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**Full title** Increased aortic wave reflection and smaller pulse pressure amplification in smokers and passive smokers confirmed by urinary cotinine levels: the Nagahama Study

**Short title** Smoking and central blood pressure

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**Keywords** Urinary cotinine, passive smoking, arterial waveform, central blood pressure

## **ABSTRACT**

**Background;** Central blood pressure (cSBP) is suggested to be a better predictor of cardiovascular risk than brachial BP. Although brachial BP levels among smokers have been reported to be the same or somewhat lower than those in nonsmokers, it is suggested that smoking might have a substantial impact on cSBP.

**Methods;** We conducted a cross-sectional study to clarify the association of smoking habit with arterial tone and cSBP in a general population of 8,557 participants using urinary cotinine levels as an objective marker of smoking intensity. Absolute pressure of the late systolic peak (SBP<sub>2</sub>) was obtained by calibrating the radial waveform with brachial systolic BP (bSBP) and considered to be the cSBP.

**Results;** Confounding factor-adjusted mean pulse pressure amplification (PPa = bSBP-cSBP) was significantly smaller in habitual smokers (current,  $9.3 \pm 0.15$ ; past,  $10.2 \pm 0.13$ ; never,  $10.6 \pm 0.10$  mmHg;  $p < 0.001$ ). Further, among smokers, PPa was linearly decreased with increasing urinary cotinine quartile (Q1,  $10.9 \pm 0.38$ ; Q2,  $10.9 \pm 0.39$ ; Q3,  $10.4 \pm 0.39$ ; Q4,  $9.7 \pm 0.41$  mmHg;  $p = 0.020$ ). Multiple linear regression analysis identified both smoking habit ( $p = 0.003$ ) and urinary cotinine levels ( $p = 0.008$ ) as independent determinants of PPa. Urinary cotinine was also detected in a small fraction of never smokers (1.8 %). These passive smokers showed a smaller PPa (passive smoker,  $9.4 \pm 0.4$ ; never smoker,  $10.4 \pm 0.12$  mmHg,  $p = 0.020$ ) but not bSBP ( $122.7 \pm 0.6$ ,  $123.1 \pm 0.2$  mmHg,  $p = 0.474$ ).

**Conclusions;** Not only habitual smoking but also passive smoking had harmful effects on AIx and central BP. Our results strongly emphasize the importance of avoiding passive smoking to the prevention of cardiovascular risks of which the subject is likely unaware.

## **INTRODUCTION**

Hypertension is a major health burden, particularly in developed countries. Although accumulated clinical and epidemiological evidence for high blood pressure (BP) risks have been based on BP measured at brachial artery, recent epidemiological studies suggest that cardiovascular risk might more closely correlated with central aortic systolic pressure (cSBP) [1-3]. Further, a large-scale clinical trial examining the impact of two different BP-lowering drugs, namely beta-blocker atenolol-based therapy and calcium channel blocker amlodipine therapy, clearly showed that differences in cSBP were more closely associated with cardiac outcome than differences in brachial systolic BP (bSBP), which in fact showed equivalent levels between the two treatment arms [4]. These results for the superiority of cSBP in estimating BP risks emphasize the importance of identifying factors that might affect the difference between bSBP and cSBP, i.e. pulse pressure amplification (PPa).

Smoking is another factor which strongly increases cardiovascular (CV) risk. Because BP levels among smokers were suggested to be the same as or somewhat lower than those in nonsmokers [5], the harmful effects of smoking on cardiovascular outcome was thought to be independent of BP risks. However, recent epidemiological study in a general population reported that augmentation index (AIx) was increased in habitual smokers, a change which can result in a higher central BP [6], and higher AIx and cSBP, but not bSBP, have been observed in persons with a smoking habit [7]. Further, several experimental trials have shown that cigarette or cigar smoking [8,9], even passive smoking [10], acutely increased both brachial and central BP, as well as arterial tone as measured by aortic pulse wave velocity or AIx of the arterial waveform, and that the effects of smoking on arteries lasted for at least 2 hours [9]. Given these previous findings, we hypothesized that the increased CV risk in smokers might be partially due to elevated aortic tone and consequent raised central BP, which could not be detect by a simple brachial BP monitoring.

Here, we conducted a cross-sectional study to clarify the association of smoking

habit with arterial tone and PPa in our large-scale general population sample in which urinary cotinine levels are recorded as an objective marker for smoking intensity.

## **METHODS**

### ***Study subjects***

The study subjects consisted of 8,557 of a total of 9,804 participants recruited from 2008 to 2010 to the Nagahama Prospective Genome Cohort for the Comprehensive Human Bioscience (The Nagahama Study) who were free from any symptomatic cardiovascular diseases and whose fasting plasma and urine samples were available. The Nagahama Study cohort was recruited from the general population living in Nagahama City, a largely rural city of 125,000 inhabitants in Shiga Prefecture, located in the center of Japan. Smoking habit was investigated using a structure questionnaire, and study subjects were classified into three sub-groups according to their smoking habit; current smoker, now smoking cigarettes every day or some days; past smoker, not smoking at the time of the interview, but have an experience of continuous smoking; never smoker, having no experience of smoking. Medical history was also investigated using a structured questionnaire. All study procedures were approved by the ethics committee of Kyoto University Graduate School of Medicine.

### ***Measurement of BP and augmentation index (AIx)***

Brachial BP and radial arterial waveform were measured simultaneously (HEM-9000AI: Omron Healthcare, Kyoto, Japan) after 5 min rest in the sitting position. Briefly, brachial BP was measured on the right upper arm using a cuff-oscillometric device, and the radial arterial waveform was simultaneously obtained from the left wrist using a multi-element tonometric sensor. Radial AIx was calculated from the waveform as the ratio of the height of the late systolic peak to that of the first peak [11-13]. Absolute pressure of the late systolic peak (SBP2) was obtained by calibrating the radial waveform with bSBP and considered to be the

cSBP. The validity of SBP2 for use in estimating cSBP has been demonstrated by invasive simultaneous measurement of ascending aorta and radial artery pressure [14, 15]. We also reported that radial SBP2 was closely related to cSBP, as calculated using the widely used generalized transfer function [16]. The difference between bSBP and cSBP was used as an index of brachial-to-central PPa ( $PPa = bSBP - cSBP$ ). Heart rate (HR) was also measured simultaneously.

### *Measurement of urinary cotinine level*

A urine sample was collected in the morning and immediately frozen until used for measurement. Cotinine levels were measured at a commercial laboratory (BML Inc., Tokyo, Japan) by gas chromatography–mass spectrometry (QP-5050, Shimadzu Corporation, Kyoto, Japan). The inter- and intra-assay coefficients of variation of the urinary cotinine assay were 1.97% and 2.70%, respectively.

### *Statistical analysis*

Values are the mean  $\pm$  standard deviation unless otherwise specified. Differences in numeric variables by smoking habit were assessed by analysis of variance, while the frequency of differences was assessed by the chi-squared test. Factors independently associated with AIX and  $\Delta$ SBP2 were identified by multiple linear regression analysis. All statistical analysis was performed using a commercially available statistical package, JMP 9.0.2 (SAS Institute, Cary, NC), with p-values less than 0.05 considered to indicate statistical significance.

## **RESULTS**

Clinical characteristics of the study subjects are summarized in Table 1. Current smokers were significantly younger and had a higher body stature and body weight, and were more commonly male.

AIx of current smokers was slightly lower than that of non-smokers and past-smokers, contrary to previous reports (Table 1). In contrast, clinical features in this group, i.e. younger age ( $r=0.407$ ,  $p<0.001$ ), higher stature ( $r=-0.416$ ,  $p<0.001$ ) and male sex (male  $76\pm 14$ , female  $83\pm 12\%$ ,  $p<0.001$ ), are well-known to show a strong inverse association with AIx. We accordingly made a separate analysis by sex, and found that the AIx of current or past male smokers was somewhat higher than that of never smokers (never  $73\pm 15$ , past  $77\pm 13$ , current  $77\pm 14\%$ ,  $p<0.001$ ), whereas no clear trend was observed in female subjects (never  $84\pm 12$ , past  $79\pm 13$ , current  $82\pm 14$ ,  $p<0.001$ ). Multiple linear regression analysis adjusted for these confounding factors identified smoking habit as an independent determinant for both AIx and PPa (Table 2), as well as AIx adjusted HR at 75 beats/min (AIx75) ( $\beta=0.051$ ,  $p<0.001$ ). Figure 1A shows adjusted mean AIx and PPa by smoking habit: habitual smokers showed significantly higher AIx and smaller PPa, whereas bSBP of current smokers was somewhat lower than that of never smokers (Table 3).

Distribution of urinary cotinine levels is illustrated in Figure 2. Urinary cotinine was chiefly detected in current smokers ( $1.08\pm 0.79$   $\mu\text{g/ml}$ ), and levels were broadly distributed among current smokers. Cotinine levels were significantly associated with AIx and PPa (Table 2), as well as AIx75 ( $\beta=0.064$ ,  $p<0.001$ ), independently of smoking habit. Although a simple correlation analysis within current smokers showed no direct relationship between cotinine level and AIx ( $r=0.033$ ,  $p=0.247$ ) or PPa ( $r=0.040$ ,  $p=0.169$ ), presumably for the same reason as that for the lower AIx and larger PPa in current smokers, adjusted mean AIx and PPa showed stepwise association with urinary cotinine quartile (Figure 1B), with mean cotinine levels of each quartile as follows: Q1,  $0.25\pm 0.14$ ; Q2,  $0.72\pm 0.13$ ; Q3,  $1.19\pm 0.16$ ; and Q4,  $2.18\pm 0.63$   $\mu\text{g/ml}$ ;  $p<0.001$ . The same relationship was seen in the analysis of smoking quantity obtained by a self-reported questionnaire (Figure 1C). Adjusted mean AIx and PPa were associated in a dose-dependent manner. Self-reported smoking quantity was also significantly associated with urinary cotinine levels ( $\leq 10$  cigarettes/day,  $0.66\pm 0.60$ ; 11-20,

1.17±0.75; >=21, 1.46±0.83 µg/ml, p<0.001).

Urinary cotinine was also detected in a small fraction of never smokers (1.8 %) (Figure 2). This sub-population, regarded as passive smokers, showed higher adjusted AIx and smaller PPa (Figure 1D) but not bSBP (Table 3). Mean AIx of passive smokers was almost equal to that of the highest quartile of current smokers.

## **DISCUSSION**

In this study, we found that habitual smoking was significantly associated with increased arterial tone as evaluated by AIx and smaller PPa in a general population sample. In smokers, AIx and PPa were linearly associated with smoking intensity. Further, passive smokers, as defined by urinary cotinine levels, also showed higher AIx and smaller PPa, with levels closely similar to those of current smokers. The major strength of this study is its large-scale sample with urinary cotinine levels, which has enabled us to detect the harmful impact of passive smoking on arterial pressure.

Our present and previous epidemiological studies have reported a weak or negative correlation between smoking habit and brachia BP. However, our results showed that the PPa of habitual smokers was substantially smaller than that of never or past smokers presumably due to increased arterial tone. Further, PPa was linearly decreased with smoking intensity as evaluated by urinary cotinine levels. Similar results were reported in an analysis of 443 normotensive Japanese men [17], namely that cSBP and AIx were significantly higher in current smokers than never smokers whereas no substantial differences were observed in brachial SBP. Given suggestions that cSBP is superior in predicting CV risks [1-3], relatively higher cSBP in smokers might partially explain the additive risk of habitual smoking on CV disease that cannot be attributed to BP.

Urinary cotinine was detected in a number of subjects without experience of smoking. These subjects, regarded as passive smokers, had increased levels of AIx and smaller PPa



which were equivalent to those of current smokers. A recent prospective study of 13,443 participants living in England and Scotland [18] clearly showed a higher incidence of CV death and all-cause death during an 8-year follow-up period in passive smokers defined by salivary cotinine levels. Further, exposure to secondhand smoke was suggested to confer an increased risk of cognitive impairment [19]. Since increased cSBP may be associated with not only CV disease but also intracerebral small vessel disease [20], relatively higher cSBP may partially explain the excessive risk in passive smokers independently of the increased systemic inflammation [18].

Smoking cessation reduces AIx and pulse wave velocity in the aorta [21], which in turn decreases aortic BP. While the decrease in cardiovascular risk enjoyed by smokers who stop smoking is well known, our results emphasize the importance of avoiding exposure to secondhand smoke by non-smokers to reduce a CV risk of which they are likely unaware.

We showed here clear relationships between smoking intensity as evaluated by urinary cotinine level and both AIx and cSBP. Smoking intensity has been usually evaluated by questionnaire, but the reliability of questionnaire-based measurements, such as the Brinkman index, has been questioned. Previous studies which investigated the relationship between self-reported smoking status and smoking intensity as confirmed by cotinine measurement in a large number of pregnant women [22], as well as a meta-analysis of 67 studies [23], have identified a trend toward underestimation in self-reported data. In the present study, analysis of self-reported smoking quantity showed that AIx and PPa tended to associate in a dose-dependent manner; however, distribution of urinary cotinine levels was largely overlapped among the subgroups. Although both urinary cotinine levels and self-reported smoking quantity were independently associated with higher AIx and smaller PPa in our cross-sectional investigation, these findings warrant further longitudinal study to clarify which of the two parameters provides a more sensitive indication risks for future CV events.

Chronic cigarette smoking has been shown to be associated with increased arterial stiffness [24, 25]. Further, cigarette smoking acutely evokes sympathetic nerve activity [26] which in turn increases arterial tone. The harmful effects of smoking on AIx and PPa might result from both chronic and acute effects of smoking. Activation of the sympathetic nervous system concomitantly increases HR, and higher HR is associated with a lower AIx and, consequently, with a larger PPa. Higher AIx and smaller PPa in smokers is therefore independent of changes in HR. By contrast, smoking habit and smoking intensity had no substantial impact on brachial BP. Measurement of ambulatory BP revealed that daytime brachial BP was significantly higher in smokers [27, 28]. The possible effects of smoking on bSBP levels might not be detectable by simple cross-sectional BP measurement.

## **STUDY LIMITATIONS**

Several study limitations also warrant mention. First, we investigated smoking habit by self-reported questionnaire. Thus, a degree of misclassification in smoking habit might have occurred; if so, however, any such misclassification might have been independent of smoking status and be non-differential. Second, our observational study design does not allow us to discriminate whether the higher AIx and smaller PPa in passive smokers was a long-lasting phenomenon due to continuous exposure to secondhand smoke, or a transient reaction to passive smoking occurring in the few days before measurements.

## **CONCLUSIONS**

In summary, we have shown that not only habitual smoking but also passive smoking had harmful effects on AIx and central BP in a large-scale general population sample. Our results suggest that the changes in aortic pressure in smokers represent one reason for the elevated CV risks of smoking, and strongly emphasize the importance of avoiding passive smoking in preventing CV disease.

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## **FIGURE LEGENDS**

### **Figure 1 Adjusted mean AIx and PP amplification by smoking status**

Values are mean  $\pm$  standard error. PP amplification was calculated by bSBP - cSBP. The following factors were adjusted by a linear regression model: sex, age, height, weight, antihypertensive medication, HR, MBP, and urinary creatinine. ND indicates urinary cotinine levels below the detection threshold (0.005 $\mu$ g/ml).

### **Figure 2 Distribution of urinary cotinine levels**

ND indicates urinary cotinine levels below the detection threshold (0.005 $\mu$ g/ml).



**Table 1 Clinical characteristics of study subjects**

	Total (8,557)	Smoking habit			p
		Never (5,591)	Past (1,764)	Current (1,202)	
Age (years)	54±13	55±13	55±14	50±13	<0.001
Sex (male/female)	2,925/5,632	743/4,848	1,301/463	881/321	<0.001
Height (cm)	160±9	157.1±7.4	165.1±7.3	166.3±8.1	<0.001
Weight (kg)	57±11	54.6±9.6	62.8±10.6	62.9±12.3	<0.001
BMI (kg/m <sup>2</sup> )	22.3±3.3	22.1±3.3	23.0±3.1	22.6±3.4	<0.001
bSBP (mmHg)	124±18	123±18	127±18	125±18	<0.001
cSBP (mmHg)	114±18	114±18	116±18	114±18	<0.001
PP amplification (mmHg)	9.5±5.8	8.9±5.4	10.9±6.1	10.7±6.6	<0.001
MBP (mmHg)	92±13	91±13	95±13	93±13	<0.001
DBP (mmHg)	76±11	75±11	79±11	77±12	<0.001
Antihypertensive medication (%)	17.6	17.3	23.1	11.3	<0.001
Heart rate (beats/min)	69±10	70±10	68±11	69±10	<0.001
Augmentation index (%)	81±13	82±13	78±13	78±14	<0.001

BMI, body mass index calculated by weight (kg)/height<sup>2</sup> (m); bSBP, brachial systolic blood pressure; cSBP, central aortic systolic pressure; DBP, diastolic BP; MBP, mean BP calculated by DBP+(SBP–DBP)/3. Pulse pressure (PP) amplification was calculated by bSBP–cSBP. Differences in numeric variables by smoking habit were assessed by analysis of variance. Frequency differences were assessed by the chi-squared test.

**Table 2 Multiple linear regression analysis for AIx and PP amplification**

	AIx		PP amplification	
	$\beta$ (s.e.)	p	$\beta$ (s.e.)	p
Sex (male)	-0.236 (0.179)	<0.001	0.215 (0.088)	<0.001
Age (years)	0.291 (0.010)	<0.001	-0.167 (0.005)	<0.001
Height (cm)	-0.192 (0.021)	<0.001	0.178 (0.010)	<0.001
Weight (kg)	-0.098 (0.013)	<0.001	0.112 (0.007)	<0.001
Antihypertensive medication	-0.058 (0.149)	<0.001	0.074 (0.073)	<0.001
Heart rate (beats/min)	-0.462 (0.010)	<0.001	0.417 (0.005)	<0.001
MBP (mmHg)	0.271 (0.010)	<0.001	-0.138 (0.005)	<0.001
Current smoking	0.049 (0.236)	<0.001	-0.041 (0.116)	0.003
Urinary creatinine (mg/dl)	0.013 (0.002)	0.116	-0.022 (0.001)	0.017
Urinary cotinine ( $\mu\text{g/ml}$ )	0.057 (0.334)	<0.001	-0.037 (0.164)	0.008

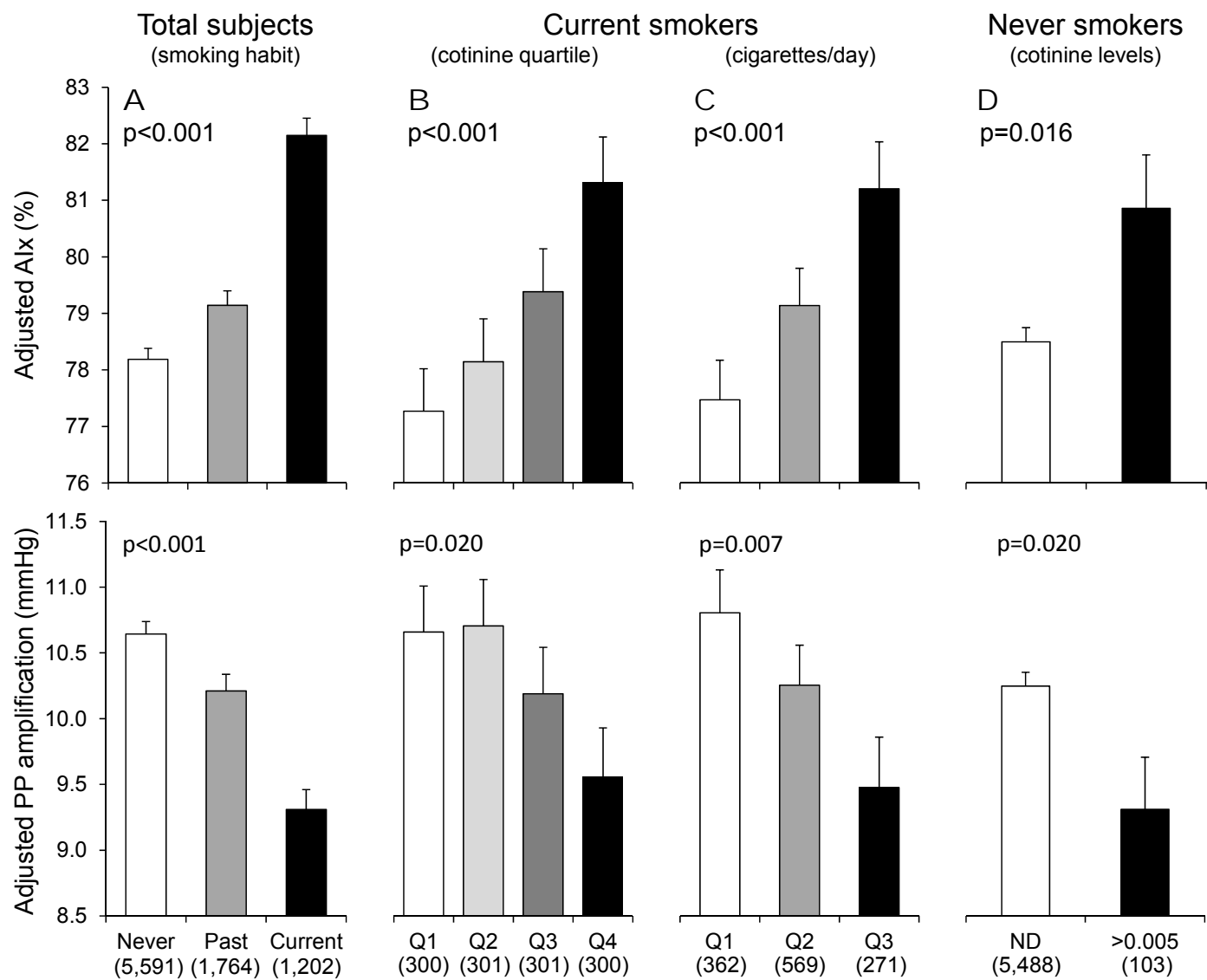
Smoking status is included as a dichotic value, namely 1=current smoker, 0=past and never smoker.

**Table 3 Adjusted mean SBP and smoking property**

		Adjusted bSBP (mmHg)	p
Smoking habit (total subjects)	never smoker	125.0±0.2	p=0.003
	past smoker	124.3±0.2	
	current smoker	124.4±0.1	
Cotinine quartile (current smokers)	Q1	124.2±0.4	p=0.004
	Q2	125.6±0.4	
	Q3	125.3±0.4	
	Q4	125.7±0.4	
Smoking quantity (current smokers)	≤10 cigarettes/day	124.8±0.4	p=0.322
	11-20 cigarettes/day	125.3±0.4	
	>21 cigarettes/day	125.5±0.4	
Cotinine levels (never smokers)	N.D.	123.1±0.2	p=0.474
	>0.05	122.7±0.6	

Values are mean ± standard error. The following factors were adjusted by a linear regression model: sex, age, height, weight, antihypertensive medication, HR, MBP, and urinary creatinine. N.D. indicates urinary cotinine levels below the detection threshold (0.005 µg/ml)

**FIGURE 1**



**FIGURE 2**

