Association of smoking with prevalence of common diseases and metabolic abnormalities in community-dwelling Japanese individuals

CHIKARA UEYAMA[1], HIDEKI HORIBE[1], YUICHIRO YAMASE[1], TETSUO FUJIMAKI[2], MITSUTOSHI OGURI[3], KIMIHIKO KATO[4] and YOSHIJI YAMADA[5,6]

[1]Department of Cardiovascular Medicine, Gifu Prefectural Tajimi Hospital, Tajimi 507-8522; [2]Department of Cardiovascular Medicine, Inabe General Hospital, Inabe 511-0428; [3]Department of Cardiology, Kasugai Municipal Hospital, Kasugai 486-8510; [4]Department of Internal Medicine, Meitoh Hospital, Nagoya 465-0025; [5]Department of Human Functional Genomics, Advanced Science Research Promotion Center, Mie University, Tsu 514-8507; [6]Core Research for Evolutionary Science and Technology (CREST), Japan Science and Technology Agency, Kawaguchi 332-0012, Japan

Received February 24, 2017; Accepted July 6, 2017

DOI: 10.3892/br.2017.991

Abstract. Smoking is a significant risk factor for cardiovascular diseases (CVDs). Given that certain common pathologies, including hypertension, dyslipidemia and type 2 diabetes mellitus, are major risk factors for CVDs, the association of smoking with CVDs may be attributable, at least in part, to its effects on common diseases. The aim of the present study was to determine the association of smoking with the prevalence of common diseases and metabolic abnormalities in community-dwelling Japanese individuals. The study included 5,959 subjects (1,302 current smokers, 1,418 past smokers and 3,239 nonsmokers) recruited to the Inabe Health and Longevity Study, a longitudinal genetic epidemiological study of atherosclerotic, cardiovascular and metabolic diseases. Various metabolic parameters and prevalence of common diseases were compared between smokers and nonsmokers using multivariable regression or logistic regression analysis with adjustments for age. Analysis indicated significantly higher serum concentrations of triglycerides and lower concentrations of high-density lipoprotein (HDL)-cholesterol in current smokers compared with nonsmokers in men and women. Serum concentrations of creatinine and systolic blood pressure were significantly lower and estimated glomerular filtration rate was higher in male current smokers. In addition, body weight was higher in female current smokers. In multivariable logistic regression analysis, smoking was significantly associated with the prevalence of dyslipidemia [$P=6.3x10^{-10}$; odds ratio (OR), 1.81], hypertriglyceridemia ($P=2.3x10^{-20}$; OR, 2.39), hypo-HDL-cholesterolemia ($P=2.0x10^{-9}$; OR, 2.14), metabolic syndrome (P=0.0003; OR, 1.61) and chronic kidney disease ($P=4.4x10^{-15}$; OR, 0.54) in men, but not in women. The results indicated that smoking is significantly associated with various metabolic abnormalities and prevalence of common diseases in Japanese individuals, with certain sex differences, which may lead to accelerated development of CVDs.

Correspondence to: Dr Hideki Horibe, Department of Cardiovascular Medicine, Gifu Prefectural Tajimi Hospital, 5-161 Maebata-cho, Tajimi 507-8522, Japan
E-mail: hideki-horibe@tajimi-hospital.jp

Key words: smoking, common disease, metabolic parameters

Introduction

Smoking is one of the major lifestyle factors that influences the health of human beings (1). It is not only a risk factor for a multitude of diseases, but also one of the leading causes of avoidable mortality worldwide. Cigarette smoking is increasing rapidly throughout the developing world (2). Among the industrialized countries, smoking is estimated to be the primary cause of 70-90% of lung cancer cases, 56-80% of chronic respiratory disease cases, and 22% of cardiovascular disease (CVD) cases (3). Furthermore, it is estimated that smoking contributes to ~6 million premature mortalities worldwide each year (4).

CVDs are a significant clinical issue based upon the associated risk of mortality. In the United States, the total number of individuals affected by coronary artery disease and stroke were 15.5 and 6.6 million in 2012, respectively (5). Smoking is one of the important risk factors for the development of CVDs, and is probably the most complex and the least understood among the risk factors of CVDs (6). Cigarette smoke contains >4,000 different chemicals, ranging in size from atoms to particular matter (7), and smoking is associated with various systemic effects, including oxidative stress, systemic inflammation and endothelial dysfunction (1). However, the exact mechanism (or mechanisms) of the detrimental effects of smoking on the development of CVDs remains unknown.

Previous studies demonstrated the association of smoking with various common diseases, including hypertension, dyslipidemia, and type 2 diabetes mellitus (T2DM) (8-10). Given

that certain common diseases, such as hypertension, T2DM, dyslipidemia, and metabolic syndrome (MetS), are major risk factors for CVDs, it was hypothesized that the association of smoking with CVDs may be attributable, at least in part, to its effects on these common diseases. The aim of the present study was to determine the association of smoking with the prevalence of various common diseases and metabolic parameters in community-dwelling Japanese individuals.

Subjects and methods

Study population. The study subjects comprised 5,959 community-dwelling Japanese individuals (1,302 current smokers, 1,418 past smokers and 3,239 nonsmokers) who were recruited to a population-based cohort study (Inabe Health and Longevity Study; Inabe General Hospital, Inabe, Japan), between 2010 and 2012. The Inabe Health and Longevity Study was a longitudinal genetic/epidemiological study of atherosclerotic, cardiovascular and metabolic diseases (11-14). The study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committees at Mie University Graduate School of Medicine (Tsu, Japan) and Inabe General Hospital. Written informed consent was obtained from all participating subjects.

Data collection and measurements. The clinical data collected in the present study included medical history, physical examination, anthropometric measurements, and self-reported questionnaires on lifestyle (e.g., smoking habit). The section regarding smoking habit consisted of questions on smoking status, average number of cigarettes smoked per day and duration of smoking habit. Physicians or trained nurses conducted all of the following measurements: Blood pressure was measured at least twice at rest in the sitting position for >5 min; the measurements were taken by a physician or trained nurse according to the guidelines of the American Heart Association (15). Venous blood samples (10 ml) were collected in the early morning after overnight fasting. Blood samples were centrifuged at 1,600 x g for 15 min at 4˚C to separate the serum. Fasting plasma glucose level, blood glycosylated hemoglobin content, and the serum concentrations of total cholesterol, triglycerides, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL) cholesterol, creatinine, and uric acid were measured as described previously (12,13).

Definitions. A smoker was defined as a subject who smoked ≥1 cigarette/day for ≥1 year. Current smoker was defined as an individual that had smoked for at least the last year. A past smoker was defined as a subject who had stopped smoking ≥1 year before enrollment in the study. A nonsmoker was defined as a subject who had never smoked. According to the daily consumption of cigarette smoking, current smokers were divided into light (1-19 cigarettes per day) and heavy (≥20 cigarettes per day) smokers. Hypertension was defined as either systolic blood pressure (SBP) ≥140 mmHg and/or diastolic BP (DBP) ≥90 mmHg, or current treatment with antihypertensive medications. T2DM was defined as either fasting plasma glucose level ≥6.93 mmol/l (126 mg/dl), blood glycosylated hemoglobin content ≥6.5%, or current use of glucose-lowering agents. Patients with T1DM were not included in the present study. Dyslipidemia was defined as either serum concentration of triglycerides ≥1.65 mmol/l (150 mg/dl), serum HDL-cholesterol concentration <1.04 mmol/l (40 mg/dl), serum LDL-cholesterol concentration ≥3.64 mmol/l (140 mg/dl), or current use of antidyslipidemic drugs. Hypertriglyceridemia was defined as either serum triglyceride concentration ≥1.65 mmol/l or current treatment of antidyslipidemic medications for hypertriglyceridemia. Hypo-HDL-cholesterolemia was defined as either serum HDL-cholesterol concentration <1.04 mmol/l. Hyper-LDL-cholesterolemia was defined as either serum LDL-cholesterol concentration ≥3.64 mmol/l or current treatment with antidyslipidemic agents for hyper-LDL-cholesterolemia. The estimated glomerular filtration rate (eGFR) was calculated using a simplified prediction equation derived from that in the Modification of Diet in Renal Disease Study (16) and proposed by the Japanese Society of Nephrology (17): eGFR (ml/min/1.73 m^2) = 194 x [age (years)]$^{-0.287}$ x [serum creatinine (mg/dl)]$^{-1.094}$ (x 0.739 for females). Chronic kidney disease (CKD) was diagnosed with eGFR of <60 ml/min/1.73 m^2, as recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines (18). Hyperuricemia was represented by a serum concentration of uric acid >416 μmol/l (7.0 mg/dl) or current treatment with uric acid-lowering medications. Obesity was diagnosed as body mass index (BMI) ≥25 kg/m^2, based on the BMI criteria of obesity for Japanese and Asian populations (19). Diagnosis of MetS was based on the modified version of the definition proposed by the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity (20). Cut-off values for waist circumference were used, which were ≥90 cm for men and ≥80 cm for women, based on the recommendation of the International Diabetes Association (20). A total of 1,546 subjects with MetS had three or more of the following five components: i) Waist circumference ≥90 cm for men and ≥80 cm for women; ii) serum concentration of triglycerides ≥1.65 mmol/l (150 mg/dl) or receiving drug treatment for elevated triglycerides; iii) serum concentration of HDL-cholesterol <1.04 mmol/l (40 mg/dl) for men and <1.30 mmol/l (50 mg/dl) for women; iv) SBP ≥130 mmHg or DBP of ≥85 mmHg, or drug treatment for hypertension; and v) fasting plasma glucose level ≥5.50 mmol/l (100 mg/dl) or use of glucose-lowering agents. History of obesity, dyslipidemia, hypertension or DM was evaluated by detailed questionnaire. The control subjects comprised 1,841 individuals who exhibited none of the five components of the diagnostic criteria for MetS.

Statistical analysis. Categorical variables were compared by the χ^2 test. The distribution of continuous variables was examined by Kolmogorov-Smirnov-Lilliefors test. Comparison between two groups was conducted by the unpaired Student's t-test (for variables with normal distribution) or by Mann-Whitney U test (for variables with skewed distribution). Comparisons among three groups were examined by one-way analysis of variance (for variables with normal distribution) or Kruskal-Wallis test (for variables with skewed distribution). Metabolic parameters were compared between current or past smokers and nonsmokers by multivariable regression analysis following adjustment for age in men and women. Metabolic parameters

Table I. Characteristics of current smokers, past smokers and nonsmokers.

Variable	Current smokers	Past smokers	Nonsmokers	P-value
Subjects, n	1,302	1,418	3,239	
Age, years	50.4±12.1	55.6±12.3	54.8±13.1	$6.1x10^{-32}$
Sex, male, %	88.8	88.2	27.6	$<1.0x10^{-61}$
Daily consumption, cigarettes per day	18.3±8.5	20.1±11.3		$2.8x10^{-8}$
Duration of smoking habit, years	27.7±11.5	21.2±11.6		$<1.0x10^{-61}$
Hypertension, %	31.0	44.9	35.3	$3.1x10^{-14}$
Dyslipidemia, %	68.0	68.5	58.2	$1.4x10^{-14}$
Type 2 diabetes mellitus, %	13.2	15.3	9.4	$5.2x10^{-9}$
Hyperuricemia, %	25.4	28.9	8.6	$<1.0x10^{-61}$
Body weight, kg	66.3±12.3	65.7±11.3	56.7±10.7	$<1.0x10^{-61}$
Body mass index, kg/m^2	23.4±3.6	23.6±3.2	22.5±3.4	$9.4x10^{-33}$
Waist circumference, cm	82.2±9.2	82.6±8.6	78.7±9.2	$1.0x10^{-53}$
Systolic blood pressure, mmHg	118.5±15.4	123.1±15.8	120.1±16.0	$1.1x10^{-14}$
Diastolic blood pressure, mmHg	74.8±12.4	77.9±11.7	73.0±11.8	$3.8x10^{-37}$
Serum triglycerides, mmol/l	1.54±1.12	1.41±0.98	1.09±0.61	$<1.0x10^{-61}$
Serum HDL-cholesterol, mmol/l	1.47±0.39	1.59±0.43	1.77±0.44	$<1.0x10^{-61}$
Serum LDL-cholesterol, mmol/l	3.15±0.86	3.19±0.78	3.18±0.78	0.2834
Fasting plasma glucose, mmol/l	5.69±1.37	5.77±1.24	5.41±0.86	$1.8x10^{-46}$
Blood glycosylated hemoglobin, %	5.76±0.87	5.71±0.73	5.65±0.54	0.1109
Serum uric acid, μmol/l	356.6±82.0	360.7±82.4	295.3±75.5	$<1.0x10^{-61}$
Serum creatinine, μmol/l	71.0±13.7	74.8±19.1	61.6±14.9	$<1.0x10^{-61}$
eGFR, ml/min/1.73 m^{-2}	80.6±14.9	74.7±14.7	77.2±15.4	$3.9x10^{-23}$

Data are presented as means ± standard deviation. Categorical variables were compared using the χ^2 test; continuous variables were compared using the Mann-Whitney U test between two groups and by the Kruskal-Wallis test among three groups (due to skewed distribution); P<0.0009 was considered to indicate a statistically significant difference. eGFR = 194 x [age (years)]$^{-0.287}$ x [serum creatinine (mg/dl)]$^{-1.094}$ (x 0.739 for female). HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate.

were also compared between heavy and light smokers by multivariable regression analysis following adjustment for age and sex. The prevalence of common diseases was compared between current or past smokers and nonsmokers by multivariable logistic regression analysis following adjustment for age in men and women. In addition, a stepwise forward selection procedure was performed to examine the effects of smoking and age on common diseases with which smoking was associated in men and women by multivariable logistic regression analysis. The P-value for inclusion in and exclusion from the model were 0.25 and 0.1, respectively. Bonferroni's correction was applied to compensate for multiple comparisons and P<0.0009 (0.05/54) was considered to indicate a statistically significant difference. Statistical tests were conducted using the JMP software (version 5.1; SAS Institute, Inc., Cary, NC, USA).

Results

Characteristics of study population. Table I presents the characteristics of subjects according to the smoking habit. There were significant (P<0.0009) differences in age, sex, and the prevalence of hypertension, dyslipidemia, T2DM and hyperuricemia, as well as various metabolic parameters among current smokers, past smokers and nonsmokers. The number of cigarettes smoked per day was significantly lower ($P=2.8x10^{-8}$) in the current smokers than in past smokers, whereas the duration of smoking habit was longer in the current smokers than in past smokers ($P<1.0x10^{-61}$). With regard to the current smokers, the number of cigarettes smoked per day (19.0±8.6 vs. 12.9±5.5 cigarettes per day; $P<1.0x10^{-61}$) and duration of smoking habit (28.8±11.3 vs. 19.5±9.8 years; $P<1.0x10^{-61}$) were significantly greater in men than in women (Table II). Amongst past smokers, the number of cigarettes smoked per day (22.1±11.4 vs. 13.0±7.1 cigarettes per day; $P<1.0x10^{-61}$) and duration of smoking habit (22.1±11.6 vs. 14.3±9.8 years; $P=4.9x10^{-13}$) were also significantly greater in men than women.

Smoking and metabolic parameters. Multivariable regression analysis after adjustment for age demonstrated significantly higher serum concentration of triglycerides ($P=7.8x10^{-15}$) and eGFR ($P=1.5x10^{-6}$) in current smokers than nonsmokers among men, whereas SBP ($P=4.6x10^{-5}$), serum HDL-cholesterol concentration ($P=1.3x10^{-11}$), and serum creatinine concentration ($P=2.6x10^{-7}$) were lower in current smokers than in nonsmokers among men (Table II). In women, current smokers also had significantly higher body weights (P=0.0003) and serum triglyceride concentrations (P=0.0003), as well as lower serum HDL-cholesterol concentration ($P=7.9x10^{-5}$), compared with nonsmokers. In men, past smokers had significantly higher body weights ($P=2.7x10^{-6}$), BMI (P=0.0006), waist

Table II. Comparisons of metabolic parameters among current smokers, past smokers, and nonsmokers in men and women.

A, Men

Variable	Current smokers	Past smokers	Nonsmokers	P-value[a]	P-value[b]
Subjects, n	1,156	1,251	894		
Age, years	50.9±12.0	56.6±12.2	54.3±15.2		
Daily consumption, cigarettes per day	19.0±8.6[c]	22.1±11.4[d]			
Duration of smoking habit, years	28.8±11.3[e]	22.1±11.6[f]			
Body weight, kg	67.5±11.9	67.4±10.7	65.8±10.9	0.1077	$2.7x10^{-6}$
Body mass index, kg/m^2	23.4±3.5	23.8±3.2	23.4±3.3	0.8567	0.0006
Waist circumference, cm	82.7±9.0	83.5±8.3	81.9±8.7	0.0477	0.0002
Systolic blood pressure, mmHg	119.1±15.5	124.5±15.4	122.9±15.7	$4.6x10^{-5}$	0.1568
Diastolic blood pressure, mmHg	75.4±12.4	78.9±11.4	76.9±12.4	0.0647	0.0003
Serum triglycerides, mmol/l	1.59±1.16	1.46±1.01	1.24±0.73	$7.8x10^{-15}$	$5.7x10^{-8}$
Serum HDL-cholesterol, mmol/l	1.43±0.37	1.56±0.42	1.55±0.39	$1.3x10^{-11}$	0.4316
Serum LDL-cholesterol, mmol/l	3.18±0.86	3.21±0.77	3.18±0.77	0.6802	0.2247
Fasting plasma glucose, mmol/l	5.75±1.40	5.83±1.27	5.65±1.00	0.0180	0.0021
Blood glycosylated hemoglobin, %	5.78±0.90	5.74±0.74	5.70±0.63	0.0014	0.4516
Serum uric acid, μmol/l	366.2±78.4	371.8±78.3	359.0±76.5	0.0955	0.0002
Serum creatinine, μmol/l	73.0±12.6	77.2±18.8	76.9±14.2	$2.6x10^{-7}$	0.8858
eGFR, ml/min/1.73 m^{-2}	80.1±14.7	74.0±14.6	74.7±15.6	$1.5x10^{-6}$	0.8169

B, Women

Variable	Current smokers	Past smokers	Nonsmokers	P-value[a]	P-value[b]
Subjects, n	146	167	2,345		
Age, years	45.8±11.8	48.2±11.1	55.0±12.2		
Daily consumption, cigarettes per day	12.9±5.5[c]	13.0±7.1[d]			
Duration of smoking habit, years	19.5±9.8[e]	14.3±9.3[f]			
Body weight, kg	56.9±11.5	53.4±8.3	53.3±8.4	0.0003	0.4382
Body mass index, kg/m^2	22.7±4.3	21.7±3.0	22.2±3.3	0.0046	0.3784
Waist circumference, cm	78.6±9.8	76.4±8.4	77.6±9.1	0.0049	0.6784
Systolic blood pressure, mmHg	113.7±13.8	113.0±14.7	119.1±16.0	0.7554	0.0428
Diastolic blood pressure, mmHg	69.9±11.4	70.0±11.4	71.5±11.3	0.8556	0.6562
Serum triglycerides, mmol/l	1.09±0.58	1.02±0.62	1.03±0.55	0.0003	0.1072
Serum HDL-cholesterol, mmol/l	1.74±0.43	1.85±0.42	1.85±0.44	$7.9x10^{-5}$	0.4955
Serum LDL-cholesterol, mmol/l	2.99±0.83	3.00±0.78	3.18±0.79	0.4680	0.2080
Fasting plasma glucose, mmol/l	5.30±1.06	5.32±0.84	5.33±0.78	0.1543	0.1400
Blood glycosylated hemoglobin, %	5.57±0.51	5.56±0.65	5.63±0.51	0.2508	0.5529
Serum uric acid, μmol/l	278.4±68.2	273.9±58.9	271.2±59.4	0.0038	0.0385
Serum creatinine, μmol/l	54.0±9.9	55.9±7.5	55.8±10.5	0.4956	0.2285
eGFR, ml/min/1.73 m^{-2}	85.0±16.4	80.0±14.0	78.1±15.2	0.1232	0.0658

Data are presented as means ± standard deviation. Categorical variables were compared using the χ^2 test; multivariable regression analysis was performed after adjustment for age; P<0.0009 was considered to indicate a statistically significant difference. [a]Comparison between current smokers and nonsmokers; [b]comparison between past smokers and nonsmokers. Daily consumption of cigarettes and duration of smoking habit were compared between men and women in current or past smokers by Mann-Whitney U test (due to variables with skewed distribution); [c]$P<1.0x10^{-61}$; [d]$P<1.0x10^{-61}$; [e]$P<1.0x10^{-61}$; [f]$P=4.9x10^{-13}$. eGFR (m/min/1.73 m^2) = 194 x [age (years)]$^{-0.287}$ x [serum creatinine (mg/dl)]$^{-1.094}$ (x 0.739 for female). HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate.

circumference (P=0.0002), and DBP (P=0.0003), as well as higher serum concentrations of triglycerides ($P=5.7x10^{-8}$) and uric acid (P=0.0002), compared with nonsmokers.

Subsequently, a battery of metabolic parameters was compared following adjustment for age between smokers and nonsmokers who did not take any medications for hypertension,

Table III. Comparisons of metabolic parameters between (current or past) smokers and nonsmokers among men and women not on medications for hypertension, dyslipidemia, type 2 diabetes mellitus or hyperuricemia.

A, Men

Metabolic parameters	Current smokers	Past smokers	Nonsmokers	P-value[a]	P-value[b]
Individuals not on antihypertensive medications					
Subjects, n	946	861	665		
Systolic blood pressure, mmHg	117.1±15.0	121.5±14.8	120.6±15.3	$3.1x10^{-5}$	0.8965
Diastolic blood pressure, mmHg	74.1±12.0	77.6±11.3	75.9±12.1	0.0083	0.0248
Individuals not on antidyslipidemic medications					
Subjects, n	1,019	1,016	725		
Serum triglycerides, mmol/l	1.55±1.13	1.43±1.04	1.19±0.68	$3.3x10^{-14}$	$3.1x10^{-8}$
Serum HDL-cholesterol, mmol/l	1.45±0.38	1.58±0.43	1.56±0.39	$6.3x10^{-9}$	0.2799
Serum LDL-cholesterol, mmol/l	3.18±0.86	3.26±0.77	3.21±0.75	0.4909	0.1459
Individuals not on antidiabetic medications					
Subjects, n	1,067	1,127	805		
Fasting plasma glucose, mmol/l	5.56±0.90	5.64±1.00	5.50±0.60	0.0306	0.0009
Subjects, n	636	831	608		
Blood glycosylated hemoglobin, %	5.62±0.50	5.62±0.62	5.60±0.43	0.0227	0.5270
Individuals not on uric acid-lowering medications					
Subjects, n	1,018	1,136	761		
Serum uric acid, μmol/l	364.8±76.7	370.5±77.6	358.7±76.2	0.1638	0.0007

B, Women

Metabolic parameters	Current smokers	Past smokers	Nonsmokers	P-value[a]	P-value[b]
Individuals not on antihypertensive medications					
Subjects, n	130	149	1,868		
Systolic blood pressure, mmHg	112.2±13.2	111.0±13.4	116.1±15.0	0.8657	0.0265
Diastolic blood pressure, mmHg	69.1±11.4	68.7±10.8	70.1±11.0	0.8412	0.4739
Individuals not on antidyslipidemic medications					
Subjects, n	135	150	1,870		
Serum triglycerides, mmol/l	1.09±0.59	0.96±0.61	0.97±0.51	$8.3x10^{-6}$	0.1883
Serum HDL-cholesterol, mmol/l	1.74±0.43	1.89±0.42	1.88±0.44	$6.5x10^{-5}$	0.8397
Serum LDL-cholesterol, mmol/l	2.99±0.82	2.96±0.78	3.21±0.80	0.5661	0.0602
Individuals not on antidiabetic medications					
Subjects, n	144	159	2,238		
Fasting plasma glucose, mmol/l	5.27±1.04	5.21±0.53	5.25±0.61	0.0467	0.5654
Subjects, n	84	121	1,862		
Blood glycosylated hemoglobin, %	5.52±0.39	5.45±0.37	5.58±0.43	0.3485	0.2502
Individuals not on uric acid-lowering medications					
Subjects, n	130	153	2,109		
Serum uric acid, μmol/l	278.4±68.2	273.1±58.2	271.0±59.3	0.0034	0.0556

Data are presented as means ± standard deviation. Multivariable regression analysis was performed after adjustment for age; P<0.0009 was considered to indicate a statistically significant difference. [a]Comparison between current smokers and nonsmokers; [b]comparison between past smokers and nonsmokers. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

dyslipidemia, T2DM or hyperuricemia. In men who were not taking antihypertensive agents, SBP was significantly lower in current smokers than nonsmokers ($P=3.1x10^{-5}$; Table III). In men not taking any lipid-lowering medications, serum triglyceride concentrations were significantly higher ($P=3.3x10^{-14}$) and serum HDL-cholesterol concentration was significantly

Table IV. Results of multivariable logistic regression analysis of smoking status and prevalence of common diseases in men and women.

A, Men

	Current smokers		Past smokers	
Common disease	Odds ratio (95% confidence interval)	P-value	Odds ratio (95% confidence interval)	P-value
Hypertension	0.83 (0.68-1.01)	0.0650	1.19 (0.99-1.44)	0.0685
Type 2 diabetes mellitus	1.33 (1.02-1.73)	0.0381	1.22 (0.95-1.57)	0.1184
Dyslipidemia	1.81 (1.50-2.19)	$6.3x10^{-10}$	1.68 (1.39-2.01)	$3.6x10^{-8}$
Hypertriglyceridemia	2.39 (1.99-2.88)	$2.3x10^{-20}$	1.85 (1.54-2.21)	$2.3x10^{-11}$
Hypo-HDL-cholesterolemia	2.14 (1.68-2.76)	$2.0x10^{-9}$	1.40 (1.09-1.81)	0.0086
Hyper-LDL-cholesterolemia	1.23 (1.03-1.46)	0.0251	1.43 (1.20-1.70)	$5.5x10^{-5}$
Obesity	1.11 (0.92-1.34)	0.2695	1.33 (1.11-1.60)	0.0019
Metabolic syndrome	1.61 (1.25-2.09)	0.0003	1.71 (1.32-2.21)	$4.2x10^{-5}$
Chronic kidney disease	0.54 (0.40-0.72)	$4.4x10^{-5}$	0.93 (0.73-1.18)	0.5476
Hyperuricemia	1.14 (0.93-1.41)	0.2173	1.37 (1.12-1.67)	0.0002

B, Women

	Current smokers		Past smokers	
Common disease	Odds ratio (95% confidence interval)	P-value	Odds ratio (95% confidence interval)	P-value
Hypertension	1.05 (0.66-1.65)	0.8230	0.64 (0.40-1.00)	0.0556
Type 2 diabetes mellitus	1.24 (0.54-2.50)	0.5718	1.36 (0.67-2.49)	0.3592
Dyslipidemia	1.05 (0.72-1.53)	0.8052	0.85 (0.59-1.20)	0.3540
Hypertriglyceridemia	1.56 (1.00-2.38)	0.0445	1.18 (0.76-1.78)	0.4359
Hypo-HDL-cholesterolemia	1.57 (0.59-3.45)	0.3066	0.83 (0.25-2.05)	0.7259
Hyper-LDL-cholesterolemia	0.75 (0.51-1.10)	0.1453	0.88 (0.62-1.24)	0.4748
Obesity	1.77 (1.21-2.56)	0.0030	0.96 (0.64-1.42)	0.8532
Metabolic syndrome	1.90 (1.10-3.20)	0.0180	0.65 (0.36-1.12)	0.1292
Chronic kidney disease	0.87 (0.37-1.86)	0.7398	0.76 (0.33-1.52)	0.4781
Hyperuricemia	2.24 (0.65-5.84)	0.1395	2.30 (0.77-5.56)	0.0904

Multivariable logistic regression analysis was performed after adjustment for age; P<0.0009 was considered to indicate a statistically significant difference. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

lower ($P=6.3x10^{-9}$) in current smokers than nonsmokers, whereas past smokers exhibited higher serum triglyceride concentrations compared with nonsmokers ($P=3.1x10^{-8}$). Fasting plasma glucose level (P=0.0009) and serum uric acid concentration (P=0.0007) were also higher in past smokers than nonsmokers in men not taking any medications for T2DM or hyperuricemia. In women not taking any lipid-lowering medications, serum triglyceride concentrations ($P=8.3x10^{-6}$) and serum HDL-cholesterol concentrations ($P=6.5x10^{-5}$) were significantly higher and lower, respectively, in current smokers than nonsmokers.

Smoking and the prevalence of common diseases. Multivariable logistic regression analysis following adjustment for age identified current smoking to be significantly associated with the prevalence of dyslipidemia [$P=6.3x10^{-10}$; odds ratio (OR), 1.81], hypertriglyceridemia ($P=2.3x10^{-20}$; OR, 2.39), hypo-HDL-cholesterolemia ($P=2.0x10^{-9}$; OR, 2.14), MetS (P=0.0003; OR 1.61), and CKD ($P=4.4x10^{-5}$; OR, 0.54) in men (Table IV). Past smoking was significantly associated with dyslipidemia ($P=3.6x10^{-8}$; OR, 1.68), hypertriglyceridemia ($P=2.3x10^{-11}$; OR, 1.85), hyper-LDL-cholesterolemia ($P=5.5x10^{-5}$; OR, 1.43), MetS ($P=4.2x10^{-5}$; OR, 1.71), and hyperuricemia (P=0.0002; OR, 1.37) in men. In women, neither current nor past smoking was associated with any common diseases.

Subsequently, a stepwise forward selection procedure was performed to examine the effects of smoking and age on various common diseases that were found to be associated with smoking by multivariable logistic regression analysis. The analysis found current smoking to be a significant (P<0.0009) and independent determinant of dyslipidemia,

Table V. Effects of smoking on various metabolic disorders in men determined by a stepwise forward selection procedure.

A, Current smokers vs. nonsmokers

Disease	Variable	R^2	P-value
Dyslipidemia	Age	0.0121	$3.8x10^{-10}$
	Smoking	0.0147	$6.3x10^{-10}$
Hypertriglyceridemia	Age	0.0292	0.0007
	Smoking	0.0041	$2.3x10^{-20}$
Hypo-HDL-cholesterolemia	Age	0.0183	0.0117
	Smoking	0.0034	$2.0x10^{-9}$
Metabolic syndrome	Age	0.0534	$1.4x10^{-18}$
	Smoking	0.0089	0.0003
Chronic kidney disease	Age	0.2096	$3.3x10^{-45}$
	Smoking	0.0107	$4.4x10^{-5}$

B, Past smokers vs. nonsmokers

Disease	Variable	R^2	P-value
Dyslipidemia	Age	0.0112	$3.9x10^{-8}$
	Smoking	0.0132	$3.6x10^{-8}$
Hypertriglyceridemia	Age	0.0016	0.0312
	Smoking	0.0166	$2.3x10^{-11}$
Hyper-LDL-cholesterolemia	Age	NA	0.4028
	Smoking	0.0058	$3.9x10^{-5}$
Metabolic syndrome	Age	0.0659	$3.6x10^{-19}$
	Smoking	0.0109	$4.2x10^{-5}$
Hyperuricemia	Age	0.0011	0.1046
	Smoking	0.0038	0.0020

P<0.0009 was considered to indicate a statistically significant difference. R^2, contribution rate; NA, not applicable; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

hypertriglyceridemia, hypo-HDL-cholesterolemia, MetS, and CKD in men (Table V). Past smoking was also a significant (P<0.0009) and independent determinant of dyslipidemia, hypertriglyceridemia, hyper-LDL-cholesterolemia and MetS in men.

Comparisons between heavy and light smokers. The differences in various metabolic parameters were compared between the light and heavy current smokers. The percentage of males ($P=2.0x10^{-15}$), number of cigarettes smoked per day ($P<1.0x10^{-61}$), and duration of smoking habit ($P=2.0x10^{-10}$) were significantly higher in heavy smokers than light smokers (Table VI). Analysis following adjustment for age and sex demonstrated that body weight (P=0.0005), BMI ($P=3.7x10^{-6}$), waist circumference ($P=5.3x10^{-6}$), and serum concentration of triglycerides (P=0.0009) were significantly higher in heavy smokers than in light smokers, whereas serum concentrations of HDL-cholesterol were significantly lower in heavy smokers than in light nonsmokers ($P=4.4x10^{-5}$).

Discussion

In the present study, the association of smoking with the prevalence of various common diseases and metabolic parameters was examined in community-dwelling Japanese individuals. This cross-sectional study demonstrated that smoking was significantly associated with higher serum triglyceride concentrations and lower HDL-cholesterol concentrations in men and women. Additionally, smoking correlated significantly with lower serum creatinine concentrations and SBP, as well as higher eGFR in men and with higher body weight in women. The current results demonstrated that smoking is significantly associated with the prevalence of dyslipidemia, hypertriglyceridemia, hypo-HDL-cholesterolemia, MetS, and CKD in men, although not in women. Furthermore, heavy smoking was associated with significantly greater serum triglyceride concentrations and reduced serum HDL-cholesterol concentrations, as well as increased body weight, BMI, and waist circumference compared with light smokers.

The association between smoking and serum lipids has been reported in numerous studies since the 1980s (9,21,22). These studies demonstrated that smoking decreased serum HDL-cholesterol levels and increased serum triglyceride and LDL-cholesterol levels. Furthermore, passive smoking was demonstrated to be associated with low HDL-cholesterol levels in children (23). A meta-analysis of cross-sectional studies indicated that smokers had increased serum concentrations of total cholesterol (3.0%), triglycerides (9.1%), very-LDL cholesterol (10.4%), and LDL-cholesterol (1.7%) and lower serum concentrations of HDL-cholesterol (-5.7%) and apolipoprotein A1 (-4.2%), compared with nonsmokers (9). The studies also demonstrated a dose-response association between the quantity of cigarette smoking and the extent of lipid abnormalities. The present findings are consistent with the above-mentioned previous reports. In addition, the current study indicated that past smoking is associated with dyslipidemia and hypertriglyceridemia in men. Cessation of smoking is reported to have relatively limited effects on lipid profiles (24,25). A meta-analysis showed that smoking cessation led to increased serum concentration of HDL-cholesterol, but no significant improvement in serum triglycerides and LDL-cholesterol (25).

The mechanisms by which cigarette smoking alters serum lipid profiles are not fully understood. One popular theory is that nicotine stimulates the secretion of catecholamines, as well as other hormones (cortisol and growth hormones), leading to increased serum concentrations of free fatty acids, which stimulate hepatic secretion of very LDL and triglycerides (26). Other proposed explanations include smoking-induced increases in cholesteryl ester transfer protein, reduction of lectin cholesterol acyltransferase activity, and alteration of apolipoprotein A1 synthesis, resulting in changes in serum lipid profiles (27). As dyslipidemia, including hypertriglyceridemia and hypo-HDL-cholesterolemia, is important in the pathogenesis of atherosclerosis, smoking may accelerate the development of CVDs indirectly via its detrimental effects on serum lipid profiles. Smoking was also reported to induce qualitative changes in serum lipids (28-30). Excess free radicals and oxidants present in cigarette smoke, as well as endogenously produced oxidants and radicals, enhance

Table VI. Comparison of metabolic parameters between light and heavy smokers.

Variable	Light smokers	Heavy smokers	P-value[a]	P-value[b]
Subjects, n	523	721		
Age, years	48.8±12.1	50.3±11.2	0.0111	-
Sex, male, %	80.5	94.9	$2.0x10^{-15}$	-
Daily consumption, cigarettes per day	11.0±3.7	23.6±7.1	$<1.0x10^{-61}$	-
Duration of smoking habit, years	25.2±12.2	29.5±10.7	$2.0x10^{-10}$	-
Body weight, kg	64.6±11.8	68.2±12.3	$6.3x10^{-7}$	0.0005
Body mass index, kg/m^2	22.9±3.5	23.9±3.7	$1.7x10^{-7}$	$3.7x10^{-6}$
Waist circumference, cm	80.6±8.8	83.5±9.3	$7.8x10^{-9}$	$5.3x10^{-6}$
Systolic blood pressure, mmHg	117.1±15.2	119.3±15.5	0.0067	0.1788
Diastolic blood pressure, mmHg	73.8±12.4	75.7±12.4	0.0107	0.1612
Serum triglycerides, mmol/l	1.38±0.99	1.67±1.22	$1.5x10^{-9}$	0.0009
Serum HDL-cholesterol, mmol/l	1.54±0.40	1.41±0.37	$2.2x10^{-9}$	$4.4x10^{-5}$
Serum LDL-cholesterol, mmol/l	3.13±0.88	3.17±0.83	0.1935	0.8931
Fasting plasma glucose, mmol/l	5.57±1.37	5.79±1.41	$1.1x10^{-5}$	0.0736
Blood glycosylated hemoglobin, %	5.67±0.85	5.84±0.92	$4.3x10^{-5}$	0.0899
Serum uric acid, μmol/l	348.4±86.5	361.9±78.9	0.0070	0.8480
Serum creatinine, μmol/l	69.5±13.6	71.8±12.4	0.0032	0.4383
eGFR, ml/min/1.73 m^{-2}	81.2±15.1	80.6±14.4	0.6302	0.5820

Data are presented as means ± standard deviation. [a]Categorical variables were compared by the χ^2 test; continuous variables were compared by the Mann-Whitney U test (due to skewed distribution); [b]multivariable regression analysis was performed after adjustment for age and sex; P<0.0009 was considered to indicate a statistically significant difference. eGFR (m/min/1.73 m^2) = 194 x [age (years)]$^{-0.287}$ x [serum creatinine (mg/dl)]$^{-1.094}$ (x 0.739 for female). HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate.

the pro-oxidative environment (6,29). It was suggested that peroxynitrite is significant in the oxidative modification of plasma LDL induced by smoking (30). The oxidation of lipids may be another way by which smoking accelerates the development of CVDs.

The current results demonstrated that smoking was significantly associated with reduced SBP in men. However, there are conflicting data regarding the association between smoking and BP. Various studies in the 1970s reported no significant differences in BP between smokers and nonsmokers (31,32), whereas a more recent study demonstrated that BP was significantly increased in elderly male smokers (8). Furthermore, a recent meta-analysis indicated that smoking was associated with lower SBP and DBP, and reduced risk of hypertension in observational analyses, although observational and Mendelian randomization analyses did not support a causal association between heaviness of smoking and BP among current smokers (33). Thus, the association between smoking and hypertension remains elusive.

MetS is a complex disease involving abdominal obesity, impaired glucose tolerance, hypertension and dyslipidemia (20). The associations between MetS and increased risk of CVDs, morbidity, and mortality have been established (34,35). The current results demonstrated that smoking was significantly associated with the prevalence of MetS in Japanese men. In addition, previous studies demonstrated a significant association between smoking and MetS (36,37). Smoking increases the risk of dyslipidemia (9,21,22) and causes glucose intolerance (38), leading to an increased risk of T2DM (10). Furthermore, smoking is associated with central fat accumulation (39,40). These observations indicate that smoking affects multiple components of the diagnostic criteria for MetS and enhances the development of CVDs.

CKD is a risk factor for end-stage renal disease, as well as for CVDs (41). The present study demonstrated that smoking was significantly associated with higher eGFR and lower prevalence of CKD in men. Previous cross-sectional studies also reported that smokers exhibited elevated GFRs compared with nonsmokers (42,43). Smoking causes glucose intolerance (38), whereas higher insulin resistance was demonstrated to be associated with increased GFR (44). These observations indicate that smoking induces a rise in GFR, at least in part, via its effects on glucose intolerance. However, recent longitudinal studies have indicated that smoking is associated with increased long-term risks of reduced GFR, glomerular hyperfiltration and proteinuria (45,46). As smoking increases the risk of T2DM and obesity, it may induce diabetic nephropathy or obesity-associated glomerulopathy, resulting in impaired renal function in the long-term. Other proposed explanations include smoking-induced renal atherosclerosis (47), impaired endothelial function (48), and alterations in systemic and renal hemodynamics (49), resulting in chronic kidney damage.

The current results demonstrated certain differences in the association of smoking with metabolic parameters, and the prevalence of common diseases between men and women. These findings may be associated with differences in the quantity of smoking between the two sexes. Notably,

numerous previous studies revealed sex differences in the effect of smoking on metabolic parameters (50-52). One longitudinal study of non-diabetic individuals demonstrated that smoking was associated with improved insulin sensitivity in women, but reduced insulin sensitivity in men (50). Reed *et al* (51) reported the association of passive smoking with greater BMIs and fasting plasma glucose levels in men, and with reduced HDL-cholesterol levels in women among the Old Order Amish population. In late adolescence, passive smoking was also associated with lower HDL-cholesterol in girls, demonstrating a sex difference in the findings (52). Furthermore, Ahonen *et al* (53) reported the different association of smoking with subclinical inflammation between sexes, with a decreased adiponectin level in women, but increased high-sensitivity C-reactive protein levels in men. Smoking is reported to be associated with lower estrogen concentrations in women (54), whereas estrogen deficiency promotes metabolic dysfunction, and predisposes individuals to obesity, MetS and T2DM (55). The effects of smoking on sex hormones may be one explanation by which smoking affects metabolic parameters with sex differences. However, the molecular mechanism underlying the observed sex differences in the effects of smoking on metabolic parameters has not been elucidated.

There were various limitations of the present study: i) As the results of the present study were not replicated, validation of the findings is required by other independent subject panels; ii) based upon the cross-sectional study design, causalities could not be confirmed; iii) data regarding other daily habits, including diet, alcohol consumption and exercise, were not evaluated and these certainly affect various metabolic parameters; iv) given that the percentages of current and past smokers were low in women (current smokers, 5.5%; past smokers, 6.3%), the statistical power may not be enough to estimate certain metabolic parameters or common diseases.

In conclusion, the current cross-sectional study demonstrated that smoking was significantly associated with various metabolic abnormalities and the prevalence of common diseases in Japanese individuals, with certain sex differences. These observations indicate that smoking affects multiple metabolic parameters, and potentially accelerates the development of CVDs with certain sex differences.

Acknowledgements

The present study was supported by CREST (grant no. JPMJCR1302) of the Japan Science and Technology Agency, and by the Japan Society for the Promotion of Science KAKENHI (grant no. JP15H04772).

References

1. Yanbaeva DG, Dentener MA, Creutzberg EC, Wesseling G and Wouters EF: Systemic effects of smoking. Chest 131: 1557-1566, 2007.
2. Edwards R: The problem of tobacco smoking. BMJ 328: 217-219, 2004.
3. World Health Organization (WHO): World Health Report 2002: Reducing Risks, Promoting Healthy Life. http://www.who.int/whr/2002/en/summary_riskfactors_chp4.pdf.
4. World Health Organization (WHO): WHO Global Report On Trends In Prevalence Of Tobacco Smoking 2015. http://apps.who.int/iris/bitstream/10665/156262/1/9789241564922_eng.pdf.
5. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Després JP, Fullerton HJ, Howard VJ, *et al*; American Heart Association Statistics Committee and Stroke Statistics Subcommittee: Heart disease and stroke statistics - 2015 update: A report from the American Heart Association. Circulation 131: e29-e322, 2015.
6. Messner B and Bernhard D: Smoking and cardiovascular disease: Mechanisms of endothelial dysfunction and early atherogenesis. Arterioscler Thromb Vasc Biol 34: 509-515, 2014.
7. Burns DM: Cigarettes and cigarette smoking. Clin Chest Med 12: 631-642, 1991.
8. Primatesta P, Falaschetti E, Gupta S, Marmot MG and Poulter NR: Association between smoking and blood pressure: Evidence from the health survey for England. Hypertension 37: 187-193, 2001.
9. Craig WY, Palomaki GE and Haddow JE: Cigarette smoking and serum lipid and lipoprotein concentrations: An analysis of published data. BMJ 298: 784-788, 1989.
10. Willi C, Bodenmann P, Ghali WA, Faris PD and Cornuz J: Active smoking and the risk of type 2 diabetes: A systematic review and meta-analysis. JAMA 298: 2654-2664, 2007.
11. Yamada Y, Matsui K, Takeuchi I, Oguri M and Fujimaki T: Association of genetic variants with hypertension in a longitudinal population-based genetic epidemiological study. Int J Mol Med 35: 1189-1198, 2015.
12. Yamada Y, Matsui K, Takeuchi I, Oguri M and Fujimaki T: Association of genetic variants of the α-kinase 1 gene with type 2 diabetes mellitus in a longitudinal population-based genetic epidemiological study. Biomed Rep 3: 347-354, 2015.
13. Yamada Y, Matsui K, Takeuchi I and Fujimaki T: Association of genetic variants with dyslipidemia and chronic kidney disease in a longitudinal population-based genetic epidemiological study. Int J Mol Med 35: 1290-1300, 2015.
14. Yamada Y, Matsui K, Takeuchi I and Fujimaki T: Association of genetic variants with coronary artery disease and ischemic stroke in a longitudinal population-based genetic epidemiological study. Biomed Rep 3: 413-419, 2015.
15. Perloff D, Grim C, Flack J, Frohlich ED, Hill M, McDonald M and Morgenstern BZ: Human blood pressure determination by sphygmomanometry. Circulation 88: 2460-2470, 1993.
16. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N and Roth D; Modification of Diet in Renal Disease Study Group: A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Ann Intern Med 130: 461-470, 1999.
17. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H and Hishida A; Collaborators developing the Japanese equation for estimated GFR: Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 53: 982-992, 2009.
18. National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Am J Kidney Dis 39 (Suppl 1): S1-S266, 2002.
19. Kanazawa M, Yoshiike N, Osaka T, Numba Y, Zimmet P and Inoue S: Criteria and classification of obesity in Japan and Asia-Oceania. World Rev Nutr Diet 94: 1-12, 2005.
20. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM and Smith SC Jr; International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity: Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 120: 1640-1645, 2009.
21. Freedman DS, Srinivasan SR, Shear CL, Hunter SM, Croft JB, Webber LS and Berenson GS: Cigarette smoking initiation and longitudinal changes in serum lipids and lipoproteins in early adulthood: The Bogalusa Heart Study. Am J Epidemiol 124: 207-219, 1986.
22. Nakamura K, Barzi F, Huxley R, Lam TH, Suh I, Woo J, Kim HC, Feigin VL, Gu D and Woodward M; Asia Pacific Cohort Studies Collaboration: Does cigarette smoking exacerbate the effect of total cholesterol and high-density lipoprotein cholesterol on the risk of cardiovascular diseases? Heart 95: 909-916, 2009.

23. Neufeld EJ, Mietus-Snyder M, Beiser AS, Baker AL and Newburger JW: Passive cigarette smoking and reduced HDL cholesterol levels in children with high-risk lipid profiles. Circulation 96: 1403-1407, 1997.
24. Gepner AD, Piper ME, Johnson HM, Fiore MC, Baker TB and Stein JH: Effects of smoking and smoking cessation on lipids and lipoproteins: Outcomes from a randomized clinical trial. Am Heart J 161: 145-151, 2011.
25. Maeda K, Noguchi Y and Fukui T: The effects of cessation from cigarette smoking on the lipid and lipoprotein profiles: A meta-analysis. Prev Med 37: 283-290, 2003.
26. Brischetto CS, Connor WE, Connor SL and Matarazzo JD: Plasma lipid and lipoprotein profiles of cigarette smokers from randomly selected families: Enhancement of hyperlipidemia and depression of high-density lipoprotein. Am J Cardiol 52: 675-680, 1983.
27. Freeman DJ and Packard CJ: Smoking and plasma lipoprotein metabolism. Clin Sci (Lond) 89: 333-342, 1995.
28. Reilly M, Delanty N, Lawson JA and FitzGerald GA: Modulation of oxidant stress in vivo in chronic cigarette smokers. Circulation 94: 19-25, 1996.
29. Solak ZA, Kabaroğlu C, Cok G, Parildar Z, Bayindir U, Ozmen D and Bayindir O: Effect of different levels of cigarette smoking on lipid peroxidation, glutathione enzymes and paraoxonase 1 activity in healthy people. Clin Exp Med 5: 99-105, 2005.
30. Yamaguchi Y, Haginaka J, Morimoto S, Fujioka Y and Kunitomo M: Facilitated nitration and oxidation of LDL in cigarette smokers. Eur J Clin Invest 35: 186-193, 2005.
31. Berglund G and Wilhelmsen L: Factors related to blood pressure in a general population sample of Swedish men. Acta Med Scand 198: 291-298, 1975.
32. Seltzer CC: Effect of smoking on blood pressure. Am Heart J 87: 558-564, 1974.
33. Linneberg A, Jacobsen RK, Skaaby T, Taylor AE, Fluharty ME, Jeppesen JL, Bjorngaard JH, Åsvold BO, Gabrielsen ME, Campbell A, *et al*: Effect of smoking on blood pressure and resting heart rate: A Mendelian randomization meta-analysis in the CARTA Consortium. Circ Cardiovasc Genet 8: 832-841, 2015.
34. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J and Salonen JT: The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 288: 2709-2716, 2002.
35. Ninomiya JK, L'Italien G, Criqui MH, Whyte JL, Gamst A and Chen RS: Association of the metabolic syndrome with history of myocardial infarction and stroke in the Third National Health and Nutrition Examination Survey. Circulation 109: 42-46, 2004.
36. Ishizaka N, Ishizaka Y, Toda E, Hashimoto H, Nagai R and Yamakado M: Association between cigarette smoking, metabolic syndrome, and carotid arteriosclerosis in Japanese individuals. Atherosclerosis 181: 381-388, 2005.
37. Park HS, Oh SW, Cho SI, Choi WH and Kim YS: The metabolic syndrome and associated lifestyle factors among South Korean adults. Int J Epidemiol 33: 328-336, 2004.
38. Houston TK, Person SD, Pletcher MJ, Liu K, Iribarren C and Kiefe CI: Active and passive smoking and development of glucose intolerance among young adults in a prospective cohort: CARDIA study. BMJ 332: 1064-1069, 2006.
39. Canoy D, Wareham N, Luben R, Welch A, Bingham S, Day N and Khaw KT: Cigarette smoking and fat distribution in 21,828 British men and women: A population-based study. Obes Res 13: 1466-1475, 2005.
40. Chiolero A, Faeh D, Paccaud F and Cornuz J: Consequences of smoking for body weight, body fat distribution, and insulin resistance. Am J Clin Nutr 87: 801-809, 2008.
41. Go AS, Chertow GM, Fan D, McCulloch CE and Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 351: 1296-1305, 2004.
42. Yoon HJ, Park M, Yoon H, Son KY, Cho B and Kim S: The differential effect of cigarette smoking on glomerular filtration rate and proteinuria in an apparently healthy population. Hypertens Res 32: 214-219, 2009.
43. Ishizaka N, Ishizaka Y, Toda E, Shimomura H, Koike K, Seki G, Nagai R and Yamakado M: Association between cigarette smoking and chronic kidney disease in Japanese men. Hypertens Res 31: 485-492, 2008.
44. Dengel DR, Goldberg AP, Mayuga RS, Kairis GM and Weir MR: Insulin resistance, elevated glomerular filtration fraction, and renal injury. Hypertension 28: 127-132, 1996.
45. Shankar A, Klein R and Klein BE: The association among smoking, heavy drinking, and chronic kidney disease. Am J Epidemiol 164: 263-271, 2006.
46. Yamagata K, Ishida K, Sairenchi T, Takahashi H, Ohba S, Shiigai T, Narita M and Koyama A: Risk factors for chronic kidney disease in a community-based population: A 10-year follow-up study. Kidney Int 71: 159-166, 2007.
47. Nicholson JP, Teichman SL, Alderman MH, Sos TA, Pickering TG and Laragh JH: Cigarette smoking and renovascular hypertension. Lancet 2: 765-766, 1983.
48. Blann AD and McCollum CN: Adverse influence of cigarette smoking on the endothelium. Thromb Haemost 70: 707-711, 1993.
49. Ritz E, Benck U, Franek E, Keller C, Seyfarth M and Clorius J: Effects of smoking on renal hemodynamics in healthy volunteers and in patients with glomerular disease. J Am Soc Nephrol 9: 1798-1804, 1998.
50. Onat A, Can G, Ciçek G, Doğan Y, Kaya H, Gümrükçüoğlu HA and Yüksel H: Diverging sex-specific long-term effects of cigarette smoking on fasting insulin and glucose levels in non-diabetic people. Clin Biochem 45: 37-42, 2012.
51. Reed RM, Dransfield MT, Eberlein M, Miller M, Netzer G, Pavlovich M, Pollin TI, Scharf SM, Shuldiner AR, Sin D and Mitchell BD: Gender differences in first and secondhand smoke exposure, spirometric lung function and cardiometabolic health in the old order Amish: A novel population without female smoking. PLoS One 12: e0174354, 2017.
52. Le-Ha C, Beilin LJ, Burrows S, Huang RC, Oddy WH, Hands B and Mori TA: Gender difference in the relationship between passive smoking exposure and HDL-cholesterol levels in late adolescence. J Clin Endocrinol Metab 98: 2126-2135, 2013.
53. Ahonen TM, Kautiainen HJ, Keinänen-Kiukaanniemi SM, Kumpusalo EA and Vanhala MJ: Gender difference among smoking, adiponectin, and high-sensitivity C-reactive protein. Am J Prev Med 35: 598-601, 2008.
54. Soldin OP, Makambi KH, Soldin SJ and O'Mara DM: Steroid hormone levels associated with passive and active smoking. Steroids 76: 653-659, 2011.
55. Mauvais-Jarvis F, Clegg DJ and Hevener AL: The role of estrogens in control of energy balance and glucose homeostasis. Endocr Rev 34: 309-338, 2013.