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Keywords:	second-hand smoke, Hypertension < CARDIOLOGY, blood pressure, KNHANES

Second-hand smoke exposure is associated with hypertension in female never smokers: a cross-sectional survey design study using data from KNHANES 2010-2012

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Running title: second-hand smoking exposure and hypertension

Abstract

Objectives: Second-hand smoke (SHS) exposure is associated with cardiovascular disease. This study aims to determine the association between SHS exposure estimated by questionnaire and hypertension in Korean female never smokers.

Setting: Korean National Health and Nutrition Examination Survey (KNHANES) V was conducted from 2010 to 2012.

Participants: We selected the female population with never smokers aged over 20.

Primary and secondary measures: SHS exposure in both the home and work place was estimated using a self-reporting questionnaire. We evaluated the association between SHS exposure and hypertension by using survey design analysis. And we calculated systolic and diastolic blood pressure according to SHS exposure.

Results: There were 8,987 female never smokers. We divided the subjects into three groups according to the amount of SHS exposure: none—group I, <2hr/day—group II, and ≥2hr/day—group III. Using multivariate analysis, hypertension was more commonly associated with group III than group I (adjusted OR=1.50, 95% CI: 1.00–2.04, *P*=0.011). Adjusted systolic and diastolic blood pressures in the population who had not been diagnosed with hypertension by their doctors and was not taking antihypertensive medication were significantly elevated in group III (*P*=0.030 and *P*=0.011, respectively).

Conclusion: SHS exposure is significantly associated with hypertension in female never smokers.

Keywords: second-hand smoke, hypertension, blood pressure, KNHANES

Strengths and limitations of this study

- This study demonstrated hypertension is more common in female never smokers with higher daily second-hand smoke (SHS) exposure and measured the differences of systolic and diastolic pressure between the groups.
- This study included the largest population (8,987) used to examine SHS exposure based on a well-structured nationwide survey.
- Survey design analysis was applied to reduce the possibility of biased estimates.
- This cross-sectional analysis could not conclude the causal relationship between SHS exposure and hypertension.

INTRODUCTION

With a global prevalence of 26.4%,[1] hypertension is a large contributor to the burden of disease in adults. Well-known risk factor of hypertension is family history, but it is non-modifiable. Active cigarette smoking is another risk factor,[2] and it is totally preventable.[3]

Active smoking causes detrimental effects on smokers themselves, but second-hand smoke (SHS) exposure can also harm innocent bystanders. About 85% of SHS exposure results from sidestream smoke, which rises from the tip of a burning cigarette.[4] Sidestream smoke is potentially more harmful because it is not filtered. In recent years, the public has paid more attention to the harmful effect of SHS exposure on cardiovascular diseases[5] and supportive evidence is accumulating.[6-8] Although the positive relationship between SHS exposure and hypertension has been reported, some studies did not confirm this relationship.[9] In Korea, the adult smoking rate was 24.1% in 2013, and there was a big difference between sexes, 42.1% in men and 6.2% in women. Therefore, women are more vulnerable to SHS exposure. The aim of this study was to elucidate the association between SHS exposure and hypertension in Korean female never smokers using national survey data.

MATERIALS AND METHODS

Study population

The detailed data obtained from the fifth Korean National Health and Nutrition Examination Survey (KNHANES) V 2010-2012 are described elsewhere.[10] KNHANES is an annual collection of data from the Korean Statistical Office census of 3,800 households from 576 randomly selected survey areas with the number selected from each area proportional to its size. Trained interviewers administer questionnaires on various health-related information, and subjects self-report their alcohol and smoking habits. KNHANES uses a complex, multi-stage probability sample design. The sample represents the total non-institutionalized civilian population of Korea. These data are available on the internet (https://knhanes.cdc.go.kr). Adult female never smokers >20 years old with second hand smoking history available were included. Never smoker was defined when the total amount of smoking was <100 cigarettes during the lifetime. If histories of smoking or SHS exposure were not available, the cases were excluded. The institutional review board of Seoul National University Hospital waived the need for written informed consent from the participants (IRB no: H1509-011-699).

Definition of SHS exposure

Daily SHS exposure time was estimated both in the workplace and home. Total SHS exposure was calculated by the summation of both values. The total amount of SHS exposure was categorized into three groups according to exposure time; none (group I), <2hr/day (group II), and ≥2hr/day (group III).

Definition of hypertension

Hypertension was defined if one or more of the criteria below were met. 1) diagnosed by physician, 2) using anti-hypertensive medications, 3) systolic blood pressure (BP)

≥140 mmHg, 4) diastolic BP ≥90 mmHg. The measurement of BP was available elsewhere.[11] In brief, after at least 5 minutes rest in seating position, BP was manually measured 3 times at 30-second intervals. Finally, the average of the 2nd and 3rd measurements were used.

Statistical analysis

Weighted analysis was used for the KNHANES V data. χ^2 test was used for categorical variables and *t*-test was used for continuous variables in univariate analysis.[12] Multivariable logistic regression with survey weight analysis was conducted to evaluate the association between SHS and hypertension. In model 1, the only variable was age and in model 2, multiple covariates included age, body mass index (BMI), education, occupation, socioeconomic status, alcohol intake, marital status, diabetes, and serum total cholesterol were adjusted. In addition, we compared SBP and DBP between groups, in which covariates were also adjusted. This analysis was limited to participants who had not been diagnosed with hypertension by their physician and were not taking antihypertensive medications. *P*-value <0.05 was considered significant. We used the STATA software version 13.1 (StataCorp, College Station, Texas, US) for statistical analysis.

RESULTS

Baseline characteristics of participants

The KNHANES V data include 25,534 participants. Among them, we found 10,915 female adults (age >20 years old). After excluding 822 participants with unknown smoking history, 1,084 ever-smokers, and 22 with unknown SHS exposure, a total of 8,987 female never smokers were available for analysis (Figure 1). Their mean age was 47.7±0.3 years. The majority of the study population was light drinkers (<1/week), and socioeconomic status was evenly distributed (Table 1). The percentages of participants categorized into group I, II, and III according to the degree of their SHS exposures were 68.1%, 24.2%and 7.7%. The participants in group I were older than those in other groups (49.6 vs. 42.9 and 45.2 years old; P<0.001). The percentages of hypertension in group I, II, and III were 29.3%, 19.3% and 25.9%, respectively (P<0.001). Systolic and diastolic BP, education level, alcohol intake, marital status, and the prevalence of diabetes were significantly different between groups.

Hypertension is associated with SHS exposure measured by questionnaire in female never smokers

Hypertension was significantly associated with SHS exposure (group III) after adjustment for age (model 1, adjusted OR=1.49, 95% CI: 1.14–1.93, P=0.003) and even after adjustment for age, height, weight, waist circumference, serum triglyceride, fasting glucose, education, occupation, alcohol intake, and marital status (model 2, adjusted OR=1.50, 95% CI: 1.10–2.04, P=0.011, Table 2).

Systolic and diastolic blood pressure is increasing according to SHS exposure

The mean systolic and diastolic BP increased proportional to the increasing SHS exposure. On average, the differences between group III and group I were 2.3 mmHg

and 1.7 mmHg in systolic and diastolic BP, respectively (P=0.030 and P=0.011) (Figure 2).

DISCUSSION

This study demonstrated the association between SHS exposure measured by self-reported questionnaire in female never smokers and hypertension, using a well-designed nationwide surveillance data.[13] Our findings strengthen the evidence of the harmful effect of chronic SHS exposure on hypertension. Additionally, we calculated the degree of elevated mean systolic and diastolic BP in group III (≥2hr/day): 2.3 and 1.7mmHg, respectively. According to a previous study, a 3mmHg systolic BP difference was observed with a 10 kg increase body weight.[14] Compared to this 3 mmHg systolic BP change accomplished by weight reduction, the value of 2.3 mmHg associated with SHS exposure is significant.

Pharmacologically, nicotine stimulates the sympathetic nervous system in active smokers.[15 16] Epinephrine and norepinephrine are released by nicotine stimulation, and these catecholamines increase myocardial contractility and promote vasoconstriction, which results in increases in BP.[17] The association between smoking and hypertension has also been observed in a mouse model,[18] and in epidemiologic studies.[2] Moreover, the amount of smoking was positively correlated with hypertension[19] and carotid artery atherosclerosis severity.[20] The biologic effect of SHS exposure on BP could be extrapolated from the effects of active smoking. Plasma nicotine level was increased after SHS exposure in healthy nonsmokers.[21] In the context of active smoking exposure,

the duration or amount of SHS exposure is also important in the evaluation of the chronic effect of passive smoking. Although the experimental studies of short-term SHS exposure did not demonstrate a change in BP.[21 22] population-based studies have shown that the habitual SHS exposure is associated with hypertension.[6 7]

Theoretically, SHS exposure can be determined by direct measurements of smoke components in the air, self-reported questionnaires, or by measurements of biomarkers from body fluid, such as serum, urine or saliva.[23] The correlation between self-reported questionnaire and biochemical assessment has been generally accurate in prior meta-analysis.[24] The association between hypertension and SHS exposure was demonstrated by using serum cotinine in the previous study[6] and self-reported questionnaire in our study. Compared to biomarkers, self-reported questionnaires are inexpensive and provide information on long-term exposure.

To our knowledge, this study included the largest population used to examine SHS exposure based on a well-structured nationwide survey (KNHANES V),[13] and a survey design analysis was applied to reduce the possibility of biased estimates.[12] In addition, we included various confounding factors, including age, height, weight, waist circumference, serum triglyceride, fasting glucose, education, occupation, alcohol intake and marital status in the statistical model to clarify the conclusion. However there were some limitations. First, we included only women, because of two considerations: the small population of male never smokers and the possibility of an association between SHS exposure and sex. In our dataset, the proportion of male never smokers was 20.2% of total never smokers. We thought that the small proportion of male never

smokers would not represent the nationwide population. Another consideration was interaction. Smoking could influence cardiovascular disease due to sex-dependent biologic effect.[25] Second, our cross-sectional analysis could not conclude the causal relationship between SHS exposure and hypertension. For example, in some cases, hypertension may have been present before exposure to SHS. Third, information on the smoke concentration and the environment where SHS exposure occurred was not available. Fourth, we could not exclude hidden smokers. The proportion of cotinine-verified active smokers was previously noted to be larger than that of self-reported smokers.[26] In our dataset (KNHANES V), urine cotinine level was available in 19% of female never smokers. In that group, 2.7% female never smokers had a urine cotinine level >200 ng/mL, the cutoff value defining an active smoker.[23] Thus, the possibility of active smoker contamination does exist. Fifth, there could be concerns that factors related with hypertension were not sufficiently investigated. For example, estrogen increases the susceptibility to hypertension [27]. Because estrogen tends to rise in perimenopausal period, perimenopausal women hence are likely to become hypertensive. Although our survey did not measure the estrogen level, the analysis in which perimenopausal participants were excluded also shows the significant relationship between SHS exposure and hypertension (data not shown). A family history of hypertension could also contribute on the development of hypertension. We did not exclude participants who had a family history of hypertension. However, even when participants with a self-reported family history of hypertension were excluded, the significant relationship between SHS exposure and hypertension was also observed (data not shown).

In conclusion, on using self-reported questionnaires, we found that SHS exposure was significantly associated with hypertension in Korean female never smokers. Both systolic and diastolic blood pressures were significantly elevated in the SHS exposed population.

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Competing interests: None declared.

Author Contributions

Conceptualization: YSP, CHL

Data curation: YSP, CHL, YIL

Methodology: YSP, CHL, KHY

Project administration: CHL

Original draft: YSP, CHL

Review & editing: YSP, CHL, YIL, CMA, JOK, JHP, SHL, JYK, EMC, THJ, KHY

Patient consent: Waived from IRB

Ethics approval: Seoul National University Hospital IRB

Data sharing statement: The original data came from Korean National Health and Nutritional Examination Survey (https://knhanes.cdc.go.kr/knhanes/eng/index.do). All the data presented this manuscript are available from the corresponding author at kauri670@empal.com.

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Figure 1. Flow diagram of study population.

Figure 2. Adjusted means of systolic (A) and diastolic (B) blood pressure according to second-hand smoke exposure in a population without previous diagnosis of hypertension or antihypertensive treatment. The mean values are adjusted for age, height, weight, waist circumference, serum triglyceride, fasting glucose, education, occupation, alcohol intake, and marital status.

Table 1. Baseline characteristics according to the degree of second-hand smoke exposure.

Variables	SHS exposure			*P* value
	None	<2hr/day	≥2hr/day	
% of total	68.1%	24.2%	7.7%	
Age (years)	49.6±0.3	42.9±0.4	45.2±0.6	<0.001*
Weight (kg)	57.5±0.2	57.5±0.3	59.2±0.5	<0.001*
Height (cm)	156.6±0.1	157.9±0.2	157.8±0.3	<0.001*
Waist Circumference (cm)	78.7±0.2	76.9±0.3	78.9±0.5	0.009*
BMI (kg/m^2)	23.5±0.1	23.1±0.1	23.8±0.2	0.536
Blood pressure				
Systole (mmHg)	117.5±0.3	113.5±0.5	117.7±0.9	<0.001*
Diastole (mmHg)	74.0±0.2	73.6±0.3	75.7±0.5	0.082
Total cholesterol (mg/dL)	190.4±0.7	186.5±1.0	192.9±1.8	0.453
HDL (mg/dL)	55.2±0.3	55.6±0.6	57.7±1.1	0.068
Triglyceride (mg/dL)	115.0±1.8	104.7±1.9	112.2±4.4	0.016*
Fasting glucose (mg/dL)	95.9±0.4	93.6±0.5	95.1±0.9	0.008*
Hypertension	29.3%	19.3%	25.9%	<0.001*
Diabetes mellitus	14.8%	9.8%	10.0%	<0.001*
Metabolic syndrome	25.6%	17.0%	18.8%	<0.001*
Alcohol intake				<0.001*
Never drinker	21.7%	11.2%	18.5%	
Former drinker	18.0%	13.9%	16.5%	
Light drinker (≤1/week)	53.9%	66.8%	57.3%	
Moderate drinker (2-3/week)	5.1%	7.1%	6.2%	
Heavy drinker (≥4/week)	1.3%	1.0%	1.5%	
Marital status	88.8%	76.9%	84.1%	<0.001*
Educational level				<0.001*
Below middle school	30.4%	18.2%	26.8%	
Middle school	9.8%	9.9%	10.2%	
High school	29.8%	39.9%	33.1%	
Above high school	30.1%	31.9%	30.0%	
Socioeconomic status				0.144
1Q	25.3%	25.3%	27.3%	
2Q	26.8%	25.7%	21.2%	
3Q	25.3%	25.9%	23.7%	
4Q	22.6%	23.1%	27.9%	
Occupation				<0.001*
Manager or professional	11.0%	15.6%	11.8%	
Office worker	5.0%	14.3%	13.3%	

Service	9.0%	22.3%	42.4%
Farmer worker or fisherman	6.0%	5.6%	5.0%
Technician	2.3%	4.8%	4.2%
Labor worker	8.0%	12.8%	11.6%
Unemployed (outside house)	58.8%	24.7%	17.4%

*: P<0.05

BMI, body mass index; SHS, second-hand smoke

Table 2. Association between second-hand smoke (SHS) exposure and hypertension.

	Model 1†			Model 2‡		
For hypertension	Adjusted OR	95% CI	*P* value	Adjusted OR	95% CI	*P* value
SHS exposure						
None	1			1		
< 2hr/day	1.06	0.90 – 1.25	0.487	1.01	0.91 – 1.33	0.314
≥ 2hr/day	1.49	1.14 – 1.93	0.003*	1.50	1.10 – 2.04	0.011*

*P<0.05

†Adjusted for age.

‡Adjusted for age, height, weight, waist circumference, serum triglyceride, fasting glucose, education, occupation, alcohol intake, and marital status.

CI, confidence interval; OR, odds ratio; SHS, second-hand smoke

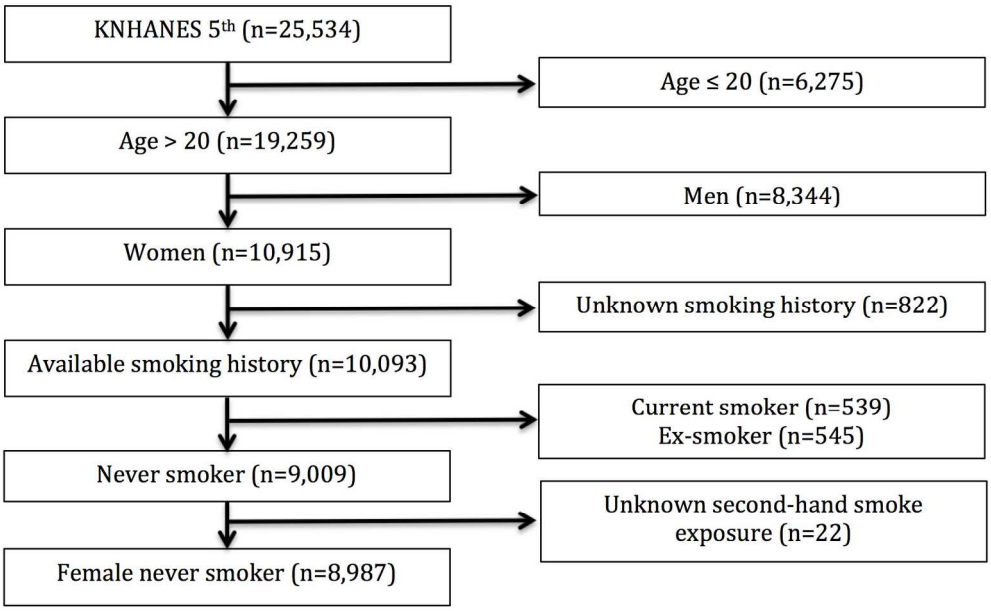

Figure 1. Flow diagram of study population.

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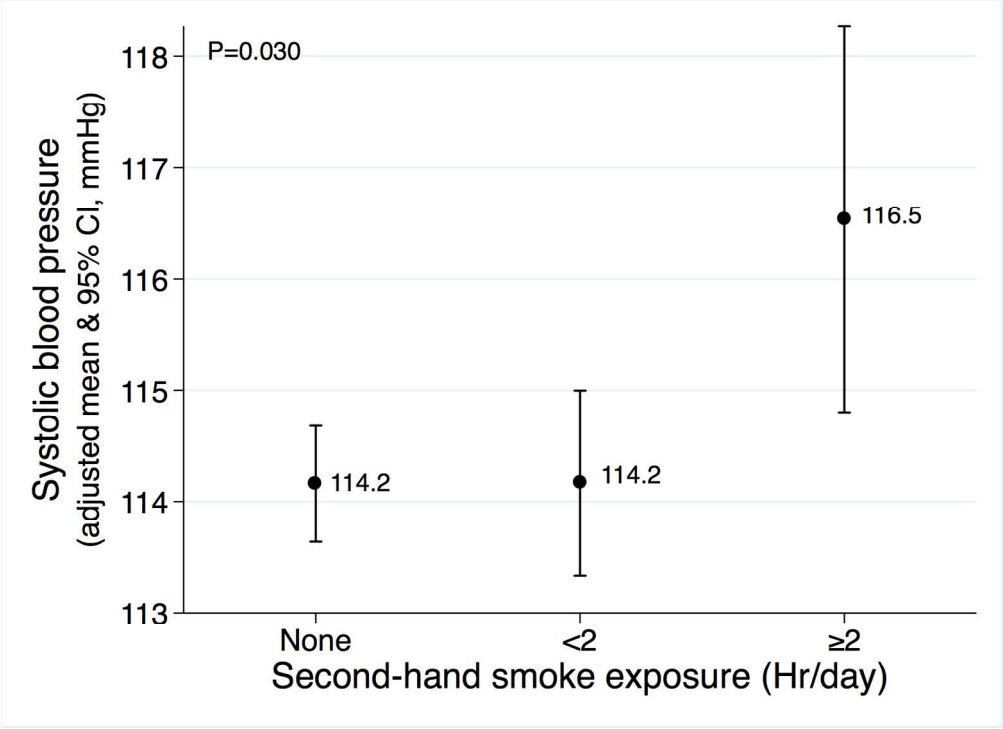
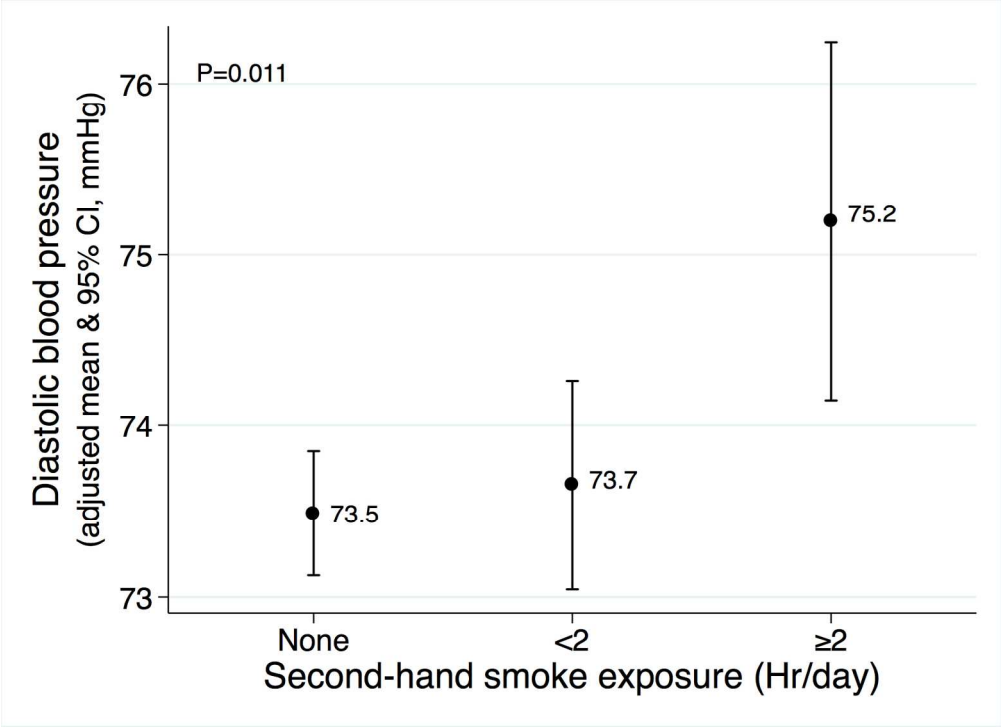


Figure 2. Adjusted means of systolic (A) and diastolic (B) blood pressure according to second-hand smoke exposure in a population without previous diagnosis of hypertension or antihypertensive treatment. The mean values are adjusted for age, height, weight, waist circumference, serum triglyceride, fasting glucose, education, occupation, alcohol intake, and marital status.

340x247mm (144 x 144 DPI)



340x247mm (144 x 144 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	NE
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	6

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	NE
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	7-8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NE
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NE
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	NE
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NE

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The association between second-hand smoke exposure and hypertension in never smokers: a cross sectional survey using data from Korean National Health and Nutritional Examination Survey V, 2010-2012

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The association between second-hand smoke exposure and hypertension in never smokers: a cross sectional survey using data from Korean National Health and Nutritional Examination Survey V, 2010-2012

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Running title: second-hand smoking exposure and hypertension

Abstract

Objectives: Second-hand smoke (SHS) exposure is associated with cardiovascular disease. This study aims to determine the association between SHS exposure estimated by questionnaire and hypertension in Korean never smokers.

Setting: Korean National Health and Nutrition Examination Survey (KNHANES) V was conducted from 2010 to 2012.

Participants: We selected the never smokers aged over 20 years who answered the question about the SHS exposure.

Primary and secondary measures: SHS exposure in both the home and work place was estimated using a self-reporting questionnaire. We investigated the association between SHS exposure and hypertension by using multivariate analysis. And we evaluated the mean systolic and diastolic blood pressure values according to SHS exposure after adjusting for possible confounding factors. All analyzes were carried out by female and male, separately.

Results: There were 10,532 (female 8,987 and male 1,545) never smokers. We divided the subjects into three groups according to the amount of SHS exposure: none—group I, <2hr/day—group II, and ≥2hr/day—group III. Using multivariate analysis, hypertension was more commonly associated with group III than group I in female (adjusted OR=1.50, 95% CI: 1.00–2.04, *P*=0.011). Adjusted mean systolic and diastolic blood pressure values in female who was not taking antihypertensive medication were significantly elevated in group III by 2.3 and 1.7 mmHg respectively.

Conclusion: SHS exposure is significantly associated with hypertension in female never smokers.

Keywords: second-hand smoke, hypertension, blood pressure, KNHANES

Strengths and limitations of this study

- This study demonstrated hypertension is more common in female never smokers with higher daily second-hand smoke (SHS) exposure and measure the differences of systolic and diastolic blood pressure means by different SHS exposure groups
- This study included the largest population (10,532) used to examine SHS exposure based on a well-structured nationwide survey.
- Survey design analysis was applied to reduce the possibility of biased estimates.
- This cross-sectional analysis could not conclude the causal relationship between SHS exposure and hypertension.

INTRODUCTION

With a global prevalence of 26.4%,[1] hypertension is a large contributor to the burden of disease in adults. Well-known risk factor of hypertension is family history, but it is non-modifiable. Active cigarette smoking is another risk factor,[2] and it is totally preventable.[3]

Active smoking causes detrimental effects on smokers themselves, but second-hand smoke (SHS) exposure can also harm innocent bystanders. About 85% of SHS exposure results from sidestream smoke, which rises from the tip of a burning cigarette.[4] Sidestream smoke is potentially more harmful because it is not filtered. In recent years, the public has paid more attention to the harmful effect of SHS exposure on cardiovascular diseases[5] and supportive evidence is accumulating.[6-8] Although the positive relationship between SHS exposure and hypertension has been reported, some studies did not confirm this relationship.[9] In Korea, the adult smoking rate was 24.1% in 2013, and there was a big difference between sexes, 42.1% in men and 6.2% in women. In terms of the prevalence, women are more vulnerable to SHS exposure. The aim of this study was to elucidate the association between SHS exposure and hypertension in Korean never smokers using national survey data.

MATERIALS AND METHODS

Study population

The detailed data obtained from the fifth Korean National Health and Nutrition Examination Survey (KNHANES) V 2010-2012 are described elsewhere.[10] KNHANES is an annual collection of data from the Korean Statistical Office census of 3,800 households from 576 randomly selected survey areas with the number selected from each area proportional to its size. Trained interviewers administer questionnaires on various health-related information, and subjects self-report their alcohol and smoking habits. KNHANES uses a complex, multi-stage probability sample design. The sample represents the total non-institutionalized civilian population of Korea. These data are available on the internet (https://knhanes.cdc.go.kr). Adult never smokers >20 years old with second hand smoking history available were included. Never smoker was defined when the total amount of smoking was <100 cigarettes during the lifetime. If histories of smoking or SHS exposure were not available, the cases were excluded. The institutional review board of Seoul National University Hospital waived the need for written informed consent from the participants (IRB no: H1509-011-699).

Definition of SHS exposure

Daily SHS exposure time was estimated both in the workplace and home. Total SHS exposure was calculated by the summation of both values. The total amount of SHS exposure was categorized into three groups according to exposure time; none (group I), <2hr/day (group II), and ≥2hr/day (group III).

Definition of hypertension

Hypertension was defined if one or more of the criteria below were met. 1) diagnosed by physician, 2) using anti-hypertensive medications, 3) systolic blood pressure (BP)

≥140 mmHg, 4) diastolic BP ≥90 mmHg. The measurement of BP has been described elsewhere.[11] In brief, after at least 5 minutes rest in a seating position, BP was manually measured 3 times at 30-second intervals. Finally, the average of the 2nd and 3rd measurements were used.

Statistical analysis

Weighted analysis was used for the KNHANES V data. χ^2 test was used for categorical variables and *t*-test was used for continuous variables in univariate analysis.[12] Multivariable logistic regression with survey weight analysis was conducted to evaluate the association between SHS and hypertension. In model 1, the only co-variable was age, while in model 2, multiple covariates such as age, height, weight, waist circumference, serum triglyceride, fasting glucose, education, occupation, alcohol intake, and marital status were included and adjusted for. In addition, we compared SBP and DBP means between groups, again adjusting for covariates. This analysis was limited to participants who were not taking antihypertensive medications. *P*-value <0.05 was considered significant. We used the STATA software version 13.1 (StataCorp, College Station, Texas, US) for statistical analysis.

Patient and Public Involvement

The KNHANES V data were released after anonymization. The study population were not involved in the design of this study.

RESULTS

Baseline characteristics of participants

The KNHANES V data include 25,534 participants. Among them, we found 19,259 adults (age >20 years old). After excluding 1,699 participants with unknown smoking history, 6,791 ever-smokers, and 236 with unknown SHS exposure, a total of 10,532 (female 8,987 and male 1,545) never smokers were available for analysis (Figure 1). Their mean age was 47.7±0.3 years in female and 39.9±0.5 years in male. The majority of the study population was light drinkers (<1/week), and socioeconomic status was evenly distributed by SHS exposure groups (Table 1). The percentages of participants categorized into group I, II, and III according to the degree of their SHS exposures were 68.1%, 24.2%, 7.7% in female and 53.3%, 39.4%, 7.2% in male. The participants in group I were older than those in the two other groups. The percentages of hypertension in group I, II, and III were 29.3%, 19.3%, 25.9% in female and 25.2%, 22.0%, 30.6% in male. BP, education level, alcohol intake were significantly different between the three SHS exposure groups.

Hypertension is associated with SHS exposure measured by questionnaire in female never smokers

In female group, hypertension was significantly associated with SHS exposure (group III) after adjustment for age (model 1, adjusted OR=1.49, 95% CI: 1.14–1.93, *P*=0.003) and even after adjustment for age, height, weight, waist circumference, serum triglyceride, fasting glucose, education, occupation, alcohol intake, and marital status (model 2, adjusted OR=1.50, 95% CI: 1.10–2.04, *P*=0.011, Table 2). But these differences were not observed in male group.

Systolic and diastolic blood pressure is increasing according to SHS exposure

The mean systolic and diastolic BP increased proportional to the increasing SHS exposure in female group. On average, the differences between group III and group I were 2.3 mmHg and 1.7 mmHg in systolic and diastolic BP, respectively (P=0.030 and P=0.011) (Figure 2). In male group, we observed the increased tendency of the mean systolic and diastolic BP.

DISCUSSION

This study demonstrated the association between SHS exposure measured by self-reported questionnaire in female never smokers and hypertension, using a well-designed nationwide survey.[13] Our findings strengthen the evidence of the harmful effect of chronic SHS exposure on hypertension. Additionally, we calculated the difference in mean systolic and diastolic BP between female group I and III by 2.3 and 1.7 mmHg, respectively. According to a previous study, a 3mmHg systolic BP difference was observed with a 10 kg increase in body weight.[14] Compared to this 3 mmHg systolic BP change accomplished by weight reduction, the value of 2.3 mmHg associated with SHS exposure is significant.

The association between hypertension and SHS exposure was observed only in female group. We postulated three possibilities. First, male never smokers were younger than female who never smoked (39.9±0.5 vs. 47.7±0.3). The influence of smoking exposure on BP could be limited in younger man.[15] Second, smoking exposure could influence

cardiovascular disease due to sex-dependent biologic effect.[16] Third, the low statistical power due to small sample size could affect results. In our dataset, the proportion of male never smokers was only 19.4% of total male population aged over 20 years. Although we did not achieve statistically significant results in male group, the changing pattern of systolic and diastolic BP was same, and it could support the biologic effect between SHS exposure and BP.

Pharmacologically, nicotine stimulates the sympathetic nervous system in active smokers.[17 18] Epinephrine and norepinephrine are released by nicotine stimulation, and these catecholamines increase myocardial contractility and promote vasoconstriction, which results in increases in BP.[19] The association between smoking and hypertension has also been observed in a mouse model,[20] and in epidemiologic studies.[2] Moreover, the amount of smoking was positively correlated with hypertension[21] and carotid artery atherosclerosis severity.[22] The biologic effect of SHS exposure on BP could be extrapolated from the effects of active smoking. Serum nicotine level was increased after SHS exposure in healthy nonsmokers.[23] In the context of active smoking exposure, the duration or amount of SHS exposure is also important in the evaluation of the chronic effect of passive smoking. Although the experimental studies of short-term SHS exposure did not demonstrate a change in BP.[23 24] population-based studies have shown that the habitual SHS exposure is associated with hypertension.[6 7]

Theoretically, SHS exposure can be determined by direct measurements of smoke components in the air, self-reported questionnaires, or by measurements of biomarkers from body fluid, such as serum, urine or saliva.[25] The correlation between self-reported

questionnaire and biochemical assessment has been generally accurate in prior meta-analysis.[26] The association between hypertension and SHS exposure was demonstrated by using serum cotinine in the previous study[6] and self-reported questionnaire in our study. Compared to biomarkers, self-reported questionnaires are inexpensive and provide information on long-term exposure.

To our knowledge, this study included the largest population used to examine SHS exposure based on a well-structured nationwide survey (KNHANES V),[13] and a survey design analysis was applied to reduce the possibility of biased estimates.[12] In addition, we included various potential confounding factors, including age, height, weight, waist circumference, serum triglyceride, fasting glucose, education, occupation, alcohol intake and marital status in the statistical model to clarify the conclusion. However there were some limitations. First, our cross-sectional analysis could not conclude the causal relationship between SHS exposure and hypertension. For example, in some cases, hypertension may have been present before exposure to SHS. Second, information on the smoke concentration and the environment where SHS exposure occurred was not available. Third, we could not exclude hidden smokers. The proportion of cotinine-verified active smokers was previously noted to be larger than that of self-reported smokers.[27] In our dataset (KNHANES V), urine cotinine level was available in 19% of female never smokers. In that group, 2.7% female never smokers had a urine cotinine level >200 ng/mL, the cutoff value defining an active smoker.[25] Thus, the possibility of active smoker contamination does exist. Forth, there could be concerns that factors related with hypertension were not sufficiently investigated. For example, estrogen increases the susceptibility to hypertension.[28] Because estrogen tends to rise in

perimenopausal period, perimenopausal women hence are likely to become hypertensive. Although our survey did not measure the estrogen level, the analysis in which perimenopausal participants were excluded also shows the significant relationship between SHS exposure and hypertension (data not shown). A family history of hypertension could also contribute on the development of hypertension. We did not exclude participants who had a family history of hypertension. However, even when participants with a self-reported family history of hypertension were excluded, the significant relationship between SHS exposure and hypertension was also observed (data not shown).

In conclusion, on using self-reported questionnaires, we found that SHS exposure was significantly associated with hypertension in Korean female never smokers. Both systolic and diastolic blood pressures were significantly elevated in the SHS exposed population.

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Author Contributions

Conceptualization: YSP, CHL

Data curation: YSP, CHL, YIL

Methodology: YSP, CHL, KHY

Project administration: CHL

Original draft: YSP, CHL

Review & editing: YSP, CHL, YIL, CMA, JOK, JHP, SHL, JYK, EMC, THJ, KHY

Patient consent: Waived from IRB

Ethics approval: Seoul National University Hospital IRB

Data sharing statement: The original data came from Korean National Health and Nutritional Examination Survey (https://knhanes.cdc.go.kr/knhanes/eng/index.do). All the data presented this manuscript are available from the corresponding author at kauri670@empal.com.

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Table 1. Baseline characteristics according to the degree of second-hand smoke exposure.

Variables	Female			*P* value	Male			*P* value
	Second-hand smoke exposure				Second-hand smoke exposure			
	None	<2hr/day	≥2hr/day		None	<2hr/day	≥2hr/day	
% of total	68.1	24.2	7.7		53.3	39.4	7.2	
Age (years)	49.6±0.3	42.9±0.4	45.2±0.6	<0.001*	41.7±0.7	37.4±0.6	40.2±1.4	<0.001*
Weight (kg)	57.5±0.2	57.5±0.3	59.2±0.5	<0.001*	70.1±0.5	71.4±0.6	72.7±1.4	0.032*
Height (cm)	156.6±0.1	157.9±0.2	157.8±0.3	<0.001*	171.4±0.3	172.2±0.3	170.6±0.8	0.783
Waist Circumference (cm)	78.7±0.2	76.9±0.3	78.9±0.5	0.009*	82.9±0.4	83.0±0.5	84.8±1.1	0.231
BMI (kg/m^2)	23.5±0.1	23.1±0.1	23.8±0.2	0.536	23.8±0.1	24.1±0.2	24.9±0.4	0.021*
Blood pressure (mmHg)								
Systole	117.5±0.3	113.5±0.5	117.7±0.9	<0.001*	119.3±0.6	118.9±0.6	120.8±1.7	0.740
Diastole	74.0±0.2	73.6±0.3	75.7±0.5	0.082	77.9±0.4	79.9±0.5	79.9±1.1	0.005*
Total cholesterol (mg/dL)	190.4±0.7	186.5±1.0	192.9±1.8	0.453	183.±1.6	182.7±1.8	186.5±3.8	0.666
HDL (mg/dL)	55.2±0.3	55.6±0.6	57.7±1.1	0.068	51.0±0.9	50.3±1.2	50.4±2.5	0.583
Triglyceride (mg/dL)	115.0±1.8	104.7±1.9	112.2±4.4	0.016*	121.8±3.5	129.6±4.7	121.4±7.2	0.339
Fasting glucose (mg/dL)	95.9±0.4	93.6±0.5	95.1±0.9	0.008*	96.6±0.9	95.7±0.8	96.6±1.8	0.658
Hypertension	29.3	19.3	25.9	<0.001*	25.2	22.0	30.6	0.197
Diabetes mellitus	14.8	9.8	10.0	<0.001*	10.0	9.2	13.1	0.527
Metabolic syndrome	25.6	17.0	18.8	<0.001*	23.2	20.2	12.9	0.325
Alcohol intake				<0.001*				<0.001*
Never drinker	21.7	11.2	18.5		11.3	7.3	7.4	
Former drinker	18.0	13.9	16.5		13.5	6.1	5.9	
Light drinker (≤1/week)	53.9	66.8	57.3		56.7	66.5	53.8	
Moderate drinker (2-3/week)	5.1	7.1	6.2		13.9	16.5	22.4	

Heavy drinker (≥4/week)	1.3	1.0	1.5		4.7	3.6	10.5	
Marital status	88.8	76.9	84.1	<0.001*	58.0	59.0	59.0	0.955
Educational level				<0.001*				<0.001*
Below middle school	30.4	18.2	26.8		9.9	2.9	7.7	
Middle school	9.8	9.9	10.2		6.2	6.4	9.0	
High school	29.8	39.9	33.1		43.0	40.3	47.6	
Above high school	30.1	31.9	30.0		40.9	50.5	35.8	
Socioeconomic status				0.144				0.116
1Q	25.3	25.3	27.3		30.2	21.8	30.5	
2Q	26.8	25.7	21.2		21.2	24.4	20.0	
3Q	25.3	25.9	23.7		25.6	25.5	26.8	
4Q	22.6	23.1	27.9		23.0	28.3	22.7	
Occupation				<0.001*				<0.001*
Manager or professional	11.0	15.6	11.8		21.8	28.6	12.5	
Office worker	5.0	14.3	13.3		7.6	15.5	15.6	
Service	9.0	22.3	42.4		7.1	15.0	13.8	
Farmer worker or fisherman	6.0	5.6	5.0		7.6	6.2	1.3	
Technician	2.3	4.8	4.2		9.1	21.5	39.5	
Labor worker	8.0	12.8	11.6		5.3	5.8	9.2	
Unemployed (outside house)	58.8	24.7	17.4		41.6	7.6	8.2	

The data were presented as mean±standard error in continuous variables and % in categorical variables.
BMI, body mass index; SHS, second-hand smoke
*P<0.05

Table 2. Association between second-hand smoke (SHS) exposure and hypertension.

For hypertension	Female						Male					
	Model 1[a]			Model 2[b]			Model 1[a]			Model 2[b]		
	aOR	95% CI	*P* value	aOR	95% CI	*P* value	aOR	95% CI	*P* value	aOR	95% CI	*P* value
SHS exposure												
None	1			1			1			1		
< 2hr/day	1.06	0.90 – 1.25	0.487	1.01	0.91 – 1.33	0.314	1.07	0.78-1.47	0.664	0.87	0.60-1.25	0.435
≥ 2hr/day	1.49	1.14 – 1.93	0.003**	1.50	1.10 – 2.04	0.011*	1.52	0.89-2.61	0.128	0.93	0.52-1.68	0.818

[a]Adjusted for age.

[b]Adjusted for age, height, weight, waist circumference, serum triglyceride, fasting glucose, education, occupation, alcohol intake, and marital status.

aOR, adjusted odds ratio; CI, confidence interval; SHS, second-hand smoke

*P<0.05; **P<0.01

Figure 1. Flow diagram of study population.

Figure 2. Adjusted means of systolic and diastolic blood pressure according to second-hand smoke exposure in female (A and B) and male (C and D) population without antihypertensive treatment. The mean values are adjusted for age, height, weight, waist circumference, serum triglyceride, fasting glucose, education, occupation, alcohol intake, and marital status.

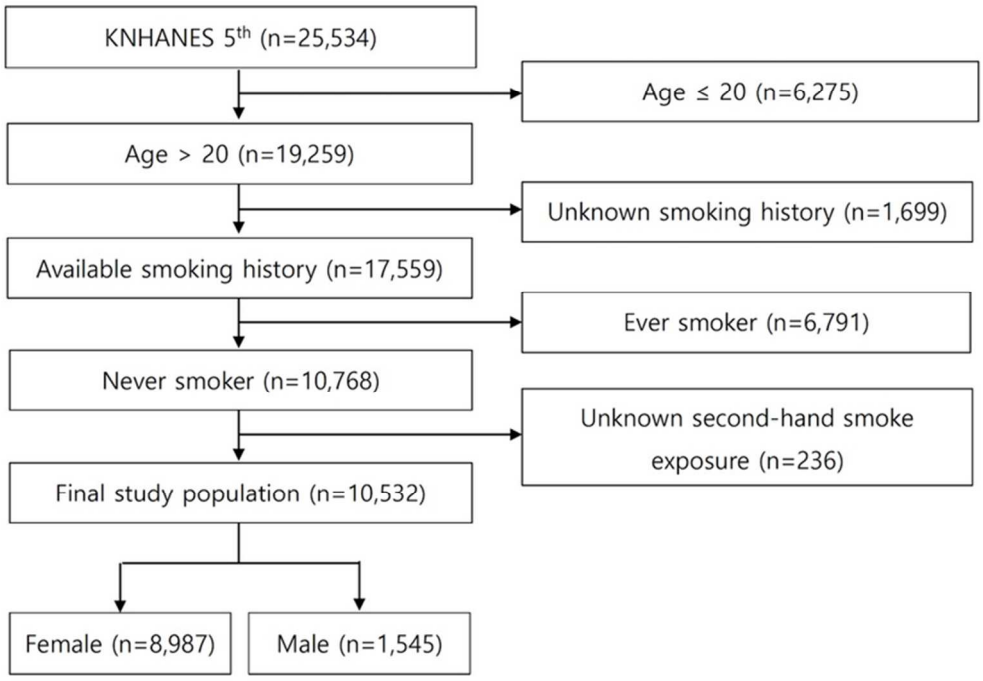

Figure 1. Flow diagram of study population.

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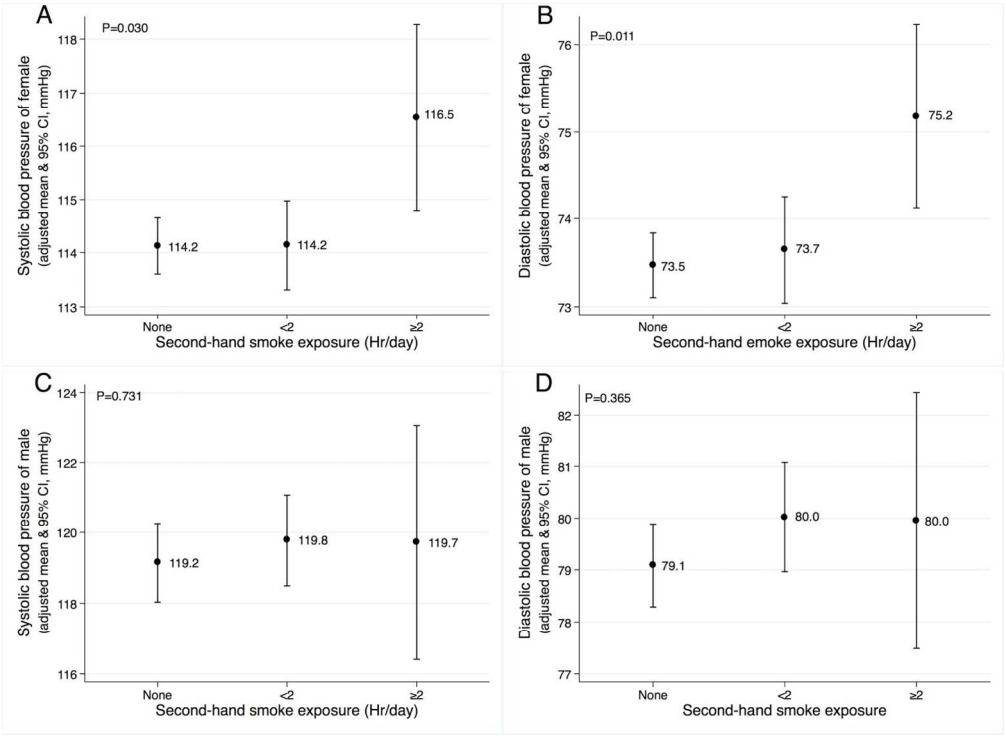

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219x160mm (300 x 300 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	NE
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	6

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	NE
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	7-8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NE
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NE
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	NE
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NE

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The association between second-hand smoke exposure and hypertension in never smokers: a cross sectional survey using data from Korean National Health and Nutritional Examination Survey V, 2010-2012

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The association between second-hand smoke exposure and hypertension in never smokers: a cross sectional survey using data from Korean National Health and Nutritional Examination Survey V, 2010-2012

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Running title: second-hand smoking exposure and hypertension

Abstract

Objectives: Second-hand smoke (SHS) exposure is associated with cardiovascular disease. This study aims to determine the association between SHS exposure estimated by questionnaire and hypertension in Korean never smokers.

Setting: Korean National Health and Nutrition Examination Survey (KNHANES) V was conducted from 2010 to 2012.

Participants: We selected the never smokers aged over 20 years who answered the question about the SHS exposure.

Primary and secondary measures: SHS exposure in both the home and work place was estimated using a self-reporting questionnaire. We investigated the association between SHS exposure and hypertension by using multivariate analysis. And we evaluated the mean systolic and diastolic blood pressure values according to SHS exposure after adjusting for possible confounding factors. All analyzes were stratified by women and men.

Results: There were 10,532 (women 8,987 and men 1,545) never smokers. We divided the subjects into three groups according to the amount of SHS exposure: none—group I, <2hr/day—group II, and ≥2hr/day—group III. Using multivariate analysis, hypertension was more commonly associated with group III than group I in women (adjusted OR=1.50, 95% CI: 1.00–2.04, *P*=0.011). Adjusted mean systolic and diastolic blood pressure values in women who was not taking antihypertensive medication were significantly elevated in group III by 2.3 and 1.7 mmHg respectively.

Conclusion: SHS exposure is significantly associated with hypertension in women never smokers.

Keywords: second-hand smoke, hypertension, blood pressure, KNHANES

Strengths and limitations of this study

- This study demonstrated hypertension is more common in women never smokers with higher daily second-hand smoke (SHS) exposure and measured the differences of systolic and diastolic blood pressure means by different SHS exposure groups
- This study included the largest population (10,532) used to examine SHS exposure based on a well-structured nationwide survey.
- Survey design analysis was applied to reduce the possibility of biased estimates.
- This cross-sectional analysis could not conclude a causal relationship between SHS exposure and hypertension.

INTRODUCTION

With a global prevalence of 26.4%,[1] hypertension is a large contributor to the burden of disease in adults. Well-known risk factor of hypertension is family history, but it is non-modifiable. Active cigarette smoking is another risk factor,[2] and it is totally preventable.[3]

Active smoking causes detrimental effects on smokers themselves, but second-hand smoke (SHS) exposure can also harm innocent bystanders. About 85% of SHS exposure results from sidestream smoke, which rises from the tip of a burning cigarette.[4] Sidestream smoke is potentially more harmful because it is not filtered. In recent years, the public has paid more attention to the harmful effect of SHS exposure on cardiovascular diseases[5] and supportive evidence is accumulating.[6-8] Although the positive relationship between SHS exposure and hypertension has been reported, some studies did not confirm this relationship.[9] In Korea, the adult smoking rate was 24.1% in 2013, and there was a big difference between sexes, 42.1% in men and 6.2% in women. In terms of the prevalence, women are more vulnerable to SHS exposure. The aim of this study was to elucidate the association between SHS exposure and hypertension in Korean never smokers using national survey data.

MATERIALS AND METHODS

Study population

The detailed data obtained from the fifth Korean National Health and Nutrition Examination Survey (KNHANES) V 2010-2012 are described elsewhere.[10] KNHANES is an annual collection of data from the Korean Statistical Office census of 3,800 households from 576 randomly selected survey areas with the number selected from each area proportional to its size. Trained interviewers administer questionnaires on various health-related information, and subjects self-report their alcohol and smoking habits. KNHANES uses a complex, multi-stage probability sample design. The sample represents the total non-institutionalized civilian population of Korea. These data are available on the internet (https://knhanes.cdc.go.kr). Adult never smokers >20 years old with second hand smoking history available were included. Never smoker was defined when the total amount of smoking was <100 cigarettes during the lifetime. If histories of smoking or SHS exposure were not available, the cases were excluded. The institutional review board of Seoul National University Hospital waived the need for written informed consent from the participants (IRB no: H1509-011-699).

Definition of SHS exposure

Daily SHS exposure time was estimated both in the workplace and home. Total SHS exposure was calculated by the summation of both values. The total amount of SHS exposure was categorized into three groups according to exposure time; none (group I), <2hr/day (group II), and ≥2hr/day (group III).

Definition of hypertension

Hypertension was defined if one or more of the criteria below were met. 1) diagnosed by physician, 2) using anti-hypertensive medications, 3) systolic blood pressure (BP)

≥140 mmHg, 4) diastolic BP ≥90 mmHg. The measurement of BP has been described elsewhere.[11] In brief, after at least 5 minutes rest in a sitting position, BP was manually measured 3 times at 30-second intervals. Finally, the average of the 2nd and 3rd measurements were used.

Statistical analysis

Weighted analysis was used for the KNHANES V data. χ^2 test was used for categorical variables and *t*-test was used for continuous variables in univariate analysis.[12] Multivariable logistic regression with survey weight analysis was conducted to evaluate the association between SHS exposure and hypertension. In model 1, the only co-variable was age, while in model 2, multiple covariates such as age, height, weight, waist circumference, serum triglyceride, fasting glucose, education, occupation, alcohol intake, and marital status were included and adjusted for. In addition, we compared SBP and DBP means between groups, again adjusting for covariates. This analysis was limited to participants who were not taking antihypertensive medications. *P*-value <0.05 was considered significant. We used the STATA software version 13.1 (StataCorp, College Station, Texas, US) for statistical analysis.

Patient and Public Involvement

The KNHANES V data were released after anonymization. The study population were not involved in the design of this study.

RESULTS

Baseline characteristics of participants

The KNHANES V data include 25,534 participants. Among them, we found 19,259 adults (age >20 years old). After excluding 1,699 participants with unknown smoking history, 6,791 ever-smokers, and 236 with unknown SHS exposure, a total of 10,532 (women 8,987 and men 1,545) never smokers were available for analysis (Figure 1). Their mean age was 47.7±0.3 years in women and 39.9±0.5 years in men. The majority of the study population was light drinkers (<1/week), and socioeconomic status was evenly distributed by SHS exposure groups (Table 1). The percentages of participants categorized into group I, II, and III according to the degree of their SHS exposures were 68.1%, 24.2%, 7.7% in women and 53.3%, 39.4%, 7.2% in men. The participants in group I were older than those in the two other groups. The percentages of hypertension in group I, II, and III were 29.3%, 19.3%, 25.9% in women and 25.2%, 22.0%, 30.6% in men. BP, education level, alcohol intake were significantly different between the three SHS exposure groups.

Hypertension is associated with SHS exposure measured by questionnaire in women never smokers

In women, hypertension was significantly associated with SHS exposure (group III) after adjustment for age (model 1, adjusted OR=1.49, 95% CI: 1.14–1.93, *P*=0.003) and even after adjustment for age, height, weight, waist circumference, serum triglyceride, fasting glucose, education, occupation, alcohol intake, and marital status (model 2, adjusted OR=1.50, 95% CI: 1.10–2.04, *P*=0.011, Table 2). But in men no statistically significant differences were seen.

Systolic and diastolic blood pressure is increasing according to SHS exposure

The mean systolic and diastolic BP increased prportional to the increasing SHS exposure in women. On average, the differences between group III and group I were 2.3 mmHg and 1.7 mmHg in systolic and diastolic BP, respectively (P=0.030 and P=0.011) (Figure 2). In men we observed a tendency toward higher mean systolic and diastolic BP values in groups II and III compared to group I.

DISCUSSION

This study demonstrated the association between SHS exposure measured by self-reported questionnaire in women never smokers and hypertension, using a well-designed nationwide survey.[13] Our findings strengthen the evidence of the harmful effect of chronic SHS exposure on hypertension. Additionally, we calculated the difference in mean systolic and diastolic BP between women group I and III by 2.3 and 1.7 mmHg, respectively. According to a previous study, a 3mmHg systolic BP difference was observed with a 10 kg increase in body weight.[14] Compared to this 3 mmHg systolic BP change accomplished by weight reduction, the value of 2.3 mmHg associated with SHS exposure is significant.

The association between hypertension and SHS exposure was observed only in women. We postulate three possibilities. First, men never smokers were younger than women who never smoked (39.9±0.5 vs. 47.7±0.3). The influence of SHS exposure on BP could be limited in younger man.[15] Second, SHS exposure could influence

cardiovascular disease due to sex-dependent biologic effect.[16] Third, there could be some limitations of statistical model 2 for men because of the many co-variables and the small numbers involved. The low statistical power due to small sample size could affect results. In our dataset, the proportion of men never smokers was only 19.4% of total men population aged over 20 years. Although we did not achieve statistically significant results in men, the changing pattern of systolic and diastolic BP was the same, and it could support the biologic effect between SHS exposure and BP.

Pharmacologically, nicotine stimulates the sympathetic nervous system in active smokers.[17 18] Epinephrine and norepinephrine are released by nicotine stimulation, and these catecholamines increase myocardial contractility and promote vasoconstriction, which results in increases in BP.[19] The association between smoking and hypertension has also been observed in a mouse model,[20] and in epidemiologic studies.[2] Moreover, the amount of smoking was positively correlated with hypertension[21] and carotid artery atherosclerosis severity.[22] The biologic effect of SHS exposure on BP could be extrapolated from the effects of active smoking. Serum nicotine level was increased after SHS exposure in healthy nonsmokers.[23] In the context of active smoking exposure, the duration or amount of SHS exposure is also important in the evaluation of the chronic effect of passive smoking. Although the experimental studies of short-term SHS exposure did not demonstrate a change in BP.[23 24] population-based studies have shown that the habitual SHS exposure is associated with hypertension.[6 7]

Theoretically, SHS exposure can be determined by direct measurements of smoke components in the air, self-reported questionnaires, or by measurements of biomarkers

from body fluid, such as serum, urine or saliva.[25] The correlation between self-reported questionnaire and biochemical assessment has been generally accurate in prior meta-analysis.[26] The association between hypertension and SHS exposure was demonstrated by using serum cotinine in the previous study[6] and self-reported questionnaire in our study. Compared to biomarkers, self-reported questionnaires are inexpensive and provide information on long-term exposure.

To our knowledge, this study included the largest population used to examine SHS exposure based on a well-structured nationwide survey (KNHANES V),[13] and a survey design analysis was applied to reduce the possibility of biased estimates.[12] In addition, we included various potential confounding factors, including age, height, weight, waist circumference, serum triglyceride, fasting glucose, education, occupation, alcohol intake and marital status in the statistical model to clarify the conclusion. However there were some limitations. First, our cross-sectional analysis could not conclude a causal relationship between SHS exposure and hypertension. For example, in some cases, hypertension may have been present before exposure to SHS. Second, information on the smoke concentration and the environment where SHS exposure occurred was not available. Third, we could not exclude hidden smokers. The proportion of cotinine-verified active smokers was previously noted to be larger than that of self-reported smokers.[27] In our dataset (KNHANES V), urine cotinine level was available in 19% of women never smokers. In that group, 2.7% women never smokers had a urine cotinine level >200 ng/mL, the cutoff value defining an active smoker.[25] Thus, the possibility of active smoker contamination does exist. Forth, there could be concerns that factors related to hypertension were not sufficiently investigated. For example, estrogen

increases the susceptibility to hypertension.[28] Because estrogen tends to rise in perimenopausal period, perimenopausal women hence are likely to become hypertensive. Although our survey did not measure the estrogen level, the analysis in which perimenopausal participants were excluded also shows the significant relationship between SHS exposure and hypertension (data not shown). A family history of hypertension could also contribute to the development of hypertension. We did not exclude participants who had a family history of hypertension. However, even when participants with a self-reported family history of hypertension were excluded, the significant relationship between SHS exposure and hypertension was also observed (data not shown).

In conclusion, on using self-reported questionnaires, we found that SHS exposure was significantly associated with hypertension in Korean women never smokers. Both systolic and diastolic blood pressures were significantly elevated in the SHS exposed population.

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Competing interests: None declared.

Author Contributions

Conceptualization: YSP, CHL

Data curation: YSP, CHL, YIL

Methodology: YSP, CHL, KHY

Project administration: CHL

Original draft: YSP, CHL

Review & editing: YSP, CHL, YIL, CMA, JOK, JHP, SHL, JYK, EMC, THJ, KHY

Patient consent: Waived from IRB

Ethics approval: Seoul National University Hospital IRB

Data sharing statement: The original data came from Korean National Health and Nutritional Examination Survey (https://knhanes.cdc.go.kr/knhanes/eng/index.do). All the data presented this manuscript are available from the corresponding author at kauri670@empal.com.

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Table 1. Baseline characteristics according to the degree of second-hand smoke exposure.

Variables	Women			*P* value	Men			*P* value
	Second-hand smoke exposure				Second-hand smoke exposure			
	None	<2hr/day	≥2hr/day		None	<2hr/day	≥2hr/day	
% of total	68.1	24.2	7.7		53.3	39.4	7.2	
Age (years)	49.6±0.3	42.9±0.4	45.2±0.6	<0.001*	41.7±0.7	37.4±0.6	40.2±1.4	<0.001*
Weight (kg)	57.5±0.2	57.5±0.3	59.2±0.5	<0.001*	70.1±0.5	71.4±0.6	72.7±1.4	0.032*
Height (cm)	156.6±0.1	157.9±0.2	157.8±0.3	<0.001*	171.4±0.3	172.2±0.3	170.6±0.8	0.783
Waist Circumference (cm)	78.7±0.2	76.9±0.3	78.9±0.5	0.009*	82.9±0.4	83.0±0.5	84.8±1.1	0.231
BMI (kg/m^2)	23.5±0.1	23.1±0.1	23.8±0.2	0.536	23.8±0.1	24.1±0.2	24.9±0.4	0.021*
Blood pressure (mmHg)								
Systole	117.5±0.3	113.5±0.5	117.7±0.9	<0.001*	119.3±0.6	118.9±0.6	120.8±1.7	0.740
Diastole	74.0±0.2	73.6±0.3	75.7±0.5	0.082	77.9±0.4	79.9±0.5	79.9±1.1	0.005*
Total cholesterol (mg/dL)	190.4±0.7	186.5±1.0	192.9±1.8	0.453	183.±1.6	182.7±1.8	186.5±3.8	0.666
HDL (mg/dL)	55.2±0.3	55.6±0.6	57.7±1.1	0.068	51.0±0.9	50.3±1.2	50.4±2.5	0.583
Triglyceride (mg/dL)	115.0±1.8	104.7±1.9	112.2±4.4	0.016*	121.8±3.5	129.6±4.7	121.4±7.2	0.339
Fasting glucose (mg/dL)	95.9±0.4	93.6±0.5	95.1±0.9	0.008*	96.6±0.9	95.7±0.8	96.6±1.8	0.658
Hypertension	29.3	19.3	25.9	<0.001*	25.2	22.0	30.6	0.197
Diabetes mellitus	14.8	9.8	10.0	<0.001*	10.0	9.2	13.1	0.527
Metabolic syndrome	25.6	17.0	18.8	<0.001*	23.2	20.2	12.9	0.325
Alcohol intake				<0.001*				<0.001*
Never drinker	21.7	11.2	18.5		11.3	7.3	7.4	
Former drinker	18.0	13.9	16.5		13.5	6.1	5.9	
Light drinker (≤1/week)	53.9	66.8	57.3		56.7	66.5	53.8	
Moderate drinker (2-3/week)	5.1	7.1	6.2		13.9	16.5	22.4	

Heavy drinker (≥4/week)	1.3	1.0	1.5		4.7	3.6	10.5	
Marital status	88.8	76.9	84.1	<0.001*	58.0	59.0	59.0	0.955
Educational level				<0.001*				<0.001*
Below middle school	30.4	18.2	26.8		9.9	2.9	7.7	
Middle school	9.8	9.9	10.2		6.2	6.4	9.0	
High school	29.8	39.9	33.1		43.0	40.3	47.6	
Above high school	30.1	31.9	30.0		40.9	50.5	35.8	
Socioeconomic status				0.144				0.116
1Q	25.3	25.3	27.3		30.2	21.8	30.5	
2Q	26.8	25.7	21.2		21.2	24.4	20.0	
3Q	25.3	25.9	23.7		25.6	25.5	26.8	
4Q	22.6	23.1	27.9		23.0	28.3	22.7	
Occupation				<0.001*				<0.001*
Manager or professional	11.0	15.6	11.8		21.8	28.6	12.5	
Office worker	5.0	14.3	13.3		7.6	15.5	15.6	
Service	9.0	22.3	42.4		7.1	15.0	13.8	
Farmer worker or fisherman	6.0	5.6	5.0		7.6	6.2	1.3	
Technician	2.3	4.8	4.2		9.1	21.5	39.5	
Labor worker	8.0	12.8	11.6		5.3	5.8	9.2	
Unemployed (outside house)	58.8	24.7	17.4		41.6	7.6	8.2	

The data were presented as mean±standard error in continuous variables and % in categorical variables.
BMI, body mass index; SHS, second-hand smoke
*P<0.05

Table 2. Association between second-hand smoke (SHS) exposure and hypertension.

	Women						Men					
For	Model 1[a]			Model 2[b]			Model 1[a]			Model 2[b]		
hypertension	aOR	95% CI	*P* value	aOR	95% CI	*P* value	aOR	95% CI	*P* value	aOR	95% CI	*P* value
SHS exposure												
None	1			1			1			1		
< 2hr/day	1.06	0.90 – 1.25	0.487	1.01	0.91 – 1.33	0.314	1.07	0.78-1.47	0.664	0.87	0.60-1.25	0.435
≥ 2hr/day	1.49	1.14 – 1.93	0.003**	1.50	1.10 – 2.04	0.011*	1.52	0.89-2.61	0.128	0.93	0.52-1.68	0.818

[a]Adjusted for age.

[b]Adjusted for age, height, weight, waist circumference, serum triglyceride, fasting glucose, education, occupation, alcohol intake, and marital status.

aOR, adjusted odds ratio; CI, confidence interval; SHS, second-hand smoke

*P<0.05; **P<0.01

Figure 1. Flow diagram of study population.

Figure 2. Adjusted means of systolic and diastolic blood pressure according to second-hand smoke exposure in women (A and B) and men (C and D) population without antihypertensive treatment. The mean values are adjusted for age, height, weight, waist circumference, serum triglyceride, fasting glucose, education, occupation, alcohol intake, and marital status.

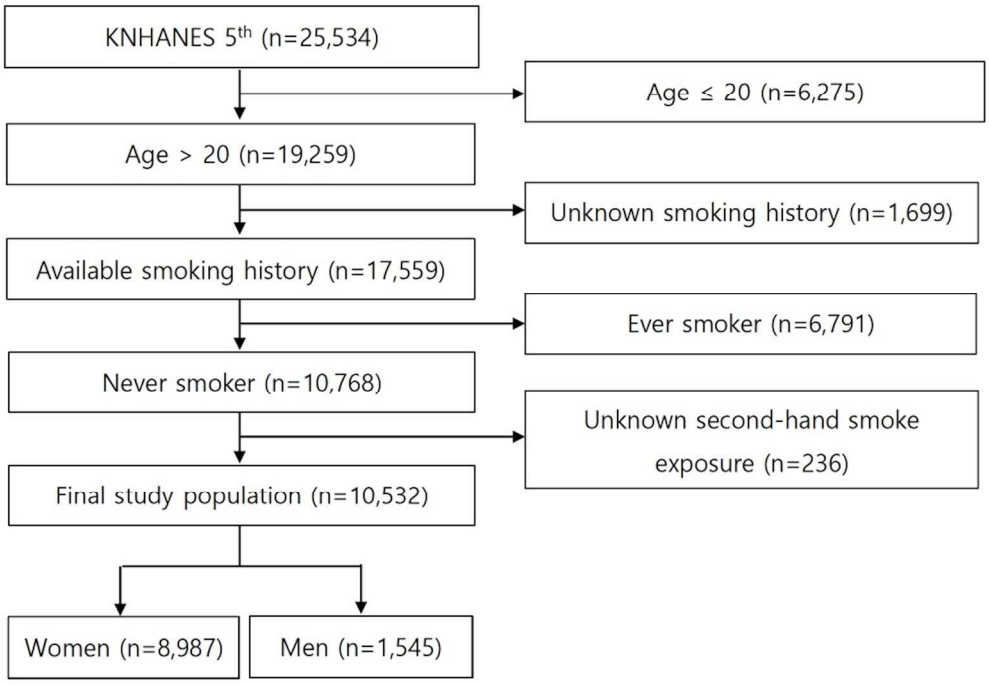

Figure 1. Flow diagram of study population.

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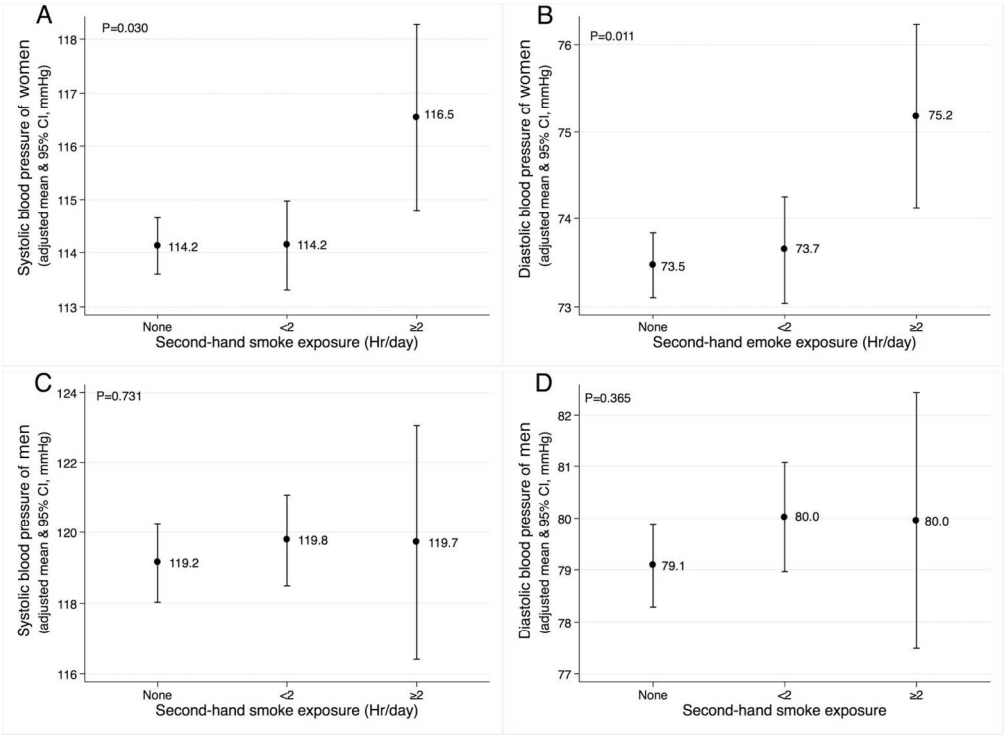

Figure 2. Adjusted means of systolic and diastolic blood pressure according to second-hand smoke exposure in women (A and B) and men (C and D) population without antihypertensive treatment. The mean values are adjusted for age, height, weight, waist circumference, serum triglyceride, fasting glucose, education, occupation, alcohol intake, and marital status.

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	NE
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	6

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	NE
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	7-8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NE
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NE
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	NE
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NE

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.