# Association between Secondhand Smoke Exposure and Metabolic Syndrome in 118,609 Korean Never Smokers Verified by Self-Reported Questionnaire and Urine Cotinine

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**Background:** No study has reported the association between secondhand smoke (SHS) exposure and metabolic syndrome (MetS) in self-reported never smokers verified by both self-reported questionnaire and urine cotinine.

**Methods:** A total of 118,609 self-reported and cotinine-verified never smokers (38,385 male; age 34.8±7.1 years) who participated in the Kangbuk Samsung Health Study between 2011 and 2016 were included. Cotinine-verified never smokers were defined as individuals with urinary cotinine <50 ng/mL. SHS exposure was defined as current exposure to passive smoking indoors at home or workplace.

**Results:** Prevalence of SHS exposure in the overall population was 22.6% (27.4% for males and 20.3% for females ($P<0.001$). The overall prevalence of MetS was 6.8% and was higher in males than in females (10.7% vs. 4.9%, $P<0.001$). In both genders, MetS prevalence was higher in the SHS exposure group than the non-SHS exposure group (11.3% vs. 10.4%, $P=0.010$ for males; 5.8% vs. 4.6%, $P<0.001$ for females). However, there was significant gender interaction for the association between SHS exposure and MetS ($P$ for interaction=0.010). In the multivariate regression analyses, SHS exposure was associated with increased MetS odds only in females (odds ratio [95% confidence interval], 1.02 [0.94 to 1.11] in male vs. 1.17 [1.06 to 1.29] in female). In particular, females with SHS exposure of ≥1 hour/day and ≥3 times showed increased odds of MetS compared with those without SHS exposure (1.22 [1.02 to 1.45], 1.30 [1.14 to 1.49]).

**Conclusion:** This cross-sectional study showed that SHS exposure was significantly associated with prevalence of MetS in self-reported and cotinine-verified female never smokers.

**Keywords:** Tobacco products; Cotinine; Metabolic syndrome; Smoking; Surveys and questionnaires

## INTRODUCTION

Cigarette smoking is a global, social, and medical hazard known as a strong risk factor for many cardiovascular and metabolic diseases including obesity, hypertension, dyslipidemia, and diabetes mellitus [1-4]. Of many toxic chemical constituents of

cigarettes, nicotine is associated with high blood pressure, dyslipidemia, and insulin resistance through various pathophysiologic means including increased sympathetic tone, accumulation of abdominal fat and inflammation of pancreatic beta cells. All the above factors are the components of metabolic syndrome (MetS) [5-7]. Secondhand smoke (SHS) is also a public health problem accounting for 0.6 million deaths and approximately 1% of the global disease burden [8]. In Korea, even though SHS exposure prevalence has declined since 2005 due to various national health policies, overall indoor SHS exposure at the workplace and home in adults over 19 years of age is still 17.4%. The indoor SHS prevalence is higher in males than in females (19.6% in males vs. 14.8% in females) [9].

Accurate evaluation of actual smoking status is critical to assess the effects of cigarette smoking and SHS. However, several previous studies, which assessed impacts of cigarette smoking using standardized self-reported questionnaires, reported underestimation of actual smoking prevalence as some current or former smoking respondents accidentally or purposely responded to the questionnaires incorrectly as never smokers [10,11]. Cotinine is a biological metabolite of nicotine that can be measured in serum, saliva, or urine [12]. Urinary cotinine is a non-invasive biomarker with a half-life of 12 to 20 hours. Based on the presence of this biomarker in the urine, differentiation between never and current smokers can be achieved with a cut-off value of 50 ng/mL with high sensitivity and specificity [13-15].

As cigarette smoking is known to cause various metabolic dysfunctions associated with key components of MetS, we hypothesized that SHS exposure may also be associated with MetS [5-7]. To the best of our knowledge, there exists no study on the assessment of the association between SHS exposure in adults over 19 years of age and MetS in the Asian population. Therefore, this large cross-sectional study involving 118,609 Korean adults was conducted to evaluate the association between SHS exposure and MetS among self-reported and urinary cotinine-verified never smokers according to gender.

## METHODS

### Study population
Between 2011 and 2016, 134,231 self-reported never smokers from the Kangbuk Samsung Health Study (KSHS) were initially enrolled in the study. Among them, 2,497 were excluded due to presence of urinary cotinine over 50 ng/mL, five were excluded due to missing urinary cotinine data and 13,130 were excluded due to missing waist circumference (WC) data. Finally,

118,609 self-reported and cotinine-verified never smokers with urinary cotinine <50 ng/mL (38,385 male; age 34.8±7.1 years) were enrolled in this study (Supplemental Fig. S1).

KSHS is an ongoing cohort study since 2002 including Koreans over 18 years of age, who have received comprehensive annual or biennial examinations at Total Healthcare Centers of Kangbuk Samsung Hospital. Written informed consent by the patients was waived due to a retrospective nature of our study. This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital (IRB No: 2020-06-002).

### Anthropometry and laboratory tests
A self-reported questionnaire was used to record underlying medical history including MetS, hypertension, and diabetes mellitus. Information on baseline smoking status (never, former, current smoking), status of current indoor SHS exposure at home or workplace, daily time of indoor SHS exposure (approximate hour and minute), weekly frequency of indoor SHS exposure (times per week), and total duration of indoor SHS exposure (approximate years and months). Information about the percentage of individuals who consumed alcohol more than 3 times per week and exercised more more than 5 times per week was also collected.

WC was measured at mid-level between the lowest rib and iliac crest. Body mass index (BMI) was calculated as weight (kilogram) divided by height (square meter). Systolic and diastolic blood pressures were measured by the hospital's registered nurse using a standardized sphygmomanometer.

Laboratory measurements including blood glucose, hemoglobin A1c (HbA1c), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglyceride (TG), high-sensitivity C-reactive protein (hsCRP), blood urea nitrogen (BUN), and uric acid were measured with an automated chemistry analyzer (Modular DPP, Roche Diagnostics, Tokyo, Japan) after at least 10 hours of the fasting period. Serum creatinine level was measured with Modular D2400 (Roche Diagnostics). Insulin resistance was defined using 'homeostatic model assessment of insulin resistance' (HOMA-IR)=[fasting blood glucose (mmol/L)×fasting insulin (μIU/mL)]/22.5. Insulin secretory function was defined using 'homeostatic model assessment of β cell function' (HOMA-β)=[20×fasting insulin (μIU/mL)/fasting blood glucose (mmol/mL)−3.5]. Urinary cotinine was measured after at least 10 hours of the smoking free period using DRI Cotinine Assay (Microgenics, Fremont, CA, USA) and Modular P800 (Roche Diagnostics).

## Definition of metabolic syndrome

MetS was defined according to the joint interim statement issued in 2009 [16]. MetS was defined as having three or more of the following: (1) WC >90 cm for male and >80 cm for female; (2) fasting TG concentrations ≥150 mg/dL or treatment with TG lowering medications; (3) HDL-C concentrations <40 mg/dL for male and <50 mg/dL for female; (4) systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg or taking antihypertensive medication; and (5) fasting glucose levels ≥100 mg/dL or taking antidiabetic medication.

## Definition of smoking status and SHS exposure

According to the self-reported questionnaire, self-reported never smoker was defined as never smoked or had smoked less than a total of five cigarette packs in one's life. Cotinine-verified never smoker was defined as having urinary cotinine <50 ng/mL after 10 hours of smoking free period. This cut-off point was used to classify current smokers from never smokers according to the recommendations from Society for Research on Nicotine and Tobacco (SRNT) [15]. Our previous studies show that this cut-off level has high sensitivity (84.8%) and specificity (98.2%) in differentiating never from current smokers [13]. SHS exposure was defined as currently experiencing passive smoking at home or the workplace.

## Statistical analysis

Continuous variables are expressed as mean±standard deviation or as median with interquartile ranges. Categorical variables are expressed as percentages (%). Serum TG, hsCRP, and HOMA-IR were log-transformed to correct for skewed distributions. Data in tables are expressed as untransformed raw data for easier interpretation.

Comparative analyses of baseline characteristics between the groups according to SHS exposure and MetS status were conducted using Student's *t* test or chi-square test. Multivariate logistic regression analyses were performed to assess the association between SHS exposure and MetS and MetS components (WC, HDL-C, fasting TG, fasting glucose, systolic and diastolic blood pressure). Also, the associations between SHS exposure and MetS according to daily time, weekly freqeuncy, and total duration of SHS exposure were assessed. The multivariate model was adjusted for variables with a univariate relationship (*P*<0.05), including age, BMI, frequency of alcohol drinking, frequency of vigorous exercise, BUN, creatinine, uric acid, and hsCRP. Statistical significance was valid when the *P* value was less than 0.05. The above statistical analyses were performed

with IBM SPPS version 24 (IBM Corp., Armonk, NY, USA).

## RESULTS

### Prevalence of SHS exposure and baseline characteristics according to SHS exposure status

The overall percentage of individuals with SHS exposure was 22.6% (Supplemental Table S1). SHS exposure prevalence was higher in males than in females (27.4% in males and 20.3% in females) (Supplemental Fig. S2). However, among individuals with SHS exposure, percentage of individuals with SHS exposure for more than 1 hour/day (26.7% vs. 37.9%), 3 times/week (32.4% vs. 37.9%), and 10 years (55.6% vs. 63.4%) was higher in females (Table 1).

In males, SHS exposure group were slightly younger with higher BMI, WC, systolic and diastolic blood pressure, glucose, HbA1c, and lower LDL-C, and HOMA-β levels. In females, SHS exposure group were slightly younger with higher BMI, WC, systolic and diastolic blood pressure, HDL-C, glucose, HbA1c, and lower LDL-C levels. Percentage of individuals who exercised and drank alcohol more than 3 times/week and had hypertension, diabetes mellitus, and MetS was higher in both male and female SHS exposure groups (Table 1).

### Prevalence of MetS and baseline characteristics according to MetS status

The overall MetS prevalence was 6.8%. MetS prevalence in males was approximately two times higher (10.7% in male vs 4.9% in female) (Supplemental Fig. S3). In males, those with MetS were older with higher BMI, WC, systolic and diastolic blood pressure, TC, TG, LDL-C, glucose, HbA1c, HOMA-IR, and lower HDL-C and HOMA-β, which are the major components of MetS diagnosis (Supplemental Table S2). Similar findings were seen throughout the comparison of variables in females. Females with MetS were also older with higher BMI, WC, systolic and diastolic blood pressure, TC, TG, HDL-C, LDL-C, glucose, HbA1c, HOMA-IR, and lower HOMA-β level (Supplemental Table S2).

### Association between SHS exposure and MetS & MetS components according to gender

In the overall study population, there was significant association between SHS exposure and MetS in both age- and sex-adjusted (odds ratio [OR], 1.19; 95% confidence interval [CI], 1.13 to 1.25) and multivariate (OR, 1.09; 95% CI, 1.02 to 1.16) regression analyses (Supplemental Table S3). However, because there

**Table 1.** Characteristics of Male and Female Never Smokers with and without Secondhand Smoke Exposure

| Characteristic | Male never smokers | | | Female never smokers | | |
|---|---|---|---|---|---|---|
| | SHS exposure (−) (n=27,854) | SHS exposure (+) (n=10,531) | P value | SHS exposure (−) (n=63,917) | SHS exposure (+) (n=16,307) | P value |
| Age, yr | 34.4±6.4 | 34.3±6.2 | 0.152 | 35.1±7.3 | 34.7±8.0 | <0.001 |
| Body mass index, kg/m² | 24.3±3.0 | 24.4±3.0 | <0.001 | 21.5±3.0 | 21.7±3.3 | <0.001 |
| Waist circumference, cm | 85.1±8.2 | 85.6±8.2 | <0.001 | 75.0±8.1 | 75.7±8.7 | <0.001 |
| Systolic blood pressure, mm Hg | 113.6±10.9 | 114.2±10.8 | <0.001 | 100.7±10.5 | 101.1±10.7 | <0.001 |
| Diastolic blood pressure, mm Hg | 72.1±8.9 | 72.5±9.1 | <0.001 | 64.3±8.0 | 64.7±8.3 | <0.001 |
| Blood urea nitrogen, mmol/L | 4.53±1.05 | 4.58±1.05 | <0.001 | 4.06±1.06 | 4.06±1.05 | 0.874 |
| Serum creatinine, μmol/L | 86.5±11.1 | 87.1±11.1 | <0.001 | 60.4±11.3 | 61.3±10.2 | <0.001 |
| Uric acid, μmol/L | 370.5±72.7 | 371.3±73.4 | 0.363 | 252.9±53.3 | 255.5±53.9 | <0.001 |
| Total cholesterol, mmol/L | 5.04±0.86 | 5.04±0.86 | 0.499 | 4.76±0.81 | 4.76±0.81 | 0.691 |
| Triglyceride, mmol/L | 1.08 (0.79–1.55) | 1.08 (0.79–1.56) | 0.296 | 0.77 (0.60–1.03) | 0.76 (0.59–1.04) | 0.333 |
| HDL-C, mmol/L | 1.40±0.33 | 1.41±0.33 | 0.705 | 1.71±0.38 | 1.71±0.39 | 0.017 |
| LDL-C, mmol/L | 3.27±0.80 | 3.25±0.80 | 0.023 | 2.80±0.74 | 2.78±0.75 | 0.008 |
| Glucose, mmol/L | 5.24±0.67 | 5.26±0.73 | 0.003 | 5.02±0.56 | 5.04±0.64 | <0.001 |
| Hemoglobin A1c, % (mmol/mol) | 5.52±0.42 | 5.54±0.43 | 0.023 | 5.52±0.35 | 5.54±0.39 | <0.001 |
| HOMA-IR | 1.28 (0.85–1.90) | 1.26 (0.83–1.89) | 0.059 | 1.11 (0.74–1.61) | 1.10 (0.73–1.64) | 0.878 |
| HOMA-β | 11.7 (10.0–13.8) | 11.5 (9.9–13.7) | 0.003 | 13.2 (11.2–16.1) | 13.2 (11.1–16.0) | <0.001 |
| hsCRP, mg/L | 0.5 (0.3–1.0) | 0.5 (0.3–1.0) | 0.019 | 0.3 (0.2–0.7) | 0.3 (0.2–0.7) | 0.668 |
| Vigorous exercise | | | <0.001 | | | <0.001 |
| None | 14,326/27,635 (51.8) | 5,104/10,464 (48.8) | | 46,480/63,032 (73.7) | 10,852/16,054 (67.6) | |
| <3 times/wk | 9,442/27,635 (34.2) | 3,842/10,464 (36.7) | | 10235/63,032 (16.2) | 3,297/16,054 (20.5) | |
| ≥3 times/wk | 3,867/27,635 (14.0) | 1,518/10,464 (14.5) | | 6,317/63,032 (10.0) | 1,905/16,054 (11.9) | |
| Alcohol consumption | | | <0.001 | | | <0.001 |
| None | 1,961/27,539 (7.1) | 546/10,391 (5.3) | | 12,325/60,145 (20.5) | 2,335/15,479 (15.1) | |
| 1–2 times/wk | 23,021/27,539 (83.6) | 8,273/10,391 (79.6) | | 44,598/60,145 (74.2) | 11,730/15,479 (75.8) | |
| 3–4 times/wk | 2,265/27,539 (8.2) | 1,413/10,391 (13.6) | | 2,697/60,145 (4.5) | 1,187/15,479 (7.7) | |
| ≥5 times/wk | 292/27,539 (1.1) | 159/10,391 (1.5) | | 525/60,145 (0.9) | 227/15,479 (1.5) | |
| Daily times of SHS exposure | | | <0.001 | | | <0.001 |
| None | 27,854/27,854 (100) | 0/5,526 (0) | | 63,917/63,917 (100) | 0/8,841 (0) | |
| <1 hr/day | 0/27,854 (0) | 4,051/5,526 (73.2) | | 0/63,917 (0) | 5,489/8,841 (62.1) | |
| ≥1 hr/day | 0/27,854 (0) | 1,475/5,526 (26.7) | | 0/63,917 (0) | 3,352/8,841 (37.9) | |
| Frequency of SHS exposure | | | <0.001 | | | <0.001 |
| None | 27,814/27,814 (100) | 0/10,460 (0) | | 63,858/63,858 (100) | 0/16,076 (0) | |
| <3 times/wk | 0/27,814 (0) | 7,071/10,460 (67.6) | | 0/63,858 (0) | 10,300/16,076 (64.1) | |
| ≥3 times/wk | 0/27,814 (0) | 3,389/10,460 (32.4) | | 0/63,858 (0) | 5,776/16,076 (35.9) | |
| Duration of SHS exposure | | | <0.001 | | | <0.001 |
| None | 27,766/27,766 (100) | 0/7,048 (0) | | 63,507/63,507 (100) | 0/10,853 (0) | |
| <10 yr | 0/27,766 (0) | 3,132/7,048 (44.4) | | 0/63,507 (0) | 3,970/10,853 (36.6) | |
| ≥10 yr | 0/27,766(0) | 3,916/7,048 (55.6) | | 0/63,507 (0) | 6,883/10,853 (63.4) | |
| Hypertension | 2,893/27,854 (10.4) | 1,252/10,531 (11.9) | <0.001 | 2,064/63,917 (3.2) | 638/16,307 (3.9) | <0.001 |
| Diabetes mellitus | 577/27,852 (2.1) | 223/10,528 (2.1) | 0.776 | 752/63,911 (1.2) | 284/16,305 (1.7) | <0.001 |
| Metabolic syndrome | 2,903/27,854 (10.4) | 1,194/10,531 (11.3) | 0.010 | 2,971/63,917 (4.6) | 943/16,307 (5.8) | <0.001 |

Values are expressed as mean±standard deviation, median (interquartile range), or number (%). Triglyceride, HOMA-IR, HOMA-β, and hsCRP and daily alcohol amount were log-transformed for this analysis. P values are based on Student's t test or chi-square test.
SHS, secondhand smoke; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-β, homeostatic model assessment of β cell function; hsCRP, high-sensitivity C-reactive protein.

**Table 2.** Multivariate Logistic Regression Analyses for the Association of Metabolic Syndrome and Its Components with Secondhand Smoke Exposure in Male and Female Never Smokers

| Variable | Male never smokers | | Female never smokers | |
|---|---|---|---|---|
| | Age-adjusted | Multivariate | Age-adjusted | Multivariate |
| Metabolic syndrome | 1.11 (1.04–1.20) | 1.02 (0.94–1.11) | 1.27 (1.17–1.37) | 1.17 (1.06–1.29) |
| Metabolic syndrome components | | | | |
| Fasting glucose ≥100 mg/dL | 1.10 (1.04–1.16) | 1.04 (0.98–1.10) | 1.14 (1.08–1.21) | 1.09 (1.02–1.16) |
| WC >90 cm | 1.11 (1.06–1.17) | 1.02 (0.94–1.11) | 1.22 (1.18–1.27) | 1.12 (1.05–1.19) |
| HDL-C <40 mg/dL | 1.02 (0.95–1.10) | 1.03 (0.96–1.12) | 1.09 (1.04–1.15) | 1.07 (1.01–1.13) |
| Fasting TG ≥150 mg/dL | 1.04 (0.99–1.10) | 1.01 (0.95–1.07) | 1.14 (1.06–1.22) | 1.06 (1.01–1.15) |
| SBP ≥130 and/or DBP ≥85 mm Hg | 1.07 (1.01–1.15) | 1.01 (0.94–1.08) | 1.19 (1.09–1.30) | 1.23 (1.02–1.24) |

Values are expressed as odds ratio (95% confidence interval). Multivariate model was adjusted for age, body mass index, frequency of alcohol drinking, frequency of vigorous exercise, blood urea nitrogen, creatinine, uric acid, total cholesterol, low-density lipoprotein cholesterol, and high-sensitivity C-reactive protein.

WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; SBP, systolic blood pressure; DBP, diastolic blood pressure.

was a significant gender interaction in SHS exposure and MetS (*P* for interaction <0.001), the analyses were conducted separately according to gender.

In the age-adjusted analysis, there were significant associations between SHS exposure and MetS in both genders with higher odds in females (OR, 1.11 [95% CI, 1.04 to 1.20] in males vs. OR, 1.27 [95% CI, 1.17 to 1.37] in females). However, multivariate analyses revealed a significant association between SHS exposusre and increased MetS only in females (OR, 1.02 [95% CI, 0.94 to 1.11] in males vs. OR, 1.17 [95% CI, 1.06, 1.29] in females) (Table 2).

In the age-adjusted regression analyses for the five components of MetS, males with SHS exposure had increased odds for high fasting glucose (fasting glucose ≥100 mg/dL; OR, 1.10; 95% CI, 1.04 to 1.16), abdominal obesity (WC >90 cm; OR, 1.11; 95% CI, 1.06 to 1.17) and hypertension (SBP ≥130 mm Hg and/or DBP ≥85 mm Hg; OR, 1.07; 95% CI, 1.01 to 1.15) compared to the non-SHS exposure group. However, in the multivariate analyses of MetS components, males with SHS exposure had no statistically significant odds compared to the non-SHS exposure group (Table 2).

In contrast, females with SHS exposure had increased odds for all five components of MetS compared to the non-SHS exposure group in both age-adjusted and multivariate analyses (Table 2).

**Association between SHS exposure and MetS according to daily time, frequency, and duration of SHS exposure**

In males, trend for increasing MetS odds according to increas-

ing daily hour, weekly frequency, and total duration of SHS exposure was observed in the age-adjusted model (*P* for trend all <0.005), but was not statistically significant in the multivariate model (Table 3).

In females, trend for increasing MetS odds according to increasing daily hour and weekly frequency was seen in both age-adjusted and multivariate models (*P* for trend all <0.005). In particular, females who were exposed for more than ≥1 hour/day and ≥3 times/week increased MetS odds by 22% and 30%, respectively (OR, 1.22 [95% CI, 1.02 to 1.45]; OR, 1.30 [95% CI, 1.14 to 1.49]) (Table 3).

## DISCUSSION

The results of this study showed that SHS exposure in female self-reported and cotinine-verified never smokers was significantly associated with increased MetS. This association was dose-dependent on increasing daily hour and weekly frequency of SHS exposure in females. In particular, female never smokers with SHS exposure for more than 1 hour/day and 3 times/week had a 20% to 30% higher risk of MetS compared to non-SHS exposure females.

MetS is a group of metabolic abnormalities including central obesity, insulin resistance, dyslipidemia and hypertension. It is associated with increased risks of type 2 diabetes mellitus and various cardiovascular diseases [17]. The pathophysiologic mechanism of MetS development is not yet fully understood. However, central obesity and insulin resistance are known as main causative triggers along with various socioeconomic, ge-

**Table 3.** Multivariate Logistic Regression Analyses for the Association between Metabolic Syndrome and Secondhand Smoke Exposure According to Daily Time, Frequency, and Duration in Male and Female Never Smokers

| Variable | Male never smokers | | Female never smokers | |
|---|---|---|---|---|
| | Age-adjusted | Multivariate | Age-adjusted | Multivariate |
| Daily time of SHS exposure | | | | |
| None | 1 (Reference) | 1 (Reference) | 1 (Reference) | 1 (Reference) |
| <1 hr | 0.96 (0.85–1.07) | 0.83 (0.73–0.95) | 1.28 (1.11–1.47) | 1.03 (0.87–1.22) |
| ≥1 hr | 1.48 (1.28–1.72) | 1.18 (0.99–1.14) | 1.48 (1.29–1.71) | 1.22 (1.02–1.45) |
| *P* for trend | <0.001 | 0.961 | <0.001 | 0.041 |
| Frequency of SHS exposure | | | | |
| None | 1 (Reference) | 1 (Reference) | 1 (Reference) | 1 (Reference) |
| <3 times/wk | 1.03 (0.94–1.12) | 1.00 (0.91–1.11) | 1.11 (1.00–1.23) | 1.07 (0.94–1.21) |
| ≥3 times/wk | 1.29 (1.16–1.44) | 1.07 (0.94–1.21) | 1.51 (1.35–1.68) | 1.30 (1.14–1.49) |
| *P* for trend | <0.001 | 0.414 | <0.001 | <0.001 |
| Duration of SHS exposure | | | | |
| None | 1 (Reference) | 1 (Reference) | 1 (Reference) | 1 (Reference) |
| <10 yr | 1.03 (0.91–1.17) | 0.94 (0.81–1.09) | 1.22 (1.03–1.45) | 1.13 (0.93–1.38) |
| ≥10 yr | 1.18 (1.06–1.31) | 0.97 (0.86–1.10) | 1.32 (1.19–1.47) | 1.12 (0.99–1.28) |
| *P* for trend | 0.004 | 0.981 | <0.001 | 0.051 |

Values are expressed as odds ratio (95% confidence interval). Multivariate model was adjusted for age, body mass index, frequency of alcohol drinking, frequency of vigorous exercise, blood urea nitrogen, creatinine, uric acid, total cholesterol, low-density lipoprotein cholesterol, and high-sensitivity C-reactive protein.
SHS, secondhand smoke.

netic and environmental factors [18,19]. The kew environmental factors associated with MetS are active smoking and SHS exposure [1,5,20,21].

Cigarette smoke is an important environmental trigger factor associated with activation and aggravation of key components of MetS. In exploration of the association between smoking and each key component of MetS, it has been identified that smoking is associated with central obesity by dose-dependent abdominal fat accumulation through increased cortisol levels, insulin resistance and decreased estrogen levels thereby leading to hormonal imbalance in both the genders [22-25]. Smoking increases serum glucose levels mainly through chronic inflammation and direct toxic dysfunction of pancreatic beta cells [2,26,27]. It also promotes dyslipidemia by increasing oxidative stress and decreasing level of antioxidants resulting in higher TC, TG, LDL-C, and lower HDL-C levels [28-30].

Multiple studies which assessed the association between smoking and hypertension have shown inconsistent results [4,13,31-33]. However, a recent cross-sectional study which assessed the association between SHS exposure and hypertension in Korean adults has shown that SHS exposure is associated

with increased odds for hypertension [34]. The pathophysiology behind this association is mainly nicotine-mediated sympathetic activation, endothelial dysfunction, hypercoagulation, and increased arterial stiffness [31,34,35].

The pathophysiology behind increased MetS prevalence in never smokers with SHS exposure is suspected to be similar to that of active smoking. Many previous studies have evaluated the association between smoking and MetS and demonstrated a positive association between the two [1,5,20,30]. Our study also showed a positive association between SHS exposure and MetS in females. To our knowledge, this is the first study that assessed the association between SHS exposure and MetS in Asian adults using a dual smoking status verification system to increase the accuracy of actual smoking status classification.

An interesting finding in our study is that the association between SHS and MetS was only significant in females (OR, 1.02 [95% CI, 0.94 to 1.11] in males vs. OR, 1.17 [95% CI, 1.06 to 1.29] in females). C-statistic value of SHS for MetS was also higher in females (OR, 0.86 [95% CI, 0.86 to 0.87] for males vs. OR, 0.92 [95% CI, 0.92 to 0.93] for females). This finding is in correlation with the result that female SHS exposed never

smokers had increased odds for all the five components of MetS compared to female non-SHS exposed group, while the association was not valid in all five components in male never smokers (Table 2). It is hypothesized that this finding was due to the that fact that even though percentage of those with SHS exposure was higher in males, percentage of female never smokers with SHS exposure who were exposed for more than 1 hour/day, 3 times/week, and total 10 years was higher. Cotinine metabolism rate is higher in females than males due to higher estrogen level [12,36]. Therefore, even though both male and female self-reported and cotinine verified never smokers had urine cotinine under 50 ng/mL, female SHS exposed never smokers may have had higher amount, frequency and duration of SHS exposure than male SHS exposed never smokers as shown in our study results. Also, the non-SHS exposed male never smokers had more unfavorable baseline characteristics inclined towards MetS including higher BMI, WC, SBP/DBP, glucose, and abnormal lipid profile. Lastly, the percentage of individuals who consumed alcohol for more than 3 times/week was nearly twice higher in male never smokers compared to female never smokers in both SHS exposure and non-SHS exposure groups. As moderate alcohol consumption is known to be associated with decreased MetS prevalence this might have served as a protective confounding factor for MetS [37,38].

Previous studies have suspected that key mechanisms through which cigarette smoking acts on MetS development are central obesity and insulin resistance [18-21]. Abdominal obesity, which is represented by WC, was a statistically valid MetS component with second-highest odds among the five MetS components in female SHS exposed never smokers. The results of this study also correlate with the results from the above studies that SHS exposure has a strong association with central obesity and this may be one of the key factors mediating the association between SHS exposure and MetS.

This study has some limitations. First, MetS prevalence in this study was relatively lower than that in Korean adults. According to the 'Metabolic syndrome fact sheet Korea 2018' which analyzed data from the 2007 to 2015 Korea National Health and Nutritional Examination Survey, overall MetS prevalence in 2015 in Koreans aged over 19 years of age was 22.4% [39]. However, MetS prevalence in this study was 6.8%. Relatively underrated MetS prevalence in this study may be because MetS prevalence tends to increase with age usually peaking at age 50 to 60 years while the average age of this study's population was mid-thirties in both genders. Unfortunately, only socioeconomic information about monthly income and educational levels were available. In the multivariate analyses including the above two socioeconomic status variables, similar trend of increased odds of MetS in female never smokers with SHS exposure was observed (OR, 1.03 [95% CI, 0.93 to 1.14] for male and OR, 1.19 [95% CI, 1.05, 1.35] for female; data not shown). However, 30% of the study cohort did not provide information regarding socioeconomic status, which could act as statistical and selection bias in the analyses and interpretation of this study. Therefore, we did not include the above variables to analyse the main results of our study, but the importance of collecting data including socioeconomic status and dietary patterns is noted.

Second, it is a cross-sectional study. Therefore, no causal association between SHS exposure and MetS can be concluded from this study. Third, the metabolism of urine cotinine is affected by various racial, genetic, and gender factors. For example, females and especially pregnant females have much higher nicotine metabolism rate compared to males [12,15,36,40]. As the mean age of females in this study was mid-30s there is a possibility that a certain portion of the female population were pregnant or had higher nicotine metabolism rate due to gender difference. Fourth, no information on underlying diseases other than diabetes mellitus, hypertension and MetS was collected. Endocrinologic diseases such as polycystic ovary syndrome (PCOS) are known to be independently associated with MetS [41,42]. PCOS is common in females of reproductive age and as the mean age of this study population was mid-thirties this could have acted as a confounding factor. Nonetheless this study has its strength as it is the first large cross-sectional study that accurately analyzed the association between SHS exposure and MetS in Korean adults using two different smoking verification systems; self-reported questionnaire and urinary cotinine level.

In conclusion, this large cross-sectional study revealed that SHS was significantly associated with MetS in a dose-dependent manner in self-reported and urinary cotinine verified female never smokers. More active regional and national campaigns should be implemented to build awareness about smoking and prevent SHS at both home and workplace to reduce MetS. Further longitudinal studies using the above two smoking verification systems are needed to clarify the causal association between SHS exposure and MetS.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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