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Relation between secondhand smoke exposure and cardiovascular risk factors in never smokers

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Objective: Secondhand smoke exposure (SHSE) in nonsmokers has been associated with premature cardiovascular mortality and ischemic heart disease. We conducted a cross-sectional, population-based study evaluating the relationship between SHSE, measured by subjective and objective methods, and conventional cardiovascular risks such as blood pressure, lipid profiles, and fasting glucose.

Methods: We extracted information on 7376 healthy adults who had never smoked, for whom there were available urine cotinine levels, from the Korea National Health and Nutrition Examination Survey 2008–2011. SHSE was defined using self-report questionnaires and urine cotinine levels. The main outcomes included SBP and DBP, serum lipid profiles, and fasting glucose.

Results: The mean age of the study population was 45.4 ± 0.4 years and 75.2% were women. Self-reported SHSE had no significant association with study outcomes except for DBP, which had marginally positive relationships ($P = 0.060$). Unadjusted analysis showed higher cotinine levels were associated with lower SBP, total cholesterol, LDL cholesterol, and triglyceride. All associations lost statistical significance after multivariable adjustment. Fasting glucose had a positive relationship with urine cotinine in quartiles but not with logarithm-transformed cotinine.

Conclusion: Although SHSE is associated with increased risk of cardiovascular mortality and morbidity, we did not find any consistent relationship among SHSE and blood pressure, lipid, or fasting glucose levels in this cross-sectional study. Using objective measurements of urine cotinine did not alter this relationship. Further long-term prospective studies are needed to evaluate the effect of SHSE as a cardiovascular risk factor.

Keywords: blood pressure, cardiovascular risk factors, fasting glucose, Korea National Health and Nutrition Examination Survey, lipid profiles, secondhand smoke exposure, self-report questionnaires, urine cotinine

Abbreviations: CHD, coronary heart disease; KNHANES, Korea National Health and Nutrition Examination Survey; SHSE, secondhand smoke exposure

INTRODUCTION

Smoking is a leading cause of death [1]. Growing evidence suggests that the harm from smoking tobacco is not confined to 'active' smokers. Passive smoking, also known as secondhand smoke exposure (SHSE), is the inhalation of smoke by persons other than the intended 'active' smoker, and it is estimated to cause 331 000 deaths worldwide [2,3].

Cardiovascular disease is the main cause of premature death associated with SHSE [4]. Two-thirds of all deaths attributable to SHSE were caused by ischemic heart disease [5]. Studies have shown that SHSE increases the risk of coronary heart disease (CHD) by 25–30% [6,7]. There are several explanations for the link between SHSE and cardiovascular effects, including impaired autonomic regulation, impaired diastolic function, and increased inflammation [8]. However, there is a paucity of data regarding the effects of SHSE on cardiovascular risk factors such as hypertension, diabetes, dyslipidemia, and fasting glucose [9].

SHSE is usually assessed using self-report questionnaires. However, this subjective method is prone to various sources of bias and cotinine levels can be used as objective markers [10,11]. Cotinine, the main metabolite of nicotine, can be measured in serum, urine, and saliva [12]. It has a long half-life and is useful in quantifying not only active but

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also passive exposure to tobacco smoke [13]. In this study, we evaluated the relationship of SHSE with cardiovascular risk factors, such as blood pressure (BP), lipid, or fasting glucose levels, in healthy Korean adults who had never smoked. The status of SHSE was assessed subjectively by self-report questionnaires as well as objectively by urine cotinine concentrations, quantifying the amount of passive exposure to tobacco smoke.

METHODS

We performed a cross-sectional study using data from the Korea National Health and Nutrition Examination Survey (KNHANES) from 2008 to 2011. In brief, KNHANES is a nationwide representative survey in Korea using a complex, stratified, multistage, clustered-sampling design, which is used to examine the general health and nutritional status of the entire Korean population [14]. We extracted data on 7376 men and women who had never smoked and whose urine cotinine levels were available from the 37 753 individuals in the database. Exclusion criteria included those aged 18 years or younger ($n = 9376$), currently pregnant ($n = 54$), who had a history of CHD or stroke ($n = 212$), or who had urine cotinine levels higher than 100 ng/ml ($n = 306$) (Fig. 1) [15–17]. Baseline characteristics of the participants included in this study were compared with those who were excluded are shown in Supplement Table 1, http://links.lww.com/HJH/A789.

SHSE status was assessed subjectively using a self-report questionnaire and objectively using results from a urinary cotinine assay. Information on age, sex, alcohol intake, income, education level, and cigarette smoking habits was obtained using standardized questionnaires during a home interview performed by trained medical personnel. BMI was categorized as normal ($\geq$18.5 and $<$25 kg/m^2), overweight ($\geq$25 kg/m^2), or obese ($\geq$30 kg/m^2). Educational attainment was categorized as not being a high school graduate (lower) or being a high school graduate or above (higher). Income status was categorized into quartiles according to medical insurance premiums that are closely correlated with an individual's yearly income status. Alcohol consumption was categorized as never, mild-to-moderate (two to four drinks per month), or heavy drinking (two to three drinks per week). Regular physical activity was defined as performing vigorous physical activity more than three times per week.

Health examination procedures were performed based on standardized protocols by trained medical personnel. All equipment was calibrated periodically. Height and body weight were measured using digital scales. BP was measured three times on the right arm using an appropriately sized arm cuff and mercury sphygmomanometer (Baumanometer; WA Baum Co., New York, New York, USA) after the study participant was at rest in a seated position for at least 5 min. The final BP value was obtained by averaging the second and third measurements [18].

Blood and urine samples were collected from participants to obtain laboratory tests [14]. Blood samples were collected from the antecubital vein after 10–12 h of fasting. All biochemical analyses were performed within 2 h of blood sampling, and laboratory performance was monitored regularly by a data quality control program. Total cholesterol (TC), HDL cholesterol, LDL cholesterol, triglyceride, and glucose were measured with enzymatic methods using a Hitachi 7600 automatic analyzer (Hitachi Instruments Inc, Tokyo, Japan) or COBAS 8000 C702 (Roche, Mannheim, Germany) [18]. Urine cotinine level was measured with gas chromatography–mass spectrometry using the Perkin Elmer Clarus 600T (PerkinElmer, Turku, Finland) [19]. Urine cotinine levels were treated as both continuous variables and categorical variables. As a categorical variable, urine cotinine levels were coded into quartiles (Q1: 0.009–0.71 ng/ml, Q2: 0.72–3.90 ng/ml, Q3: 3.91–12.00 ng/ml, and Q4: 12.01–99.52 ng/ml); the lowest quartile was considered the reference. When treated

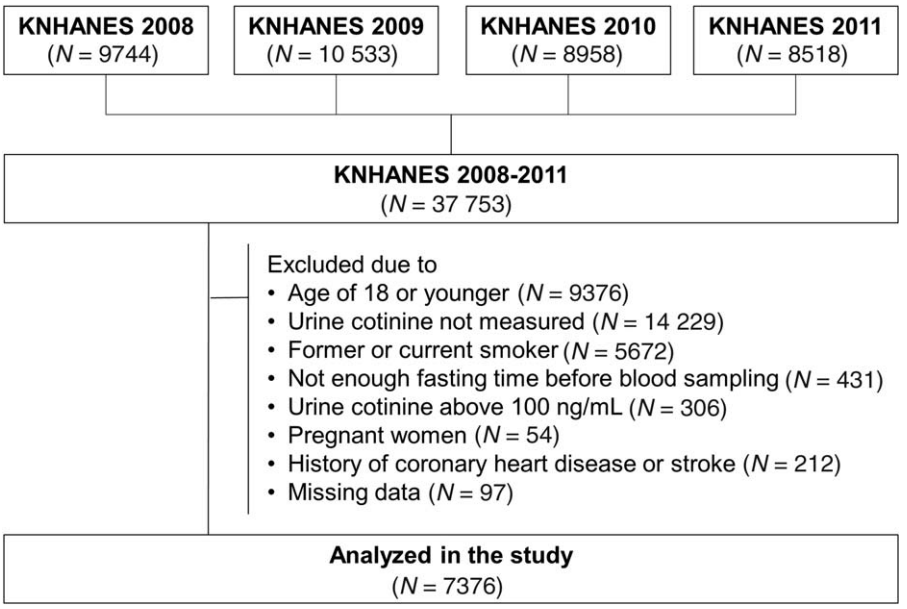

FIGURE 1 Study flow. KNHANES, Korean National Health and Nutrition Examination Survey.

as a continuous variable, urine cotinine levels were log-transformed because of their skewed distribution.

The outcome variables were SBP, DBP, lipid profiles including TC, HDL cholesterol, LDL cholesterol, triglyceride levels, and fasting glucose. Hypertension was defined as SBP at least 140 mmHg, DBP at least 90 mmHg, or taking antihypertensive drugs. Dyslipidemia was defined as HDL cholesterol less than 40 mg/dl, LDL cholesterol at least 160 mg/dl, triglyceride at least 200 mg/dl, or taking cholesterol-lowering drugs. Diabetes was defined as fasting glucose level at least 126 mg/dl, use of antidiabetic medication or insulin, or diagnosis of diabetes by physicians.

Data were presented as mean ± standard error (SE) or % (SE). Sampling weights based on the sample design of each KNHANES were used for all statistical analyses [14]. Baseline characteristics were compared using two sample *t* tests for continuous variables and chi-square test for categorical variables. Considering the complex survey design of KNHANES, linear and logistic models were used with survey-weighted generalized linear models. The linear regression models were constructed to calculate the association between dependent and independent variables, and the logistic regression models were for the association of SHSE and dichotomous dependent variables. We performed multivariable-adjusted analyses. The first model was adjusted for age, sex, and BMI, whereas the second model was adjusted for education (higher versus lower), low-income status, alcohol consumption, regular physical activity, sodium intake, total caloric intake, fat proportion among total calories, and the variables included in the first model. When analyzing BP, individuals who were taking antihypertensive medications were not included in the model to eliminate the effects of the drugs. Similarly, those taking cholesterol-lowering agents and antidiabetic medications were excluded from the analysis of lipid levels and fasting glucose, respectively. Sensitivity analyses were also performed, including all study participants regardless of medication status, which has been adjusted. The association between urine cotinine and cardiovascular risk factors were stratified by SHSE at home and at work, which results were presented as another sensitivity analysis. All analyses were conducted using SAS (version 9.2; SAS Institute, Cary, North Carolina, USA) software and 'survey' package of the R program (R Foundation, Vienna, Austria). Two-sided *P* values less than 0.05 were considered statistically significant.

RESULTS

Baseline characteristics of the study population are shown in Table 1. None of the individuals included in the analysis were active or former smokers. The mean age of our population was 45.4 ± 0.4 years, 75.2% were women and 6.6% of population had diabetes mellitus. The mean calorie intake, sodium consumption, and fat proportion among total calories of this study population were 1790.0 ± 12.7 kcal, 4489.5 ± 43.7 mg, and 17.4 ± 0.1%, respectively. The mean SBP and DBP were 115.3 ± 0.3 and 75.3 ± 0.2 mmHg, respectively. The mean TC, HDL, LDL, and triglyceride were 186.0 ± 0.6, 50.0 ± 0.2, 113.8 ± 0.5, and 94.0 (92.4–96.0) mg/dl, respectively. The differences in baseline characteristics between individuals included in this study and those who were excluded are described in Supplement Table 1, http://links.lww.com/HJH/A789.

TABLE 1. Baseline characteristics

Characteristics	Values
Total sample size	7376
Age (years)	45.4 ± 0.4
Male sex (%)	24.8 (0.7)
Diabetes (%)	6.6 (0.3)
Hyperlipidemia (%)	31.1 (0.7)
Education of high school or above (%)	69.7 (0.8)
Alcohol consumption (%)	
Never drinking	30.6 (0.7)
Mild-to-moderate drinking	66.4 (0.7)
Heavy drinking	3.0 (0.3)
Regular physical activity (%)	21.5 (0.8)
Income quartiles (%)	
Q1	15.4 (0.6)
Q2	25.4 (0.8)
Q3	28.5 (0.8)
Q4	30.7 (1.0)
Urban habitats (%)	81.9 (1.4)
Total calorie intake (kcal)	1790.0 ± 12.7
Total sodium consumption (mg)	4489.5 ± 43.7
Proportion of calories from fat (%)	17.4 ± 0.1
BMI (kg/m^2)	23.4 ± 0.1
Waist circumference (cm)	79.0 ± 0.2
SBP (mmHg)	115.3 ± 0.3
DBP (mmHg)	75.3 ± 0.2
Total cholesterol (mg/dl)	186.0 ± 0.6
HDL cholesterol (mg/dl)	50.0 ± 0.2
LDL cholesterol (mg/dl)	113.8 ± 0.5
Triglyceride (mg/dl)	94.0 (92.4–96.0)
Fasting glucose (mg/dl)	94.9 ± 0.3
Calculated GFR (ml/min per 1.73 m^2)	96.1 ± 0.4
Current medication (%)	
Antihypertensive participants	12.8 (0.4)
Cholesterol lowering agents	3.2 (0.2)
Oral hypoglycemic agents	3.9 (0.2)

Data are presented as mean ± SE or % (SE). Geometric means as log transformed are presented for triglyceride. GFR, glomerular filtration rate.

The status of SHSE was assessed subjectively and objectively. Table 2 describes the results of SHSE when assessed subjectively by self-report questionnaires. For most dependent variables, no significant associations were observed except for DBP, which had marginally positive associations ($P = 0.060$). When dependent variables were coded binomially, that is, hypertension, low HDL, high LDL, high triglyceride, dyslipidemia, and diabetes mellitus, there were still no significant associations with subjectively accessed SHSE (Supplemental Table 2, http://links.lww.com/HJH/A789).

Table 3 shows the results of the unadjusted and adjusted models in which participants were divided into quartiles according to their urine cotinine levels. Unadjusted analysis showed that higher cotinine levels were significantly associated with lower SBP, TC, LDL cholesterol, and triglyceride. After multivariable adjustment, all associations lost statistical significance, whereas increasing cotinine showed a positive relationship with higher fasting glucose. When the analysis was performed stratified according to sex, the results were similar among women (Supplemental

TABLE 2. Association of self-reported secondhand smoke exposure status with blood pressure, lipid profiles, and fasting glucose levels

	n	SBP	DBP	Cholesterol	HDL cholesterol	LDL cholesterol	Triglyceride	Fasting glucose
SHSE, all								
No	4913	114.5 ± 0.4	74.5 ± 0.2	190.1 ± 1.1	49.7 ± 0.3	117.6 ± 0.9	96.5 (94.0–99.1)	93.0 ± 0.3
Yes	2463	115.2 ± 0.5	75.2 ± 0.4	190.1 ± 1.3	49.9 ± 0.4	117.0 ± 1.1	99.3 (95.8–102.9)	93.4 ± 0.4
P values		0.203	0.060	0.990	0.574	0.665	0.219	0.442
SHSE at work								
No	5470	114.2 ± 0.4	74.4 ± 0.2	189.5 ± 1.0	49.6 ± 0.3	116.9 ± 0.8	97.0 (94.7–99.4)	92.9 ± 0.3
<1 h	1403	115.2 ± 0.6	75.6 ± 0.5	191.5 ± 1.3	50.0 ± 0.4	118.9 ± 1.2	97.0 (93.3–100.8)	93.4 ± 0.5
≥1 h	397	115.7 ± 1.3	75.5 ± 0.8	188.4 ± 2.6	51.2 ± 0.8	114.8 ± 2.2	97.6 (89.1–106.8)	93.9 ± 0.8
P values		0.242	0.029	0.266	0.114	0.145	0.991	0.496
SHSE at home								
No	6336	114.7 ± 0.4	74.7 ± 0.2	190.3 ± 1.0	49.8 ± 0.2	117.7 ± 0.8	96.7 (94.6–98.9)	93.0 ± 0.3
<1 h	831	114.9 ± 0.7	74.8 ± 0.6	188.1 ± 2.5	49.1 ± 0.7	115.2 ± 2.1	101.7 (95.6–108.2)	93.7 ± 0.6
≥1 h	195	113.7 ± 1.5	74.6 ± 0.9	191.0 ± 3.4	49.9 ± 0.9	117.8 ± 3.2	100.1 (89.2–112.2)	92.8 ± 1.2
P values		0.770	0.981	0.700	0.580	0.547	0.293	0.480
SHSE at work or home								
No	4913	114.5 ± 0.4	74.5 ± 0.3	190.1 ± 1.1	49.7 ± 0.3	117.6 ± 0.9	96.5 (94.0–99.1)	93.0 ± 0.3
<1 h	1915	115.2 ± 0.5	75.2 ± 0.4	190.0 ± 1.5	49.6 ± 0.4	117.1 ± 1.2	99.3 (95.5–103.3)	93.3 ± 0.4
≥1 h	548	115.1 ± 1.1	75.2 ± 0.6	190.3 ± 2.2	51.0 ± 0.6	116.7 ± 2.0	99.0 (91.8–106.8)	93.6 ± 0.7
P values		0.441	0.169	0.995	0.125	0.889	0.469	0.687
Smokers at home								
No	6197	114.7 ± 0.4	74.8 ± 0.2	190.3 ± 1.0	49.8 ± 0.2	117.7 ± 0.8	96.8 (94.7–99.0)	93.0 ± 0.3
Yes	1179	114.6 ± 0.6	74.6 ± 0.5	189.1 ± 2.0	49.3 ± 0.6	115.9 ± 1.6	100.1 (95.0–105.4)	93.7 ± 0.6
P values		0.909	0.797	0.590	0.394	0.309	0.255	0.215

n means unweighted number of participants. Data are presented as mean ± SE. Geometric means as log transformed are presented for triglyceride. Linear regression adjusted with age, sex, BMI, education (high versus low), low-income status, alcohol consumption, regular physical activity, sodium intake, total calorie intake, and fat proportion among total calories were used. SHSE, secondhand smoke exposure.

Table 3, http://links.lww.com/HJH/A789). Among male participants, no relationship was statistically significant.

Analyses were also performed using logarithm-transformed urine cotinine levels treated as a continuous variable (Table 4). None of the dependent variables were significantly associated with urine cotinine levels in the unadjusted model. After multivariable adjustment, serum triglyceride has a negative relationship with urine cotinine. However, after further analysis with adjusted model 2, the relationship lost statistical significance. When stratified according to sex, LDL cholesterol was positively correlated with urine cotinine among men. SBP, cholesterol, LDL cholesterol, and triglyceride showed a significant relationship with logarithm-transformed cotinine among women, but lost statistical significance after multivariable adjustment (Supplemental Table 4, http://links.lww.com/HJH/A789).

Sensitivity analysis was performed without excluding participants who were taking medications that can affect the values of dependent variables and with adjustment for medication status. They showed mostly similar results with the main analysis. When urine cotinine was divided into quartiles, SBP decreased with higher cotinine, whereas fasting glucose had no significant relationship (Supplemental Table 5, http://links.lww.com/HJH/A789). Log-transformed cotinine was not associated with any

TABLE 3. Association of urine cotinine level in quartiles with cardiovascular risk factors

	SBP	DBP	Cholesterol	HDL cholesterol	LDL cholesterol	Triglyceride	Fasting glucose
Unadjusted model							
Q1	115.1 ± 0.9	74.9 ± 0.5	189.7 ± 1.7	50.0 ± 0.4	115.2 ± 1.1	101.3 (96.2–106.7)	92.7 ± 0.4
Q2	114.8 ± 0.6	75.1 ± 0.4	190.0 ± 1.5	49.8 ± 0.4	117.4 ± 1.3	96.6 (92.8–100.6)	92.8 ± 0.5
Q3	113.0 ± 0.5	74.4 ± 0.4	187.2 ± 1.4	49.7 ± 0.5	115.5 ± 1.2	92.5 (88.5–96.7)	93.0 ± 0.6
Q4	113.0 ± 0.6	74.6 ± 0.5	184.5 ± 1.5	50.1 ± 0.4	112.5 ± 1.2	92.1 (88.2–96.2)	93.2 ± 0.4
P for trends	0.038	0.620	0.045	0.880	0.047	0.019	0.390
Adjusted model 1							
Q1	115.5 ± 0.8	75.2 ± 0.5	189.8 ± 1.5	49.8 ± 0.4	115.4 ± 1.1	102.3 (98.0–106.8)	92.9 ± 0.4
Q2	115.0 ± 0.6	75.0 ± 0.3	191.1 ± 1.4	49.8 ± 0.4	118.4 ± 1.2	97.8 (94.2–101.6)	92.9 ± 0.4
Q3	114.2 ± 0.5	74.6 ± 0.4	190.1 ± 1.5	49.5 ± 0.4	118.0 ± 1.2	95.7 (92.0–99.5)	93.6 ± 0.6
Q4	114.4 ± 0.6	74.9 ± 0.4	188.0 ± 1.4	49.8 ± 0.4	115.4 ± 1.2	96.5 (92.9–100.3)	94.0 ± 0.4
P for trends	0.443	0.729	0.395	0.959	0.122	0.123	0.026
Adjusted model 2							
Q1	115.2 ± 0.6	74.8 ± 0.4	190.8 ± 1.7	50.1 ± 0.4	116.0 ± 1.1	102.2 (97.6–107.0)	92.8 ± 0.4
Q2	115.0 ± 0.6	74.8 ± 0.4	190.8 ± 1.4	49.6 ± 0.4	118.9 ± 1.3	96.1 (92.8–99.5)	92.7 ± 0.4
Q3	114.1 ± 0.5	74.3 ± 0.4	189.9 ± 1.6	49.5 ± 0.5	117.7 ± 1.3	95.8 (91.8–100.0)	93.2 ± 0.6
Q4	114.5 ± 0.6	75.0 ± 0.5	188.5 ± 1.4	49.9 ± 0.4	115.8 ± 1.2	97.1 (93.1–101.3)	94.1 ± 0.4
P for trends	0.436	0.875	0.254	0.604	0.661	0.181	0.030

Data are presented as mean ± SE. Geometric means as log transformed are presented for triglyceride. Adjusted model 1 was analyzed with the use of linear regression model adjusted for age, and BMI. Adjusted model 2 was adjusted for age, BMI, education (higher versus lower), low income status, alcohol drinking, regular physical activity, sodium intake, total calorie intake, and fat proportion among total calories.

TABLE 4. Association of logarithm-transformed urine cotinine levels with cardiovascular risk factors

	β	Standard error	*P* value
Unadjusted			
SBP	−0.412	0.229	0.073
DBP	−0.048	0.167	0.775
Cholesterol	−0.532	1.002	0.595
HDL cholesterol	0.140	0.373	0.708
LDL cholesterol	−0.119	0.869	0.892
Triglyceride	−0.024	0.013	0.068
Fasting glucose	0.055	0.083	0.512
Adjusted model 1			
SBP	−0.404	0.232	0.082
DBP	−0.053	0.172	0.758
Cholesterol	−0.206	0.963	0.830
HDL cholesterol	0.228	0.349	0.514
LDL cholesterol	0.265	0.847	0.755
Triglyceride	−0.028	0.013	0.030
Fasting glucose	0.128	0.077	0.093
Adjusted model 2			
SBP	0.010	0.098	0.917
DBP	0.009	0.069	0.900
Cholesterol	−0.048	0.245	0.845
HDL cholesterol	−0.069	0.072	0.335
LDL cholesterol	0.108	0.203	0.596
Triglyceride	−0.005	0.004	0.203
Fasting glucose	0.129	0.076	0.090

Adjusted model 1 was analyzed with the use of linear regression model adjusted for age, and BMI. Adjusted model 2 was adjusted for age, BMI, education (high versus low), low income status, alcohol drinking, regular physical activity, sodium intake, total calorie intake, and fat proportion among total calories.

dependent variables after adjustment (Supplemental Table 6, http://links.lww.com/HJH/A789). The effects of SHSE did not change remarkably when study participants were stratified by exposition at home or at work (Supplemental Tables 7–10, http://links.lww.com/HJH/A789).

DISCUSSION

In this cross-sectional population-based study, we evaluated the relationship between SHSE and conventional cardiovascular risk factors in the general Korean population using the urine cotinine level, a well established, major proximate metabolite of nicotine [20,21]. This study found no significant adverse relationship between any dependent variables and SHSE as assessed by self-report questionnaires. Quantitative assessment of SHSE using urine cotinine levels did not alter this relationship.

There is strong and consistent evidence that SHSE increases the risk of morbidity and mortality, specifically cardiovascular mortality and ischemic heart disease. Studies have shown that SHSE increases the risk of CHD by 25–30% [6,8]. A number of studies have shown that SHSE not only increases the risk of CHD but also impacts morbidity and mortality associated with acute coronary syndrome [22–24]. Several mechanisms have been proposed such as platelet and endothelial dysfunction, increased arterial stiffness, atherosclerosis, increased oxidative stress and inflammation, and decreased energy metabolism [25]. Aside from chronic effects, acute effects have been proposed, including an increase in resting heart rate (HR), BP, blood level of carboxyhemoglobin, and carbon monoxide, and a marked reduction in microcirculatory flow and HR variability [26,27].

Hypertension and dyslipidemia are established cardiovascular risk factors. Active smoking has been shown to have adverse effects on BP and lipid profiles [28–31]. However, for SHSE, there is a paucity of data regarding its association with cardiovascular risk factors. There are a few studies that have shown the association between SHSE and hypertension. Makris *et al.* [32] found that passive smoking is associated with masked hypertension in a dose-related manner in 790 normotensive nonsmokers who were self-referred to an outpatient hypertensive clinic. Li *et al.* [31] also found that passive smoking was a significant risk factor for hypertension in 392 Chinese nonsmoking women. Alshaarawy *et al.* [9] revealed higher SHSE, measured objectively by serum cotinine levels, was associated with SBP and hypertension. Regarding blood lipid levels, a previous study showed deteriorations in lipid profiles with higher cotinine levels among nonsmokers [33]. However, another study found no significant differences according to subjectively assessed SHSE [32]. In summary, there have been limited studies with inconsistent results.

In this study, we failed to find any consistent and meaningful changes in BP, cholesterol, and fasting glucose levels attributable to SHSE. One potential explanation is publication bias. Studies lacking statistically significant associations tend not to be published. Second is a difference in the study population. Previous studies focused on a specific subset of the population, whereas our study participants were from the general population [31–33]. Finally, the source for measuring cotinine levels differed. Urine cotinine levels were used in this study, whereas previous studies measured serum or salivary levels [7,33]. To our knowledge, however, there is no evidence that urinary cotinine measurements are less precise than other measurements [21,34].

There were several findings that were statistically significant in this study. Some were in the opposite direction than what was expected. A higher cotinine level was linked to lower SBP and triglyceride levels. However, those relationships were not consistently observed. For example, triglyceride had a negative relationship with log-transformed cotinine but had no significant relationship with cotinine in quartiles. Subjectively assessed SHSE was associated with higher DBP, whereas objectively assessed SHSE was not. Thus, false positivity that can be caused by multiple testing should be considered.

The current study suggested a possible increase in fasting blood glucose levels with SHSE, although the relationship was not consistent. The relationship was NS with the unadjusted model, but became significant after multivariable adjustment, when cotinine was stratified into quartiles. The linear regression model using logarithm-transformed urine cotinine showed a similar pattern, but the statistical significance was only marginal. Previous studies have also suggested increased risk of type 2 diabetes with SHSE [35,36]. A previous study using the US nationally representative National Health and Nutrition Examination Surveys showed that serum cotinine levels were positively associated with diabetes mellitus [37]. However, the association

between serum cotinine levels and glycohemoglobin was NS. The results of this study are potentially hypothesis-generating and need to be tested in future studies.

The finding of no significant association between SHSE and major cardiovascular risk factors may sound contradictory to previous studies. The evidence supporting increased risk of cardiovascular disease and mortality due to SHSE is strong. One explanation is that SHSE may affect cardiovascular disease directly without mediation of major risk factors in the pathway. In addition, the cross-sectional nature of this study needs to be considered. The effects of SHSE on cardiovascular risk factors may be seen only in the long term but not in the short term or cross-sectionally.

The main novelty of our study is that it is the first reported evaluation of the association between conventional cardiovascular risk factors and SHSE using both subjective and objective methods in a large Korean population. We believe that the use of urine cotinine level minimized the potential for misclassification bias that could occur with the use of self-report questionnaires alone.

The main limitation of this study is the cross-sectional nature. Future studies with a longitudinal design would provide better insight into the impact of SHSE on major cardiovascular risk factors. Second, selection bias is possible. Among 37 753 participants who underwent surveys during the study period, 7376 (19.5%) were included in this analysis. In addition, most nonsmokers were women and urine cotinine was less likely to be available in men. Further, more than three-fourths of this study population was woman. Third, although we excluded participants with major cardiovascular disease (i.e., CHD and stroke), there is still a possibility that patients with subclinical cardiovascular disease might have been included in this study. This is another potential source of bias. Forth, the office BP measurements have shown to have lower prognostic value than ambulatory BP monitoring measures [38,39]. Finally, we cannot exclude the possibility that residual confounding and unmeasured confounders are present.

We performed a cross-sectional, population-based study of healthy adults who had never smoked and who were without known cardiovascular diseases with a purpose to evaluate the relationship between SHSE and cardiovascular risk factors. There was no consistent relationship between SHSE measured subjectively by self-report questionnaires and objectively by urine cotinine levels and BP, lipid, or fasting glucose levels. When stratified according to sex and verified by total study population with adjustment of medication, the results did not change. As there has been cumulated evidence that SHSE is associated with an increased risk of cardiovascular mortality and morbidity; this study's findings suggest further long-term prospective studies are needed to evaluate the effect of SHSE as a cardiovascular risk factor.

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Conflicts of interest

There are no conflicts of interest.

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Reviewer's Summary Evaluation

Reviewer 1

Among contributions, the finding of unexpected lack of significant results for most relations analyzed in the context of limited number of studies on this issue with generally positive results.

Among limitations, the cross-sectional design of the study, which indicate that further prospective studies are needed to clarify this interesting issue.