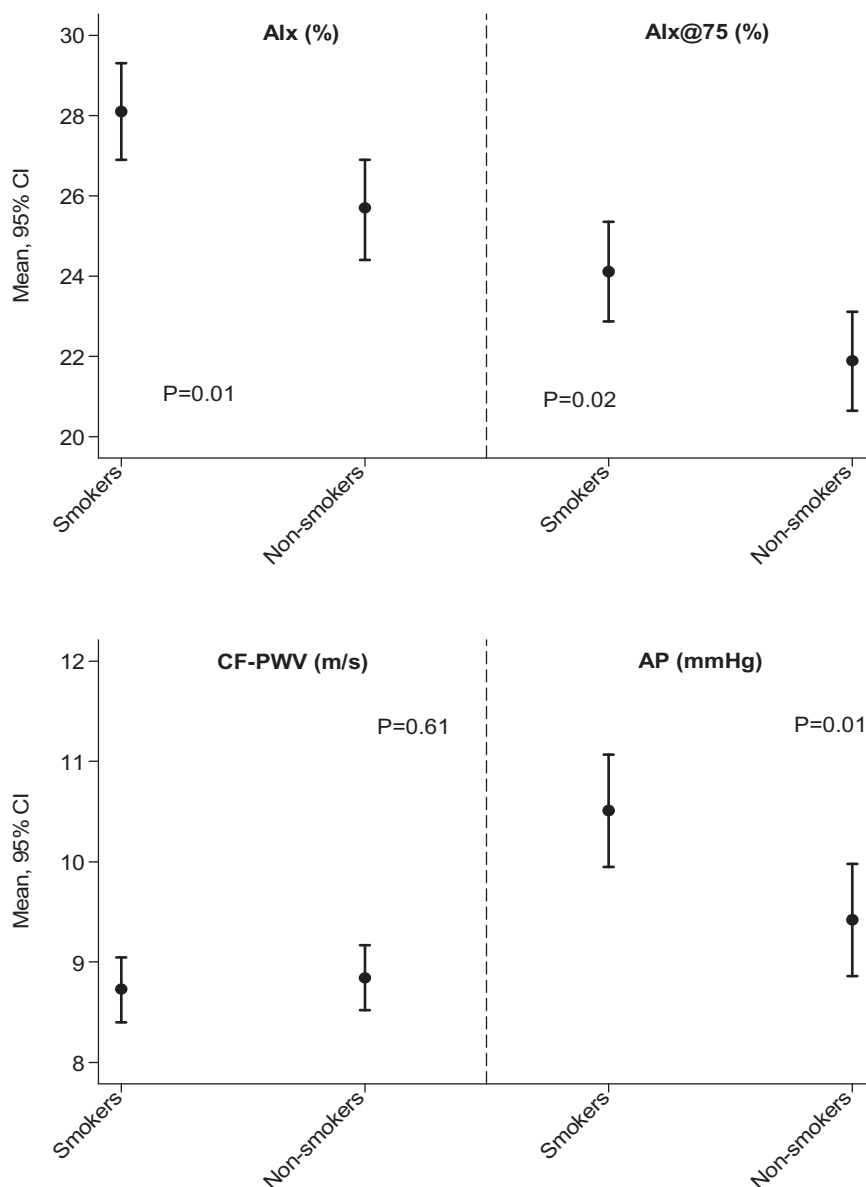


Figure 1. Carotid femoral pulse wave velocity (CF-PWV), augmentation pressure (AP), index (Alx) and heart rate-adjusted index (Alx@75) in waterpipe smokers and non-smokers, adjusted for: age, sex, site, body mass index, alcohol, caffeine, exercise, tonometry heart rate; high-density lipoprotein, total cholesterol, lipid lowering medication; anti-hypertension medications and family history of cardiovascular disease (angina, myocardial infarction, coronary heart disease, congestive heart failure, coronary revascularization), brachial systolic blood pressure.

smoking poses a cardiovascular health hazard even in apparently healthy individuals.

The magnitude of the adjusted differences in AIx between waterpipe smokers and non-smokers of 2.5% point is comparable to the previously reported 3.5% difference in AIx between individuals with and without CAD [8]. Increased arterial stiffness and pulse wave reflection causes an increased central systolic BP, lower diastolic PP and widening of the PP, potentially damaging blood vessels, impacting organs such as the brain or kidneys [18]. Furthermore, increased

central SBP increases cardiac load and over time could cause left ventricular hypertrophy and remodeling, and eventually leads to heart failure [19]. Finally, lower diastolic pressure decreases myocardial perfusion pressure, thus promoting myocardial ischaemia [18].

Several studies have also shown that AIx is higher in cigarette smokers compared to non-smokers [20–24]. AIx was also associated with the extent of cigarette smoking ($\beta=0.31\%$ per pack-year) among young males from the community [22]. Moreover,

Table 3. Association of augmentation pressure and index and carotid femoral pulse wave velocity with waterpipe smoking and its extent (number of waterpipes smoked per day, duration of waterpipe smoking, their products in waterpipe-years, and plasma cotinine).

Model	Augmentation Pressure, (AP), mmHg		Augmentation Index, AIx (AP/Pulse Pressure), %		Carotid femoral pulse wave velocity (CF-PWV), m/s		
	β (95 % CI)	<i>p</i>	β (95% CI)	<i>p</i>	β (95 % CI)	<i>p</i>	
Waterpipe smoking	Demographic	0.63 (−0.30; 1.55)	0.19	2.20 (0.55; 3.85)	0.009	−0.03 (−0.48; 0.41)	0.88
	Full	1.12 (0.30; 1.94)	0.01	2.49 (0.71; 4.26)	0.006	−0.09 (−0.56; 0.38)	0.7
Waterpipes smoked per day	Demographic	0.32 (0.03; 0.61)	0.03	0.93 (0.42; 1.44)	<0.001	−0.07 (−0.21; 0.07)	0.33
	Full	0.49 (0.25; 0.74)	<0.001	1.04 (0.50; 1.58)	<0.001	−0.08 (−0.23; 0.06)	0.26
Waterpipe smoking duration (by 10 years)	Demographic	0.30 (−0.02; 0.62)	0.06	0.72 (0.15; 1.29)	0.01	0.05 (−0.10; 0.20)	0.50
	Full	0.37 (0.09; 0.65)	0.01	0.77 (0.16; 1.38)	0.01	0.009 (−0.15; 0.17)	0.92
Waterpipe-years (by 10 units)	Demographic	0.11 (0.01; 0.20)	0.03	0.27 (0.11; 0.44)	0.001	−0.007 (−0.05; 0.04)	0.74
	Full	0.14 (0.06; 0.22)	0.001	0.30 (0.12; 0.47)	0.001	−0.01 (−0.07; 0.03)	0.45
Cotinine levels, ng/ml	Demographic	0.14 (−0.09; 0.37)	0.22	0.54 (0.12; 0.95)	0.01	−0.07 (−0.19; 0.05)	0.24
	Full	0.24 (0.04; 0.43)	0.02	0.56 (0.14; 0.98)	0.01	−0.05 (−0.17; 0.06)	0.37

Demographic model adjusts for: age, sex, site and tonometry heart rate.

Full model adjusts for: age, sex, site, body-mass index, alcohol, caffeine, exercise, tonometry heart rate; high-density lipoprotein, total cholesterol, lipid lowering medication; anti-hypertension medications and family history of cardiovascular disease (angina, myocardial infarction, coronary heart disease, congestive heart failure, coronary revascularization), brachial systolic blood pressure.

Bold *p*-values are <0.05.

similar to our results, two studies that evaluated both CFPWV and AIx in community-based samples, found an association of cigarette smoking with AIx, but not with CFPWV [20,23]. Additionally, AIx decreased 4 weeks after smoking cessation, but CFPWV was unchanged [23]. Although cigarette smoking was associated with a 1.5-fold higher risk of incident aortic stiffness, defined as CFPWV >8 m/s in middle-aged Japanese men [25], CFPWV was not associated with smoking in women in another study [26]. A study that used ultrasound to evaluate aorto-femoral PWV found increased aortic stiffness in smokers while studies that evaluated the association of cigarette smoking and brachial-ankle-PWV also found conflicting results [24,27].

The difference in AIx between young (mean age = 38 years) cigarette smokers and non-smokers was 5.5%-point [23], and 6.4%-point in an even younger sample (mean age =22 years) [21]. The 2.5%-point difference in AIx between waterpipe smokers and non-smokers in our study was smaller. However, since age is an important determinant of wave reflection, our older sample precludes direct quantitative comparison with cigarette smoking [28]. Likewise, an interaction between age and cigarette smoking was previously reported in the association with wave reflection among individuals with an average age of

38 (SD = 10) years [28]. We also observed an additive interaction of age and waterpipe smoking; nevertheless, our older population, (average age 52 years), precluded a quantitative comparison of the interactive effect of age with waterpipe vs. cigarette smoking.

In stiffer arteries, arterial pressure waves travel faster, resulting in higher CFPWV and the reflected arterial pulse waves return to the heart earlier and augment the systolic pressure peak rather than the diastolic trough resulting in PP amplification and higher AP and AIx [18]. The amplitude of the reflected pulse wave also increases with peripheral arterial vasoconstriction [20]. As such, the association of waterpipe smoking with increased AP and AIx, but not with CFPWV suggests that waterpipe smoking is associated with impaired peripheral muscular artery properties and not necessarily with increased stiffness of central arteries.

The mechanisms by which waterpipe smoking increases precapillary artery resistance are likely multifactorial [29] and mediated by waterpipe smoke toxins [30,31]. Exposure of arteries and arterioles to nicotine acutely stimulates vascular smooth muscle contraction, leading to the early reflection of the incident pulse wave [31,32]; but it is unclear whether chronic nicotine exposure results in sustained increase pulse wave reflection [33]. Both acute and chronic

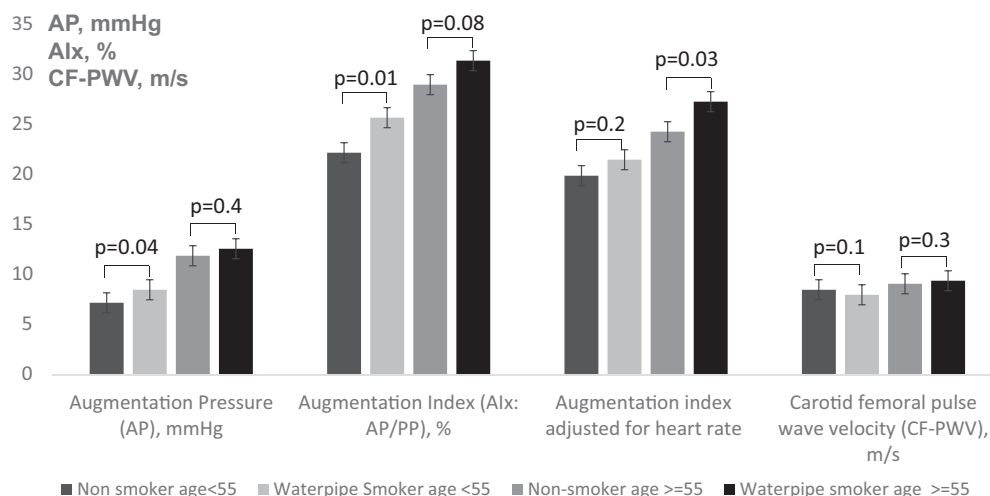


Figure 2. Arterial pressure wave reflection and stiffness in waterpipe smokers and non-smokers, further subdivided by age \geq and $<$ 55 years. *p*-Value reflects comparison of waterpipe smokers vs. non-smokers within the same age group. Interaction term (age group \times waterpipe smoking) $p < 0.001$. *p* for trend < 0.001 across groups for all variables.

waterpipe smoking in humans has been also associated with endothelial dysfunction [34], increased BP [4] and increased oxidative stress [35], mechanisms that could mediate the association of waterpipe smoking with increased wave reflection [24]. In addition, waterpipe smoke reduces endothelial nitric oxide synthase (eNOS) levels *in vitro* and abolishes eNOS activation, which are determinants of NO bioavailability and vascular health [36]. Mice exposed to waterpipe smoke demonstrated increased inflammation (IL-6 and TNF alpha), oxidative stress (SOD) and lipid peroxidation [37,38] which are intermediate mechanisms associated with increased arterial stiffness.

In contrast to AIx, waterpipe smoking in our middle-aged participants was not associated with CFPWV, a surrogate of stiffness of the central elastic arterial system. Increased central arterial stiffness is associated with the destruction and reduction of elastic fibres, usually a degenerative process independent of the effects of vasoactive substances [39]. In healthy normotensive individuals, AIx rises with age and plateau at 50–55 years while CFPWV increases after the age of 50 years [32,39]. As the age of the cohort in our study is younger than 55–60 years, CFPWV is expected to be normal.

Our study is limited by the cross-sectional observational design, which limits our ability to draw firm conclusions regarding causality. Also, 46.2% of non-smokers in our data were exposed to second-hand smoking, which may have increased CFPWV in non-smokers and biased the association of waterpipe smoking with CFPWV towards the null. Caffeine and nicotine could cause an acute increase in the variables

of interest, thus an acute carry-over effect could not be ruled out. Nevertheless, participants were asked to abstain from smoking or consuming caffeine for 8 h before testing and regression models adjusted for caffeine consumption, which was highly prevalent in both smokers and non-smokers. Furthermore, tonometry measures were similar in waterpipe smokers with low plasma cotinine (< 10 ng/ml) vs. high plasma cotinine levels (≥ 10 ng/ml). Therefore, a residual acute effect of waterpipe smoking is unlikely to explain the increased arterial wave reflection noted in waterpipe smokers. Several strengths balance these limitations and include the study sample that consisted of individuals recruited from the community independent of their cardiovascular risk or symptoms, the selection of exclusive waterpipe smokers with no concurrent cigarette or other tobacco smoking, the use of validated measures of smoking and arterial stiffness, and adjustment for relevant confounders.

In conclusion, in a community-based sample and after adjustment for confounders, exclusive waterpipe smoking and its extent were associated with higher arterial stiffness and wave reflection as measured by AP and AIx but not CFPWV. This study adds to the evidence that links waterpipe smoking with impaired cardiovascular health and provides further justification to implement measures to curb waterpipe smoking and raise awareness about its health effects. Further prospective research that longitudinally evaluates the impact of waterpipe smoking on arterial stiffness would enhance the evidence implicating waterpipe smoking in cardiovascular disease.

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Disclosure statement

Dr. Mitchell is the president of Cardiovascular Engineering, Inc., a small business that designs and manufactures the device that measures arterial stiffness. Other authors disclosed no conflict of interest. The funder had no role in the design, management, data collection, analyses, or interpretation of the data or in the writing of the manuscript or the decision to submit for publication.

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