Original Article

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한국 비흡연 성인의 간접흡연과 우울감의 연관성: 국민건강영양조사 2016년 자료 요코티닌 분석

김율희, 김병성, 원장원, 김선영, 장혜진

경희의료원 가정의학과

Urine Cotinine for Assessing the Association between Secondhand Smoke Exposure and Depression in Adult Non-Smokers in Korea: Analysis of the Korea National Health and Nutrition Examination Survey 2016

Yul Hee Kim, Byung Sung Kim, Chang Won Won, Sunyoung Kim, Hye Jin Jang

Department of Family Medicine, Kyung Hee University Medical Center, Seoul, Korea

Background: Exposure to secondhand smoke (SHS) has been shown to cause health problems. Recent studies demonstrated an association of SHS with depression and poor mental health. The urinary cotinine concentration (Ucot) is an objective indicator of exposure to SHS. In this study, we evaluated the association between depression and Ucot in adult non-smokers adults in Korea.

Methods: We analyzed the data of 3,417 adults, aged ≥19 years, who participated in the seventh Korea National Health and Nutrition Examination Survey (2016). The eligible subjects were non-smokers. Depression was evaluated using the Patient Health Questionnaire-9 (PHQ-9). The subjects were dichotomized into two groups: the high depressive symptom group (PHQ-9 ≥10 [n=185]) and the low depressive symptom group (PHQ-9 <10 [n=3,232]). The demographic, socioeconomic, and clinical characteristics of the subjects were retrieved from the survey data. Ucot was dichotomized into high-Ucot (≥10 ng/mL) and low-Ucot (<10 ng/mL). The Ucot and other characteristics were compared between the two groups. To adjust for confounding variables, we conducted a logistic regression analysis and determined the difference in Ucot between the two groups.

Results: After adjusting for confounders, the high depressive symptom group was found to be associated with high-Ucot (odds ratio, 1.824; 95% confidence interval, 1.020-3.262). Sex, education, socioeconomic status, marital status, occupational status, limitation of activity, and the presence of an underlying diseases (diabetes and dyslipidemia) had a significant effect on depression.

Conclusion: This concluded that depression was associated with high urine cotinine level in adult non-smokers.
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Keywords: Non-smokers, Tobacco, Cotinine, Depression, Korea National Health and Nutrition Survey

INTRODUCTION

Secondhand smoke (SHS) means involuntary exposure to smokers' tobacco smoke. Tobacco smoke can be divided into mainstream smoke from smokers and sidestream smoke from the end of burning cigarettes. Approximately 80% of cigarette smoke inhaled by SHS is sidestream smoke.[1)]

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■ Corresponding author : **Byung Sung Kim, MD, PhD**
Department of Family Medicine, Kyung Hee University Medical Center, 23 Kyungheedae-ro, Dongdaemun-gu, Seoul 02447, Korea
Tel: +82-2-958-8700, Fax: +82-2-958-8699
E-mail: bskim7@khmc.or.kr
ORCID: https://orcid.org/0000-0002-3293-9640

Tobacco smoke contains about 4,000 kinds of toxic chemicals and 60 kinds of carcinogens. Among them, sidestream smoke do not pass through filters and experience incomplete combustion, and the concentration of harmful substances is higher than that of mainstream smoke.[2)]

Numerous studies have reported that indirect exposure, as well as direct exposure to smoking, increases the risk of obstructive pulmonary diseases such as asthma and chronic obstructive pulmonary disease (COPD),[3)] cardiovascular disease,[4)] thyroid disease, diabetes, cerebrovascular disease, and cancer.[5)] Similarly, in recent years, attention has been focused not only on the physical effects of SHS, but also on the impact on mental health. Smoking is already a major risk factor for depression and other mental illnesses.[6)]

In a large-scale follow-up study of non-smokers' exposure to SHS in the United Kingdom, people exposed to SHS had a high incidence of sleep disturbances and major depressive symptoms. In addition, as a result of evaluating the concentration of cotinine in saliva, the incidence of mental illness was determined to be twice as high in those who had more exposure to SHS.[7)] The results of domestic studies in Korea showed that SHS was related to depression, perceived stress, and suicidal ideation in women.[8)] Also, It has been reported that exposure to SHS in the home leads to a significant increase of depression and anxiety.[9)]

Cotinine is a major metabolite of nicotine and is usually stable but is produced only when nicotine is metabolized, so it is the test of choice when evaluating tobacco use or tobacco smoke exposure. Since nicotine has a half-life of 1-4 hours, whereas cotinine has a half-life of 7-40 hours in the body, detection of cotinine concentration in the body of non-smokers implies actual exposure to SHS.[10)] In addition, since it is present in body fluids at a higher level than nicotine, measurement through urine or saliva can be used as an objective measure of exposure.[11,12)]

In this context, the importance of objective assessment of the effects of exposure to SHS on mental health, especially depression, has emerged. The aim of this study was to investigate the relationship between exposure to SHS and depression in Korean non-smokers through an analysis of urinary cotinine concentration (Ucot) data from 2016 the seventh Korea National Health and Nutrition Examination Survey.

METHODS

1. Research data and subjects

This study used data from the Korea National Health and Nutrition Examination Survey for the seventh period (2016). The total number of subjects in the first year of the seventh period was 10,806. Of these, there were 6,382 adult men and women aged 19 and over. The final study included 3,417 non-smokers who did not have more than 100 cigarettes smoking experiences in their lifetime and who were not missing the Patient Health Questionnaire-9 (PHQ-9). According to the definition of the World Health Organization, current smoker is defined as someone who has smoked more than 100 cigarettes in their lifetime and who currently smokes cigarettes. Ex-smokers are people who have smoked more than 100 cigarettes in their lifetime but do not smoke presently. A never smoker is an adult who has never smoked or who has smoked less than 100 cigarettes in his or her lifetime.[13)]

2. Sociodemographic factors and physical measurements

Sociodemographic factors including age, sex, education level, socioeconomic status, marital status, and occupational status were analyzed. In health-related factors, the followings were analyzed: activity limitation, alcohol drinking experience, body mass index (BMI), exposure to SHS (domestic exposure, occupational exposure, public institution exposure), presence of chronic diseases (thyroid disease, hypertension, diabetes, dyslipidemia), and Ucot.

Self-report questionnaire method was used to investigate whether there is any restriction on the activities of daily living or social activities due to current health problems or physical or mental disorders. Exposure to SHS was assessed as exposure to tobacco smoke within the last 7 days in a home, workplace, or public institution.

3. Evaluation of depression

The PHQ-9 is a self-report questionnaire used to assess depression. It consists of nine questions that act as diagnostic criteria for major depressive disorder according to The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Based on the optimal cutoff point, sensitivity

and specificity are high.[14]

The questions are associated with little interest or pleasure in doing things, depressed mood, sleep disorders, lack of energy and fatigue, poor appetite or overeating, unreasonableness or inadequate guilt, trouble concentrating on things, dullness and slowness, and thoughts of suicide. The results were graded as follows: 0 to 4, normal; 5 to 9, mild; 10 to 14, moderate; 15 to 19, moderately severe; and 20 or over is severe. In this study, the optimal cut point was 10 points.[15,16]

4. Evaluation of SHS exposure

Self-report questionnaires and biomarkers were used to assess exposure to SHS. The self-report questionnaire surveyed exposure to SHS in the home, in the workplace, and in public institutions. The biochemical indicator of nicotine metabolite, urine cotinine, was measured.

Many studies reported that non-smokers who were not exposed to SHS have a Ucot of less than 10 ng/mL. Therefore, in this study, non-smokers with a Ucot ≥10 ng/mL were considered exposed to SHS.

The Ucot was determined by high performance liquid chromatography-mass spectrometry, and the test and analysis were performed at the National Cancer Center in Korea. The reagents were methylene chloride (Fisher Scientific, Waltham, MA, USA), methanol (Merck, Darmstadt, Germany), hydrochloric acid (Sigma-Aldrich, St. Louis, MO, USA), acetonitrile (Fisher Scientific), formic acid (Sigma-Aldrich), and ammonium formate (Fluka Analytical, Tokyo, Japan), and the analytical equipment was Agilent 1100 Series with API 4000 (AB Sciex, Framingham, MA, USA).

5. Statistical analysis

The characteristics of the subjects were presented as frequency (n) and percentage (%) for categorical variables and mean±standard deviation for continuous variables. Chi-square and *t*-tests were conducted to verify the statistical significance of the differences between the high depression group and the low depression group.

To analyze the associations between depression, Ucot, and other sociodemographic and health-related factors, a multiple logistic regression analysis was performed with PHQ-9 scores of 10 or more and less than 10.

Two models were used to analyze the association between SHS and depression through Ucot. Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, education level, socioeconomic status, marital status, occupational status, activity limitation, alcohol drinking experience, BMI, chronic diseases, and exposure to SHS.

All statistical analyses were performed using the SPSS ver. 25.0 statistical package (SPSS Inc., Chicago, IL, USA), and statistical significance was established at $P<0.05$.

RESULTS

1. General characteristics of the study population

Of the 3,417 non-smokers aged 19 years and older, 3,232 subjects (94.6%) were in the low depression group and 185 (5.4%) were in the high depression group. The mean age of the subjects was 50.3 years (standard deviation [SD], ±16.8) in the low depression group and 57.3 (SD, ±17.5) in the high depression group. Of the 3,232 subjects with low depression, 606 (18.7%) were males and 2,626 (81.3%) were females. Of the 185 subjects with high depression, 11 (5.9%) were males and 174 (94.1%) were females.

The depressed group was older ($P<0.001$), had a high proportion of women ($P<0.001$), the education level was lower ($P<0.001$), and the socioeconomic status was lower ($P<0.001$). In addition, the depressed group had a high rate of unemployment ($P<0.001$), limited activity ($P<0.001$), no drinking experience ($P=0.002$), and high BMI ($P=0.005$). Comparing the characteristics according to chronic diseases, the prevalence of hyperthyroidism, hypertension, diabetes, and hyperlipidemia were higher in the depressed group ($P=0.006$, $P<0.001$, $P<0.001$, $P<0.001$, respectively). The Ucot was significantly higher in the depressed group ($P=0.007$; Table 1).

2. Distribution of study variables according to depression

To analyze the effects of socio-demographic and health-related factors, especially secondhand smoking, on depression, a multiple logistic regression analysis was performed by dividing the PHQ-9 score of the study group by the cut-off value of 10. In Model 1, the relationship between Ucot and depression was analyzed by adjusting for age and sex.

As a result of the analysis, the age was higher (odds ratio

[OR], 1.024; 95% confidence interval [CI], 1.014-1.034) and the female ratio was higher than that of the males in the depressed group (OR, 3.347; 95% CI, 1.805-6.208). High Ucot level was significantly associated with depression (OR, 1.967; 95% CI, 1.140-3.393).

In addition to age and sex, Model 2 was also adjusted for the education level, socioeconomic status, marital status, occupational status, BMI, drinking experience, chronic disease status (thyroid disease, hypertension, diabetes, dyslipidemia), and SHS exposure through a self-questionnaire.

As a result of the analysis, the depressed group had a high proportion of women (OR, 2.937; 95% CI, 1.529-5.640), low education level (OR, 0.542; 95% CI, 0.339-0.869), low socioeconomic status (OR, 0.499; 95% CI, 0.344-0.722), and high ratios of non-married (OR, 0.524; 95% CI, 0.284-0.967) and unemployed (OR, 0.656; 95% CI, 0.463-0.930) subjects. Among the health-related factors, activity limitation was significantly high in the depressed group (OR, 6.072; 95% CI, 4.230-8.715). Among the chronic illnesses, diabetes (OR, 1.832; 95% CI, 1.176-2.852) and dyslipidemia (OR, 1.921; 95% CI, 1.300-2.837) were significantly related with depression. In addition, the depressed group had a significantly higher Ucot (OR, 1.824; 95% CI, 1.020-3.262; Table 2).

Table 1. Characteristics of the participants with high and low depressive symptoms

Characteristic	PHQ-9 ≥10 (n=185)	PHQ-9 <10 (n=3,232)	Total	*P*[a]
Age, y	57.3±17.5	50.3±16.8	50.7±16.9	<0.001
Female	174 (94.1)	2,626 (81.3)	2,800 (81.9)	<0.001
Education, y				<0.001
<9	88 (47.6)	727 (22.5)	815 (23.9)	
9-11	24 (13.0)	307 (9.5)	331 (9.7)	
12-15	40 (21.6)	1,013 (31.3)	1,053 (30.8)	
≥16	33 (17.8)	1,185 (36.7)	1,218 (35.6)	
Socioeconomic status				<0.001
Low	86 (46.5)	576 (17.8)	662 (19.4)	
Low-moderate	44 (23.8)	772 (23.9)	816 (23.9)	
Moderate-high	40 (21.6)	887 (27.4)	927 (27.1)	
High	15 (8.1)	997 (30.8)	1,012 (29.6)	
Marital status (married)	159 (85.9)	2,732 (84.5)	2,891 (84.6)	0.604
Occupational status (employed)	60 (32.4)	1,759 (54.4)	1,819 (53.2)	<0.001
Activity limitation	75 (40.5)	224 (6.9)	299 (8.8)	<0.001
Alcohol intake[b]	138 (74.6)	2,697 (83.4)	2,835 (83.0)	0.002
BMI, kg/m^2	24.5 (4.0)	23.7 (3.5)	23.7 (3.6)	0.005
Comorbidity				
Thyroid disease	12 (6.5)	93 (2.9)	105 (3.1)	0.006
HTN	68 (36.8)	699 (21.6)	767 (22.4)	<0.001
Diabetes	42 (22.7)	254 (7.9)	296 (8.7)	<0.001
Dyslipidemia	61 (33.0)	439 (13.6)	500 (14.6)	<0.001
Ucot, ng/mL				0.007
0-9.999	169 (91.4)	3,091 (95.6)	3,232 (94.6)	
≥10	16 (8.6)	141 (4.4)	185 (5.4)	
Secondhand smoking[c]	45 (24.3)	744 (23.0)	789 (23.1)	0.682

Values are presented as mean±standard deviation for continuous variables or number (%) for categorical variables.
Abbreviations: BMI, body mass index; HTN, hypertension; PHQ-9, Patient Health Questionnaire-9; Ucot, urinary cotinine concentration.
[a]Analyzed using Student's *t*-test for continuous variables and chi-square test for categorical variables.
[b]Experience of drinking more than one unit of alcohol.
[c]Self-reported survey.

Table 2. Logistic regression analysis of the association between urinary cotinine concentration and depression

Variable	Model 1			Model 2		
	OR	95% CI	P^a	OR	95% CI	P^a
Age, y	1.024	1.014-1.034	<0.001	0.989	0.972-1.006	0.207
Female	3.347	1.805-6.208	<0.001	2.937	1.529-5.640	0.001
Ucot ≥10 ng/mL	1.967	1.140-3.393	0.015	1.824	1.020-3.262	0.043
Education (≥12 years vs. <12 years)				0.542	0.339-0.869	0.011
Socioeconomic status (higher vs. lower)				0.499	0.344-0.722	<0.001
Marital status (married vs. single)				0.524	0.284-0.967	0.039
Occupational status (employed vs. unemployed)				0.656	0.463-0.930	0.018
Activity limitation				6.072	4.230-8.715	<0.001
Alcohol intake				0.973	0.653-1.450	0.893
BMI, kg/m^2				1.015	0.970-1.062	0.519
Comorbidity						
Thyroid disease				1.342	0.665-2.709	0.412
HTN				0.869	0.575-1.315	0.507
Diabetes				1.832	1.176-2.852	0.007
Dyslipidemia				1.921	1.300-2.837	0.001
Secondhand smoking				1.366	0.934-1.998	0.108

Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, education, socioeconomic status, marital status, occupation, activity limitation, BMI, thyroid disease, HTN, diabetes, dyslipidemia, and secondhand smoking.
Abbreviations: BMI, body mass index; CI, confidence interval; HTN, hypertension; OR, odds ratio; Ucot, urinary cotinine concentration.
[a]Analyzed using multiple logistic regression.

DISCUSSION

The authors investigated the association between SHS exposure and depression by assessing the level of Ucot in Korean non-smoking adults using the Korea National Health and Nutrition Examination Survey (2016).

The results showed that Ucot greater than 10 ng/mL, which means exposure to SHS, was significantly associated with depression. According to the Korea National Health and Nutrition Examination Survey (2016), in-home exposure to SHS was 6.4%, occupational exposure was 17.4%, and public exposure was 22.3%, which decreased by 1.8%, 9.5%, and 13.1%, respectively. Exposure to public SHS has been decreasing for three consecutive years since the first survey in 2013.

In contrast, the smoking rate for men and women were 40.7% and 6.4% in 2016, which increased by 1.3% and 0.9%, respectively. The decrease in SHS exposure despite the increase in the smoking rate can be seen as a result of the government's policy efforts to reduce smoking in public places.

There have been few biochemical mechanisms that clearly reveal the relationship between SHS and depression. However, some recent studies have suggested theories about the possibility. Similar to smokers, nicotine can directly affect the central nervous system of non-smokers when exposed to SHS. Nicotine binds primarily to nicotinic acetylcholine receptors (nAChRs) and affects the secretion of neurotransmitter such as glutamate, gamma-aminobutyric acid, dopamine, norepinephrine, and serotonin.[17-20] Initially, nicotine activates nAChRs and inhibits dopamine reuptake, resulting in elevated level of dopamine in the blood. However, long-term exposure may result in down-regulation of dopamine receptors in the brain, resulting in depression.[21,22] Additionally, short-term exposure to nicotine increases cerebral serotonin, but chronic and repeated exposure decreases serotonin.[20,23] Smoke from cigarettes also induces oxidative stress, which can make permanent state of inflammation and/or the chronic hypoxia that are hallmarks of COPD.[24,25] This may explain the depression that is elevated in the COPD

population. Likewise, oxidative stress due to exposure to SHS would be related to the depression. In addition, exposure to SHS can be a psychological stressor that increases depression.

The limitations of this study are as follows. Firstly, this study provides information on the relationship between SHS and depression through Ucot at the time of study, but there is a limit to explaining the change over time. Secondly, this study could have included subjective or inaccurate responses because it uses historical data and information from a self-report questionnaire. Thirdly, in this study, the exposure to SHS surveyed by the questionnaire did not significantly affect depression. However, a high Ucot, which indicates exposure to SHS, was significantly associated with depression. This can be explained in two ways. Firstly, as described above, this study is based on a self-report questionnaire and may differ from actual SHS exposure. Secondly, this study did not include tobacco smoke exposure from unspecified smokers in public places, so it was impossible to investigate exposure that respondents did not recognize.

Despite these limitations, the strengths of the present paper are as follows. Firstly, this study was conducted as a large-scale study using the National Health and Nutrition Survey. Secondly, we used an objective evaluation measure of SHS exposure by using the Ucot, and depression was measured by setting the optimal cut-off point using PHQ-9.

In conclusion, we found a significant relationship between SHS exposure and mental health problems, especially depression, in Korean non-smoking adults. It is important to control and monitor cigarette smoke exposure at home and at work, as well as in an unspecified number of public places. Future prospective cohort studies and clinical studies should be performed to clarify the causal relationship between SHS exposure and depression.

요 약

연구배경: 최근 연구 결과에 따르면 간접흡연 노출은 다양한 신체질환뿐 아니라 우울증과 같은 정신질환과도 연관성이 제시되고 있다. 따라서 본 연구는 간접흡연 노출을 평가하는 객관적인 지표인 요코티닌 농도 측정을 통해 한국 비흡연 성인의 요코티닌 농도와 우울감과의 연관관계를 분석하였다.

방법: 본 연구는 제7기 국민건강영양조사(2016년)에 참여한 19세 이상 비흡연 성인 총 3,417명을 분석하였다. 참여자는 PHQ-9을 통해 우울감이 높은 군(PHQ-9 ≥10 [n=185])과 우울감이 낮은 군(PHQ-9 <10 [n=3,232])으로 분류하였다. 요코티닌 농도는 고 요코티닌 농도군(≥10ng/mL)과 저 요코티닌 농도군(<10 ng/mL)으로 이분화하여 분석하였다. 그 외 참여자의 인구학적, 사회경제학적, 임상적 특성을 국민건강영양조사 자료에서 추출하였다. 혼란변수를 보정하기 위해 로지스틱 회귀분석을 이용하여 우울감 정도에 따른 요코티닌 농도의 차이를 분석하였다.

결과: 혼란변수를 보정한 결과, 우울감이 높은 군에서 요코티닌 농도가 유의미하게 높았다(오즈비, 1.824; 95% 신뢰구간, 1.020-3.262). 그 외 성별, 교육수준, 사회경제수준, 결혼유무, 직업 유무, 활동제한 여부, 기저질환(당뇨병, 고지혈증) 여부가 유의미하게 우울감에 영향을 미치는 것으로 확인되었다.

결론: 본 연구 결과 비흡연자의 요 중 코티닌 농도가 높은 경우 우울감과 유의미한 연관관계가 있었다.

중심 단어: 비흡연자, 담배, 코티닌, 우울증, 국민건강영양조사

ORCID

Yul Hee Kim https://orcid.org/0000-0003-2116-5827
Byung Sung Kim https://orcid.org/0000-0002-3293-9640
Chang Won Won https://orcid.org/0000-0002-6429-4461
Sunyoung Kim https://orcid.org/0000-0003-4115-4455
Hye Jin Jang https://orcid.org/0000-0001-9465-5160

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