Associations between smoking habits and major adverse cardiovascular events in patients who underwent coronary computed tomography angiography as screening for coronary artery disease

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Short title: smoking and major adverse cardiovascular events

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Abstract

Aims: We analyzed that smoking could induce major adverse cardiovascular events (MACE) and the progression of coronary atherosclerosis as assessed by coronary computed tomography angiography (CCTA) as screening for coronary artery disease (CAD).

Methods: We enrolled 443 patients who had all underwent CCTA and either were clinically suspected of having CAD or had at least one cardiovascular risk factor. We divided the patients into smoking (past and current smoker) and non-smoking groups or males and females, and evaluated the presence of CAD, severity of coronary atherosclerosis and MACE (cardiovascular death, ischemic stroke, acute myocardial infarction and coronary revascularization) with a follow-up of up to 5 years.

Results: %CAD and severity of coronary atherosclerosis in the smoking group was significantly higher than those in the non-smoking group. %MACE in males and smokers were significantly higher than those in females and non-smokers, respectively. Kaplan-Meier curves showed that smokers and females tended to show greater freedom from MACE than non-smokers and males, respectively (log-rank test p=0.057 and p=0.073, respectively). More interestingly, Kaplan-Meier curves also showed that non-smokers in females significantly greater freedom from MACE than smokers in females (p=0.007), whereas there was no significant difference in freedom from MACE between non-smokers and smokers in males (p=0.984). Although there were no significant predictors of MACE in all patients according to a multiple logistic regression analysis,

smoking was useful for predicting MACE in females, but not males.
Conclusion: Smoking was significantly associated with MACE in females, but not males, who underwent CCTA as screening for CAD.

Key words: smoking; coronary artery disease; coronary computed tomography angiography; major adverse cardiovascular events.

Introduction

Thrombosis underlies most acute complications of atherosclerosis, notably unstable angina and acute myocardial infarction (AMI) [1]. Inflammation plays a decisive role in the pathophysiology of these acute thrombotic events. Smoking, like hypertension (HTN), dyslipidemia (DL), diabetes mellitus (DM) and obesity, is related to coronary atherosclerotic cardiovascular disease (ASCVD) and is associated with an increased risk of the onset of atherosclerotic cardiovascular diseases such as cerebral infarction, coronary artery disease (CAD) and peripheral arterial disease. Smoking impacts all phases of atherosclerosis from endothelial dysfunction to acute clinical events, the latter being largely thrombotic [2]. Cigarette smoking is a major risk factor for acute coronary thrombosis. Indeed, a majority of sudden cardiac deaths attributable to acute thrombosis are in cigarette smokers [3].

Coronary computed tomography angiography (CCTA) has become more widely available in many general hospitals and has emerged as a potential non-invasive method in worldwide, in particular in Japan. CCTA is useful tool for screening CAD in patients were clinically suspected of having CAD. Evaluation of coronary arteries stenosis can be done using volume-rendering, multi-planar reformation and cross-sectional images obtained by CCTA. Significantly stenosed coronary vessels are defined as those with at least 50% coronary stenosis. Over the past decade, many researchers have investigated the prognostic value of CCTA [4-9]. The prognostic value of CCTA for evaluating CAD is controversial.

We previously reported that pack-year, but not the duration of cessation in smokers, may be the most important factor that was associated with the severity of coronary stenosis in terms of the number of significant stenosis vessels (VD) and the Gensini score in patients who had undergone CCTA [10]. Since the study was cross-sectional, we did not determine their prognosis. If we can confirm smoking as a critical predictor for MACE at the time of screening CAD, the patients could be received aggressive treatment for prevention of major adverse cardiovascular events (MACE). Here, we hypothesized that smoking induced MACE and the progression of coronary

atherosclerosis as assessed by CCTA as screening for CAD. Therefore, we investigated the associations between smoking habits and the presence or severity of CAD as assessed by CCTA or MACE.

Methods

Subjects

We enrolled 443 patients who had undergone CCTA and either were clinically suspected of having CAD or had at least one cardiovascular risk factor. We divided the patients into smoking (past and current smoker) and non-smoking groups. We evaluated pack-year and duration of cessation in the smoking group. The number of pack-years was calculated as [packss (where 1 pack consists of 20 cigarettes) smoked per day × years as a smoker. Patients with creatinine >2.0 mg/dl or contrast-induced allergy did not undergo MDCT. The protocol in this study was approved by the ethics committee of Fukuoka University Hospital, and all subjects gave their written informed consent to participate.

Evaluation of coronary stenosis using CCTA

We evaluated coronary stenosis using CCTA as previously described [11, 12]. Briefly, the region of interest was placed within the ascending aorta, and the scan was started when the CT density reached 100 Hounsfield Units higher than the baseline CT density. The scan was performed between the tracheal bifurcation and diaphragm. Overall, 15 coronary artery segments were assessed in all patients. Narrowing of the normal contrast-enhanced lumen to ≥ 50 % that could be identified in multiplanar reconstructions or cross-sectional images was defined as significantly stenosed coronary vessels. In addition, in all patients, the atherosclerotic severity of coronary artery disease was assessed by the number of significantly stenosed coronary vessels (VD) and the Gensini score [13]. Coronary artery calcification (CAC) was defined on CT images as the presence of more than two contiguous pixels with greater than 130 Hounsfield Units. The CAC score in each lesion was then computed by the Agatston method [14].

Evaluation of various hemodynamic and biochemical parameters

Data of body mass index (BMI), systolic blood pressure (SBP), diastolic BP (DBP), pulse rate (PR), the areas of visceral fat (VFA) and subcutaneous fat (SFA), serum levels of triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting blood glucose (FBG), hemoglobin A1c (HbA1c), estimated glomerular filtration rate (eGFR), uric acid (UA), family history

(FH) [myocardial infarction, angina pectoris or sudden death], history of HTN, DL, DM and history of smoking (past and current smokers), chronic kidney disease (CKD) and medication use were obtained from medical records.

BMI was calculated as weight (kg)/height $(m)^2$. BP was determined as the mean of two measurements obtained in an office setting by the conventional cuff method using a mercury sphygmomanometer after at least 5 minutes of rest. To measure the VFA and SFA, a CT scan was performed. The values were measured from CT cross-sectional scans at the level of the umbilicus with a workstation on a Ziostation (Ziosoft Inc., Tokyo. Japan). All of the blood samples were drawn in the morning after the patients had fasted overnight. Patients who had a current SBP/DBP ≥ 140/90mmHg or who were receiving antihypertensive therapy were considered to have HTN [15]. Patients with LDL-C ≥ 140 mg/dl, TG ≥ 150 mg/dl, and/or HDL-C < 40 mg/dl or who were receiving lipid-lowering therapy were considered to have DL [16]. DM was defined using the American Diabetes Association criteria [17] or the administration of a glucose-lowering drug. CKD was defined as an estimated glomerular filtration rate of < 60 $mL/min/1.73m^2$ and/or proteinuria.

Medications

The medications were obtained from medical records. Medications were included in angiotensin II receptor blocker and/or angiotensin-converting-enzyme inhibitor (ARB/ACEI), calcium channel blocker (CCB), β-blocker, diuretic (DU), statin, eicosapentaenoic acid (EPA), sulfonylurea (SU), biguanide, dipeptidyl peptidase-4 inhibitor (DPP4I) and insulin.

Evaluation of MACE

We determined MACE (cardiovascular death, ischemic stroke, acute myocardial infarction and coronary revascularization) as a primary endopoint in patients with a follow-up of up to 5 years (average: 3.5±0.7 years). When the patients had significant coronary stenosis assessed by CCTA and received coronary intervention immediately after CCTA, the intervention did not include in MACE as coronary revascularization.

Statistical analysis

A statistical analysis was performed using Excel 2016 (SSRI, Tokyo, Japan) and the Stat View statistical software package (Stat View 5; SAS Institute Inc, Cary, NC, USA) Continuous variables are shown as the mean ± standard deviation. Categorical and continuous variables were compared between the groups by a chi-square analysis and t-

test, respectively. Kaplan-Meier analysis (log-rank test) was applied to verify the time-dependent occurrence of MACE in groups stratified according to whether they did or did not have smoking (smoking and non-smoking groups). A multivariate analysis was performed by a logistic regression analysis for independent variables that were related to the presence or absence of CAD. A value of $p<0.05$ was considered significant.

Results

Patient characteristics in all patients and the non-smoking and smoking groups

Table 1 shows the characteristics of the 443 patients, who consisted of 220 males and 222 females. The frequencies of HTN, DM and DL in all patients were 70 %, 22 % and 65 %, respectively. The mean age was 66 ± 11 years and BMI was 24.0 ± 3.6 kg/m^2. There were several significant differences in patient characteristics between the non-smoking and smoking groups. The patients in the smoking group was younger than those in the non-smoking group. In the smoking group, %male, %DM, and %biguanide administration were significantly higher than those in the non-smoking group.

Next, we analyzed patient characteristics in males versus females. In all patients, females showed significantly older, higher %FH, %CKD and % CCB, and lower %DM and DPP4I than males. Males in the smoking group showed significant higher %HTN and %DM than males in the non-smoking group. In addition, in the non-smoking group, females showed significantly older and higher %CKD than males. In the smoking group, females showed a significant lower %DL, %DM, %SU or %DPP4I compared with males.

Various hemodynamic and biochemical parameters in all patients and the smoking and non-smoking groups

Table 2 shows various hemodynamic and biochemical parameters. In the smoking group, VFA, TG, FBG, HbA1c and UA were significantly higher, and HR, SFA and HDL-C were significantly lower than those in the non-smoking group.

Next, we analyzed various hemodynamic and biochemical parameters in males versus females. In all patients, females showed significantly higher PR, LVEF, SFA and HDL-C, and lower SBP, DBP, VFA, TG, BS, HbA1c and UA than males. Males in the smoking group showed significant higher levels of TG and HbA1c than males in the non-smoking group. In addition, in the non-smoking group, females showed significantly lower levels of DBP, VFA and UA, and higher levels of LVEF, SFA, HDL-C than males. In the smoking group, females showed significant lower levels of SBP, DBP, VFA and HbA1c, and higher levels of LVEF compared with males.

%CAD, the number of VD, CAC score and Gensini score in the smoking and non-smoking groups

%CAD, the number of VD, CAC score and Gensini score were shown in Figure 1. %CAD and the number of VD in the smoking group (63 % and 1.3 ± 1.1, respectively) were significantly higher than those in the non-smoking group (49 % and 0.8± 1.0, respectively). In addition, the CAC score and Gensini scores in the smoking group (326 ± 835 and 16.8 ± 22.2, respectively) were also significantly higher than that in the non-smoking group (161 ± 492 and 10.5 ± 12.1, respectively).

%MACE in males versus females and smokers versus non-smokers

%MACE values in males (12.7 %) and smokers (13.5 %) were significantly higher than those in females (5.4 %) and non-smokers (6.4 %), respectively (Figure 2AB).

Associations between duration of cessation or pack-year and MACE in past smokers

In past smokers, we analyzed the associations between pack-year or duration of cessation and MACE. Duration of cessation and pack-year in past smokers was 16 ± 13 years? and 46 ± 30, respectively. There were no differences between duration of cessation or pack-year and MACE in past smokers (Figure 2DE). In addition, a lthough there was no difference in duration of cessation between males (16±12 years?) and females (17 ± 19 years?), pack-year in males (49 ± 35) was significantly higher than that in females (35 ± 26).

Kaplan-Meier curves for freedom from MACE

Kaplan-Meier curves show freedom from MACE in males vs. females and smoking vs. non-smoking in Figure 3AB. Non-smokers and females tended to show greater freedom from MACE than smokers and males (p=0.057 and p=0.073, respectively).

Figure 3CD shows Kaplan-Meier curves for freedom from MACE in males or females. Kaplan-Meier curves also showed that non-smokers in females significantly greater freedom from MACE than smokers in females (p=0.007), whereas there was no significant difference in freedom from MACE between non-smokers and smokers in males (p=0.984).

Predictors of MACE in all patients, males and females

Table 3A shows predictors of MACE in all patients using independent variables by a

logistic regression analysis. We selected conventional coronary risk factors (age, gender, BMI, smoking, FH, BMI, HTN, DL, DM and CKD). There were no predictors of MACE in all patients. Since there was a significant difference in %MACE between males and females, we separately analyzed predictors of MACE according to gender (Table 3BC). Although there were no predictors of MACE in males, smoking was useful for predicting MACE in females (p=0.03).

Discussion

In the present study, we hypothesized that smoking could induce MACE and the progression of coronary atherosclerosis as assessed by CCTA as screening for CAD. Most important founding was that smoking was a predictor for MACE in females, but not males, although smoking was not a significant predictor for MACE in all patients. In addition, there were no associations between duration of cessation or pack-year and MACE in past smokers.

In this study, smoking was not a predictor for MACE in all patients group, in particular in males. This situation is not to say that smoking is not a risk of occurrence of MACE. Smoking is associated with an increased risk of MI, stroke, sudden death, worsening heart failure [18]. Since the patients have multiple conventional risk factors, only one risk factor may not cause MACE. Smoking affects men and women equally, which might not be true for all diseases including ASCVD. Most importantly, smoking was more associated with MACE in females than in males.

Previous studies indicated that the risk of development of CAD due to smoking is greater among females than males [19-22]. The relative risk of MI was 50 % higher in female smokers than male smokers across all ages in Copenhagen [20]. The relative risk of CAD in smokers compared to non-smokers was 25 % greater in females compared to males according to a meta-analysis of 17 cohort studies [21]. Smoking was a risk factor for CAD in females compared with males in 75 cohorts [22]. Although the patient background in these reports were different from those in the present study, our results in gender difference was consistent with these previous reports. Although the prevalence of smoking is higher in males than in females, the reason for the differential impact of smoking on development of ASCVD in females versus males is not fully understood. Some reports speculated the mechanisms in gender difference that smoking with the use of oral contraceptives [23], the negative effect of smoking on HDL-C levels [24], and increased levels of hormones including insulin, free testosterone [25] and arginine vasopressin [26] lead to higher CVD risks. Among these mechanisms, there were no significant differences in HDL-C levels between smokers (57 ± 17 mg/dL) and non-

smokers (58 ± 16 mg/dL) in females in this study, although there were significant differences in HDL-C levels between smokers and non-smokers in all patients. Next, the levels of free testosterone may not associate with female patients because their average age was 68 ± 10 years in this study. Generally, smoking is relatively infrequent in females compared with males in some regions of the world, especially in regions of Asia [27]. In this study, %smoking in females (13 %) was much lower than that in males (61 %). The difference in %smoking may affect gender difference of smoking. Since other factors were not determined, further detail studies will be needed to resolve the issues.

We also found that there were no associations between duration of cessation or pack-year and MACE in past smokers. Smoking cessation has been consistently associated with a mortality benefit in both stable CAD and post acute coronary syndromes [28, 29]. There is a discrepancy between previous reports and our present report with regard to the effect of cessation. The benefit according to previous reports are mainly for secondary prevention. In this study, %MACE in past smokers was 17.2 %, and it was significantly higher than that in non-smokers (6.4 %) ($p<0.01$). Since the duration of cessation in past smokers was 16.4 ± 13.0 years, the duration may be enough for preventing cardiac events. Because previous reports indicated that the cardiovascular risk associated with smoking appears to dissipate within 3 years of cessation [30, 31]. On the other hand, past smokers had already smoked at 46.9 ± 32.8 pack-year before cessation. Kim *et al*. reported that the prevalence of coronary arteriosclerosis in current smokers of more than 20 pack-years was significantly higher than that in never smokers [32]. The amount of smoking may be enough for inducing irreversible endothelial dysfunction and damaging to coronary arteries before cessation.

Study limitations

This study has several important limitations. First, patients with creatinine >2.0 mg/dl or contrast-induced allergy did not undergo MDCT because of limitation of volume of contrast medium. Since severe renal function associates with more prevalence of CAD, such CAD patients may also be excluded. Second, smoking group included both past and current smokers. Because past smokers had high volume of smoking as described before. Third, the presence and severity of CAD was evaluated under various medications. A large-scale prospective study will be needed to address these issues.

Conclusion

Smoking was significantly associated with MACE in females, but not males, who

underwent CCTA as screening for CAD.

Conflict(s) of Interest

We have no Conflict of Interest.

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Acknowledgment
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Figure legend

Figure 1.

%coronary artery disease (CAD) (A), the number of significantly stenosed coronary vessels (VD) (B), coronary artery calcification (CAC) score (C) and Gensini score (D) in the smoking and non-smoking groups. *p<0.05, **p<0.01 versus non-smoking group. AU, arbitrary unit.

Figure 2.

%MACE in males versus females (A) and smokers versus non-smokers (B). **p<0.01 versus females; $^{\#\#}$p<0.01 versus non-smokers.
Pack-year (C) and duration of cessation (D) in past smokers with and without MACE.

Figure 3.

Kaplan-Meier curves freedom from MACE in the smoking group versus non-smoking group in all patients (A), males versus females in all patients (B), in the smoking group versus non-smoking group in males (C) or in females (D).

Table 1. Patient characteristics in all patients and the non-smoking and smoking groups.

	All patients			Non-smoking group			Smoking group		
	All (n=443)	Males (n=220)	Females (n=223)	All (n=280)	Males (n=85)	Females (n=195)	All (n=163)	Males (n=135)	Females (n=28)
Age (years)	66±11	64±11	68±10**	67±11	62±13	69±9**	64±10*	65±10	62±12**
Male, n (%)	220 (50)			85 (30)			135 (83)		
BMI (kg/m^2)	24.0±3.6	24.3±3.5	23.7±3.7	23.8±3.7	24.3±3,6	23.7±3.7	24.1±3.5	24.2±3.5	23.9±3.8
HTN, n (%)	310 (70)	158 (72)	152 (68)	188 (67)	54 (64)	134 (69)	122 (75)	104 (77)*	18 (64)
DL, n (%)	286 (65)	149 (68)	137 (61)	176 (63)	53 (62)	123 (63)	110 (67)	96 (71)	50 (14)*
DM, n (%)	98 (22)	64 (29)	34 (15)**	49 (18)	18 (21)	31 (16)	49 (30)**	46 (34)*	3 (11)*
FH, n (%)	110 (25)	45 (20)	65 (29)*	73 (26)	18 (21)	55 (28)	37 (23)	27 (20)	10 (36)
CKD, n (%)	54 (12)	19 (3.8)	35 (15.7)*	35 (13)	5 (5.9)	30 (15)*	19 (12)	14 (10)	5 (18)
Medication									
ARB/ACEI, n (%)	173 (39)	90 (41)	83 (37)	105 (38)	33 (39)	72 (37)	68 (42)	57 (42)	11 (39)
β-blocker, n (%)	43 (9.7)	24 (11)	19 (9)	24 (9)	8 (9.4)	16 (8.2)	19 (12)	16 (12)	3 (11)
CCB, n (%)	157 (35)	68 (31)	89 (40)*	102 (36)	25 (29)	77 (39)	55 (34)	43 (32)	12 (43)
Diuretic, n (%)	49 (9.7)	20 (9.1)	29 (13)	32 (11)	8 (9.4)	24 (12)	17 (10)	12 (8.9)	5 (18)
Statin, n (%)	158 (36)	79 (36)	79 (35)	104 (37)	32 (38)	72 (37)	54 (33)	47 (35)	7 (25)
EPA, n (%)	14 (3.2)	6 (2.7)	8 (3.6)	9 (3.2)	3 (3.5)	6 (3.1)	5 (3.1)	3 (2.2)	2 (7.1)
SU, n (%)	44 (10)	27 (12)	17 (7.6)	22 (7.9)	7 (8.2)	15 (7.7)	22 (13)	20 (15)	2 (7.1)
Biguanide, n (%)	34 (7.7)	26 (12)	8 (3.6)	16 (5.7)	8 (9.4)	8 (4.1)	18 (11)*	18 (13)	0 (0)*
DPP4I, n (%)	47 (11)	31 (14)	16 (7.2)*	26 (9.3)	10 (12)	16 (8.2)	21 (13)	21 (16)	0 (0)*
Insulin, n (%)	15 (3.4)	7 (3.2)	8 (3.6)	8 (2.9)	2 (2.4)	6 (3.1)	7 (4.3)	5 (3.7)	2 (7.1)

BMI, body mass index; HTN, hypertension; DL, dyslipidemia; DM, diabetes mellitus; FH, family history; CKD, chronic kidney disease; ARB, angiotensin receptor II blocker; ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; EPA, eicosapentaenoic acid; SU, sulfonylurea; DPP4I, dipeptidyl peptidase-4 inhibitor. **p<0.01, *p<0.05 vs. Non-smoking.

Table 2. Various hemodynamic and biochemical parameters in all patients and the smoking and non-smoking groups.

	All patients			Non-smoking group			Smoking group		
	All (n=443)	Males (n=220)	Females (n=223)	All (n=280)	Males (n=85)	Females (n=195)	All (n=163)	Males (n=135)	Females (n=28)
SBP (mmHg)	137±19	139±18	134±20*	136±20	138±18	135±20	137±18	139±18	130±18**
DBP (mmHg)	78±12	81±12	75±12**	77±12	81±12	75±12**	79±13	80±12	73±13**
PR (/min)	74±13	72±14	76±13**	76±13	74±14	77±13	72±13**	72±13	73±12
LVEF (%)	69±10	67±10	70±9**	69±10	66±11	70±9**	68±10	67±9	72±10*
WC (cm)	87±9	88±9	87±10	87±9	87±9	87±10*	88±9	88±19	87±9
SFA (cm^2)	155±78	124±62	185±80**	169±80	128±67	187±79**	131±67**	121±60	175±81
VFA (cm^2)	116±57	130±59	102±50**	109±53	125±57	102±50**	129±60**	134±61	107±52*
eGFR (ml/min)	68±17	64±14	66±19	68±18	70±12	67±20	67±16	68±15	66±18
TG (mg/dl)	137±88	154±104	120±50**	124±66	135±79	119±59	159±112**	165±116**	129±87
LDL-C (mg/dl)	113±32	110±30	116±33	114±33	111±33	116±33	110±29	109±29	113±32
HDL-C (mg/dl)	54±16	50±14	58±16**	56±16	51±15	58±16**	50±14**	49±13	57±17
BS (mg/dl)	109±31	113±36	104±24**	105±29	109±37	104±24	114±29**	115±35	105±23
HbA1c (%)	5.9±1.2	6.0±1.3	5.8±1.1*	5.8±1.3	5.8±1.7	5.8±1.1	6.1±1.1*	6.2±1.0**	5.6±1.2**
UA (mg/dl)	5.3±2.0	5.8±2.2	4.7±1.6**	5.0±1.6	5.7±1.4	4.7±1.5**	5.7±2.6**	5.9±2.6*	4.6±2.0

SBP, systolic blood pressure; DBP, diastolic BP; PR, pulse rate; LVEF, left ventricular ejection fraction; WC, waist circumference; SFA, subcutaneous fat area; VFA, visceral fat area; eGFR, estimated glomerular filtration rate; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBS, fasting blood glucose; HbA1c, hemoglobin A1c; UA, uric acid.
**p<0.01, *p<0.05 vs. Non-smoking group.

Table 3. Predictors of MACE in all patients (A), males (B) and females (C).

(A) All patients		(A) All patients	
Variables	Odds ratio	Variables	Odds ratio
Age	1.02	Age	1.02
Gender (males)	2.31	Gender (males)	2.31
BMI	0.94	BMI	0.94
Smoking	1.53	Smoking	1.53
FH	0.6	FH	0.6
HTN	1.26	HTN	1.26
DL	0.69	DL	0.69
DM	1.2	DM	1.2
CKD	2.02	CKD	2.02
(B) Males		(B) Males	
Variables	Odds ratio	Variables	Odds ratio
Age	1.02	Age	1.02
BMI	0.89	BMI	0.89
Smoking	1.1	Smoking	1.1
FH	0.31	FH	0.31
HTN	1.08	HTN	1.08
DL	0.65	DL	0.65
DM	0.84	DM	0.84
(A) All patients		(A) All patients	
Variables	Odds ratio	Variables	Odds ratio
Age	1.27722222	Age	1.27722222
Gender (males)	1.27555556	Gender (males)	1.27555556
BMI	1.27388889	BMI	1.27388889
Smoking	1.27222222	Smoking	1.27222222
FH	1.27055556	FH	1.27055556
HTN	1.26888889	HTN	1.26888889
DL	1.26722222	DL	1.26722222
DM	1.26555556	DM	1.26555556
CKD	1.26388889	CKD	1.26388889

MACE, major cardiovascular events; CI, confidence Interval; BMI, body mass index; FH, family history; HTN, hypertension; DL, dyslipidemia; DM, diabetes mellitus; CKD, choronic kidney disease.

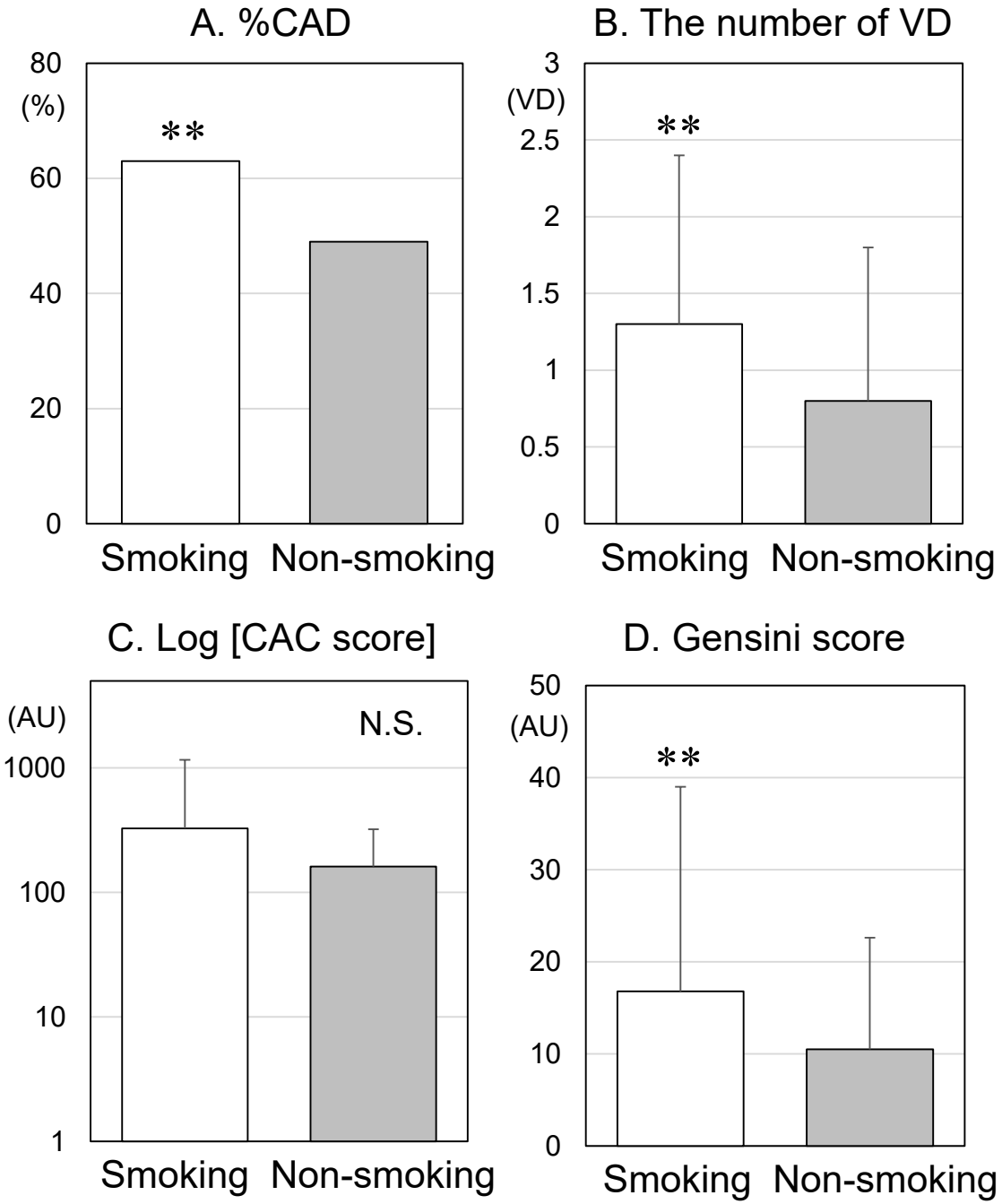

Figure 1.
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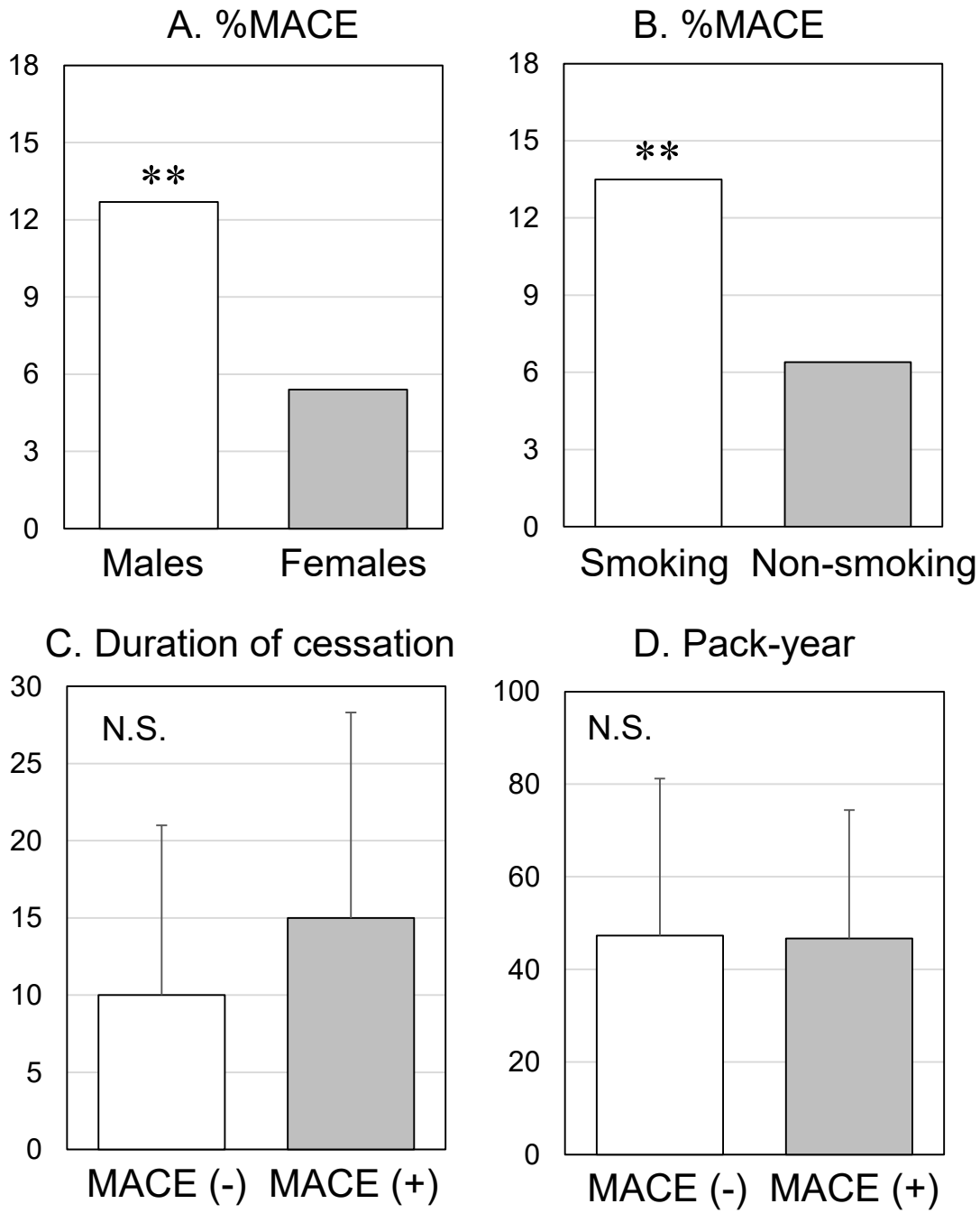

Figure 2.
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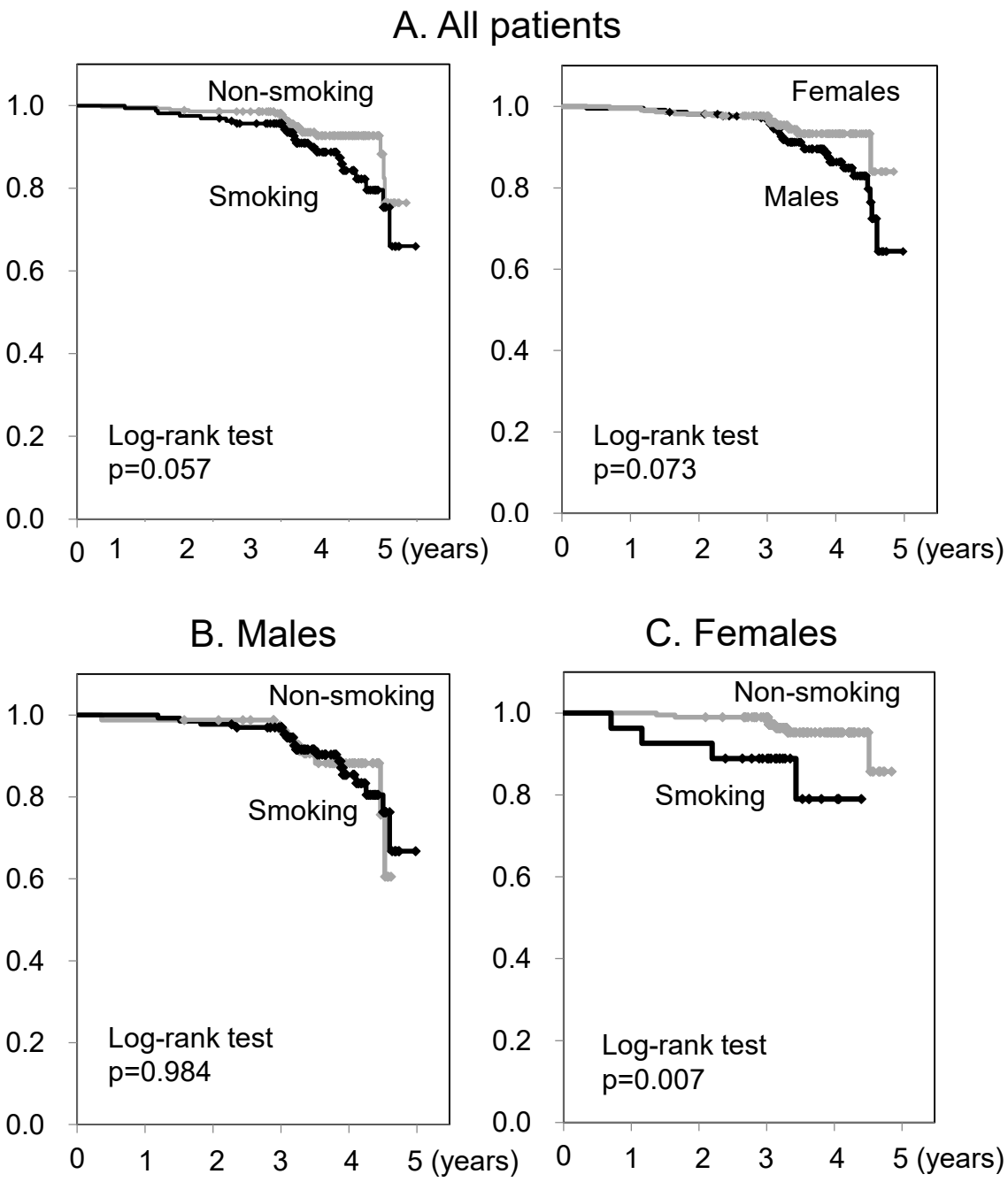

Figure 3.
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