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 (≥18.5 and <25 kg/m²), overweight (≥25 kg/m²), or obese (≥30 kg/m²). 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). Geometric means as log transformed are shown in Table 1. None of the individuals included in this study 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.

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 12.7 ± 0.2, 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.

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 assessed 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 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 (%)          |                | 0.1 (0.1) |
| 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) |

Data are presented as mean ± SE or % (SE). Geometric means as log transformed are presented for triglyceride. GFR, glomerular filtration rate.
The image contains a table showing the association of self-reported secondhand smoke exposure status with blood pressure, lipid profiles, and fasting glucose levels. The table includes data for SBP, DBP, cholesterol, HDL cholesterol, LDL cholesterol, triglyceride, and fasting glucose. The table is structured in a tabular format with columns for each variable and rows for different categories of exposure status. The data are presented as mean ± SE, with geometric means as log-transformed for triglyceride. Adjusted models were used to control for age, sex, BMI, education, smoking status, alcohol consumption, physical activity, sodium intake, total calorie intake, and fat proportion. Sensitivity analyses were conducted without excluding participants taking medications that could affect blood pressure or triglyceride levels.

Table 3, [http://links.lww.com/HJH/A789](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](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](http://links.lww.com/HJH/A789)). Log-transformed cotinine was not associated with any

### 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 |
|---|-----|-----|-------------|-----------------|-----------------|--------------|----------------|
| 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 |

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

| SBP | DBP | Cholesterol | HDL cholesterol | LDL cholesterol | Triglyceride | Fasting glucose |
|-----|-----|-------------|-----------------|-----------------|--------------|----------------|
| No  | 6197 | 114.7 ± 0.4 | 74.8 ± 0.2 | 190.3 ± 1.0 | 49.8 ± 0.2 | 117.7 ± 0.8 | 96.7 (94.6–98.9) | 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 |

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

|                | \( \beta \) | Standard error | \( P \) value |
|----------------|------------|----------------|--------------|
| 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

|                | \( \beta \) | Standard error | \( P \) value |
|----------------|------------|----------------|--------------|
| 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

|                | \( \beta \) | Standard error | \( P \) value |
|----------------|------------|----------------|--------------|
| SBP            | 0.010      | 0.098          | 0.917        |
| DBP            | 0.009      | 0.069          | 0.900        |
| Cholesterol    | −0.048     | 0.245          | 0.695        |
| 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 BP 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

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Author contributions: S.K., S.-H.K., and T.-J.Y. were responsible for conception and design of the study, D.H., S.-H.K., H.-J.K., K.-D.H., and I.-Y.O. were contributed to data collection and analysis. J.J.P., Y.C., Y.E.Y., C.-H.Y., J.-W.S., and H.-Y.L. were contributed to data interpretation. Y.-S.C., G.-Y.C., I.-H.C., and D.-J.C. gave advice on the first draft. S.K. and S.-H.K. wrote the first draft of the article. T.-J.Y. accept responsibility for the final content of the article; all of the authors approved the study before submission.

Conflicts of interest
There are no conflicts of interest.

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