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Secondhand Smoke Exposure and Endothelial Stress in Children and Adolescents

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Abstract

Objective—Links between secondhand smoke exposure and cardiovascular disease in adults are well established. Little is known about the impact of this exposure on cardiovascular status during childhood. The purpose of this study was to investigate relationships between secondhand smoke exposure in children and adolescents and cardiovascular disease risk—systemic inflammation, endothelial stress, and endothelial repair.

Methods—A total of 145 subjects, aged 9 to 18 years, were studied. Tobacco smoke exposure was determined by hair nicotine level. Cardiovascular risk was assessed by markers of systemic inflammation (C-reactive protein [CRP] and adiponectin); by soluble intercellular adhesion molecule 1 (s-ICAM1), which measures endothelial activation after surface vascular injury; and by endothelial repair. This was measured by prevalence of endothelial progenitor cells (EPCs), which are bone marrow–derived cells that home preferentially to sites of vascular damage.

Results—Hair nicotine was directly correlated with s-ICAM1 ($r = 0.4090$, $P < .0001$) and negatively correlated with EPC prevalence ($r = -0.2002$, $P = .0195$). There was no relationship between hair nicotine and CRP, and a trend toward a weak relationship with adiponectin. Hair nicotine and body mass index were independent variables in a multivariate model predicting s-ICAM1; hair nicotine was the only significant variable in a model predicting EPC prevalence.

Conclusions—Secondhand smoke exposure during childhood and adolescence is detrimental to vascular health because s-ICAM1 is a marker for endothelial activation and stress after vascular surface injury, and EPCs contribute to vascular repair. The fact that body mass index is also a factor in the model predicting s-ICAM1 is concerning, in that 2 risk factors may both contribute to endothelial stress.

Keywords

child hair nicotine; endothelial stress; secondhand smoke exposure; tobacco smoke exposure

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ADULT CARDIOVASCULAR DISEASE is now considered to be a progressive inflammatory disease initiated in childhood.^{1,2} Exposure to secondhand smoke is a known risk factor for the development of atherosclerotic heart disease in adults and increases the risk of cardiovascular disease by about 30% in nonsmoking adults.^{3–5} Although smoke-exposed nonsmokers have a considerable risk of cardiovascular disease, their exposure to tobacco smoke is less than 1% of the exposure of an active smoker of 20 cigarettes per day.⁴ The most likely cause of elevated cardiovascular disease risk among smoke-exposed nonsmokers appears to be oxidant gas exposure, leading to inflammation and subsequent endothelial dysfunction.⁶ Animal models have led to the current understanding that endothelial dysfunction is the primary causative factor in the origin of atherosclerotic cardiovascular disease.⁷

Despite an encouraging overall decrease in secondhand smoke exposure among children,⁸ a subgroup of vulnerable children who are at risk for the multiple health consequences of this exposure persists.⁹ National Health and Nutrition Examination Survey (NHANES) data from 2007 to 2008 suggests that half of 3- to 19-year-olds had detectable levels of a nicotine metabolite, cotinine, in their blood.¹⁰ Smoking prevalence varies inversely with socioeconomic status, with exposure rates in low-income communities as high as 79%.¹¹

Although there is a robust literature on the respiratory effects of tobacco exposure on children, research on the cardiovascular implications of secondhand smoke exposure during childhood is limited because children and adolescents do not have clinical manifestations of acquired (non-congenital) heart disease. However, research in this area has used a variety of proxy measures to assess cardiovascular health and risk, which include both traditional and nontraditional markers of adult cardiovascular disease.

Children and adolescents exposed to secondhand smoke have been shown to have abnormal lipid profiles. A dose-dependent inverse relationship between smoke exposure and endothelial function as measured by flow-mediated dilation in 11-year-old children has also been demonstrated,¹² as well as recent evidence that exposure to parental smoking in childhood is associated with increased carotid intima media thickness in adulthood.¹³ Investigations using NHANES data have found a significant association between biochemically validated secondhand exposure and systemic inflammation among nonsmoking youth.¹⁴ Soluble intercellular adhesion molecule 1 (s-ICAM1), a measure of endothelial stress, has been found to be elevated in the bronchoalveolar lavage fluid of secondhand smoke-exposed children compared to unexposed children.¹⁵ This molecule induces firm adhesion of inflammatory cells to vascular surface after injury¹⁶; soluble forms in circulation are released from activated or stressed endothelium.¹⁷ It is a clinical risk predictor of cardiovascular effects in adults¹⁷; s-ICAM1 levels go down among adult smokers after smoking cessation.¹⁸ Therefore, elevations in circulating s-ICAM1 levels are indicative of specific perturbations in endothelial health status.

An additional method to indirectly assess cardiovascular health is to measure endothelial repair via endothelial progenitor cells (EPCs). An important component to long-term maintenance of a healthy endothelium in humans is its reliable turnover and repair via

blood-borne EPCs. These are bone marrow–derived stem cells that circulate in the blood and home preferentially to sites of vascular or tissue injury, contributing significantly to both endothelial repopulation and neovascularization.¹⁹ EPCs have been recognized as a potential surrogate biological marker for vascular function and cumulative cardiovascular risk in adults.^{20,21} Heiss and colleagues²² found increased EPCs after a short experimental exposure to secondhand smoke in nonsmokers but decreased function of these cells. Among active smokers, EPCs levels are lower than those of nonsmokers.^{20,21}

The purpose of this study was to investigate relationships between secondhand smoke exposure in children and adolescents and cardiovascular disease risk, using conceptually sound, well-established markers of adult cardiovascular risk—systemic inflammation, endothelial stress, and endothelial repair.

Methods

Human Subject Recruitment and Study Eligibility

Participants were youth and adolescents ages 9 to 18 years. They were recruited via convenience sampling through recruiting in Nationwide Children's Hospital (NCH) (Columbus, Ohio) Primary Care Network, the NCH Center for Healthy Weight and Nutrition, and via advertising in the NCH internal hospital e-mail system. The Primary Care Network serves low-income, urban children in Columbus, Ohio, and the Center for Healthy Weight and Nutrition is a multidisciplinary referral center for obese children and adolescents. The protocol was approved by the NCH institutional review board; parents provided informed consent, and youth and teens provided consent and assent. We oversampled obese youth and teens because obese children are a target group of interest. The inclusion criteria were healthy children and adolescents both exposed and unexposed to tobacco smoke by parental report. The exclusion criteria were presence of 1 or more of the following: active smoker (defined as 1 puff of a cigarette or more in the past 7 days), acute febrile illness or other active infections, congenital heart disease, diabetes (type 1 or 2), elevated fasting glucose (>100 mg/dL), family history of elevated cholesterol, use of oral or inhaled steroids within 1 month of testing, caffeine (because it may alter blood pressure readings) within 2 days of testing, and not having enough hair for hair sampling for nicotine.

Study Procedure

The study was introduced to most subjects (except those recruited via e-mail advertising) at a clinic visit. Subjects were subsequently scheduled for testing at a research site in the morning between 8 and 10 AM, after overnight fasting. The protocol was carried out as follows: 1) study procedures were described with parental informed consent and youth/teen assent and consent obtained, 2) anthropomorphic measurements were obtained, 3) a structured interview was conducted with the subject and a parent (demographics and smoke exposure history), 4) a hair sample was obtained, and 5) a 7 mL blood sample was collected to assess for biomarkers and covariates. After serum sample collection, all assays were stored on ice and used within 12 hours of collection (24 hours for EPC counting).

Measures

Height and weight were obtained using a Tanita BWB800 scale and Seca stadiometer. Weights were recorded to the nearest 0.1 kg. Heights were measured to the nearest 0.5 cm. Body mass index (BMI) was determined according US Centers for Disease Control and Prevention (CDC) guidelines (BMI = weight [kg]/height [m²]), and percentile norms to define normal weight, overweight, and obese were from CDC guidelines (http://www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.htmlref). Covariates were blood pressure, lipid profiles, glucose, and insulin levels. Blood pressure and resting heart rate were measured using a Critikon-Dinamap Compact T vital sign monitor. The fasting subject was allowed to sit calmly for at least 5 minutes in an upright position; then the measurement was taken on the subject's left arm while sitting in an upright position. Percentages for height, age, and gender were determined by National Heart, Lung, and Blood Institute tables (http://www.nhlbi.nih.gov/guidelines/hypertension/child_tbl.htm). Lipid profiles and glucose were measured at the NCH core lab facility. Insulin resistance was determined using the homeostatic method (HOMA). Insulin levels were determined with enzyme immunoassay (Cat# 40-056-205011; GenWay Biotech Inc, San Diego, Calif). HOMA provides an accurate estimate of insulin sensitivity in multiple studies investigating impaired glucose tolerance and type 2 diabetes (including obese adults and children).²³ HOMA assessment was used to calculate indices of insulin resistance (IR) for each subject, as follows: HOMA-IR = fasting glucose (mg/dL) × fasting insulin (μU/mL)/405.

Secondhand smoke exposure was assessed by questionnaire and hair nicotine. Exposure to tobacco smoke was defined as living in a home with a smoker, regardless of whether the smoker claimed indoor or outdoor smoking. A smoker was defined as an individual who has smoked at least 1 cigarette per day during the previous 7 days. Hair nicotine was used as a biological marker of secondhand smoke exposure because this measure provides a long-term evaluation of smoke exposure because nicotine is incorporated in the growing hair shaft over several months.²⁴ Additionally, samples are easy to obtain, handle, and store. Approximately 20 to 40 shafts of hair 2 to 3 cm in length were cut at the root at the occipital area. Hairs were stored and later sent for assay at established contract research facility (Specialist Biochemistry Laboratory; Wellington Hospital, Wellington, New Zealand). The hair nicotine assay involves washing the hair sample before analysis and therefore is designed to measure inhaled nicotine, and not ambient nicotine that has adhered to hair.²⁴ The method is reverse-phase high-performance liquid chromatography with electrochemical detection, as described previously.²⁴ All samples were run in duplicate; samples found to have hair nicotine values of 100 ng/mg were run 6 times to confirm values in that range. Hair nicotine level is expressed as ng/mg of hair. The lowest sensitivity of the assay is 0.004 ng/mg hair when 2 mg of hair is used.

Because active smoking needed to be considered for the teens in the study, serum cotinine levels were analyzed at the NCH core lab. Subjects with serum cotinine levels above 10 ng/mL were to be considered active smokers,¹⁰ and their data would be discarded from the analysis.

Endothelial stress was assessed by measurement of s-ICAM1. Serum s-ICAM1 levels were determined using a sensitive commercially available assay kit (Cat # BBE 1B; R&D

Systems, Minneapolis, Minn). This is a quantitative sandwich enzyme immunoassay technique (ELISA) with a reported detection limit of <0.35 ng/mL. Intra- and interassay variations are less than 5% and 10%, respectively (manufacturer's guidelines).

Systemic inflammation was assessed by measurement of high-sensitivity CRP (hsCRP) and adiponectin, and anti-inflammatory marker. hsCRP has been linked to secondhand smoke exposure in both adults and children^{14,25} and is a strong independent predictor of cardiovascular risk in adults. Serum hsCRP was measured using a protein enzyme immunoassay test kit (Cat# BC-1119; BioCheck Inc, Foster City, Calif). Adiponectin, an adipocyte-derived peptide, is reduced in obese individuals,²⁶ is reduced in individuals with cardiovascular disease,²⁶ and is inversely correlated with insulin resistance.²⁷ Recent studies suggest that adiponectin is both anti-inflammatory and cardioprotective. Adiponectin levels were determined with ELISA (BD OptEIA; Cat # 555839). Sensitivity of this ELISA was <0.05 pg/mL.

Endothelial repair was assessed by EPC prevalence. They were defined by cell surface markers: CD34⁺/CD133⁺/CD45⁻ and counted by flow cytometry. CD133 and CD34 are appropriate markers of mesenchymal stem cells that are capable of endothelial differentiation.²⁸ A volume of 50 μ L anticoagulated peripheral blood is incubated with 50 μ L 3% bovine serum albumin in phosphate-buffered saline (without Ca²⁺ and Mg²⁺) at room temperature for 30 minutes. In the dark, fluorescence-labeled antibodies (2.5 μ L of each) PE-CD133, FITC-CD34, and PECy5-CD45 are added and incubated for 30 minutes at room temperature. FACS lysis buffer (450 μ L) is then added and incubated for 30 minutes at room temperature in the dark. Samples are then analyzed on a FACSCalibur flow cytometer; where total counts are >400,000 cells.

Statistical Analyses

All analyses were performed by SAS JMP 9.0 statistical software (SAS Institute, Cary, NC). Nonnormally distributed continuous data were log transformed. Pearson's *r* values were used for correlations, and all variables with correlation having a *P* value of < .25 were considered as potential predictors. They were log(34_45count), log(133_34_45count), mean BP [blood pressure], diastolic BP, age, systolic BP, adiponectin, log(cholesterol/HDL) [high-density lipoprotein], log(TGL) [triglyceride], log(TGL/HDL), log(insulin), log(HOMA-IR), BMI, log(CRP), log(CRP/ADIP [adiponectin]), log(VLDL) [very low-density lipoprotein], and log(hair nicotine). Among groups of correlated predictors, the ones with the smallest *P* value were used to build the model (eg, mean BP was used and systolic BP and diastolic BP were not). Stepwise regression analysis with forward selection was used to arrive at the final model. The level for a predictor to enter the model was 0.25, and the level for a predictor to leave the model was 0.10. Residuals were examined for normality and outliers.

Results

One hundred fifty-nine subjects were recruited. Fourteen subjects were not analyzed because they had medical conditions, such as diabetes, sleep apnea, hypothyroidism, and rheumatoid arthritis, or because they were receiving medications that would affect the end points we were measuring, such as anti-inflammatory and atypical antipsychotic medications. Serum

cotinine levels were analyzed on 37 of 54 subjects over age 14. None were above 10 ng/mL, and therefore no subject needed to be excluded because of high serum cotinine levels. As a result of incomplete data for all variables, 131 subjects were available for the multivariate analysis.

A description of the 145 subjects used in our analysis is found in Table 1. Slightly over half of the subjects were insured by Medicaid. Our subjects were African American (31%), white (44%), and multiracial (23%). The mean age was 12.2 years; the age distribution is shown in Table 1. Because one of our recruitment sites was a pediatric clinic that served low-income children and teens where smoking prevalence among parents is high, it is not surprising that subjects from lower-income and educational backgrounds were highly represented. Over half (57%) of subjects reporting a family income of less than \$40,000 per year, and only 35% had mothers who had graduated from college.

Secondhand smoke exposure information is found in Table 2. Overall, the prevalence of exposure was high, with 46% reporting living with a smoker; 30% of the subjects reported being exposed to 2 or more smokers per day. Hair nicotine levels ranged from 0.004 to 35.239 ng/mg; the median level was 0.415 ng/mg, and the mean (SD) was 1.541 (4.044) ng/mg. Hair nicotine levels were correlated with self-reported measures of secondhand smoke exposure. Both the number of smokers the subjects lived with and the number of smokers that the subjects were in contact with in the past 24 hours were highly correlated with hair nicotine (Table 2). The BMI distribution was as follows: 66 (45%) were normal weight as defined by CDC standards (BMI <85% for age and gender), 16 (11%) were overweight (BMI 85% and <95% for age and gender), and 64 (44%) were obese (95% for age and gender).

Bivariate Analyses

Bivariate relationships with hair nicotine and s-ICAM1 are found in Table 3. Hair nicotine was significantly related to s-ICAM1 and was negatively correlated with EPC prevalence. There was no relationship between hair nicotine levels and hsCRP, and there was a trend toward a weak inverse relationship with adiponectin. There was no relationship between age, gender, glucose, insulin level, lipid profile, and blood pressure with hair nicotine. There was a strong relationship between hair nicotine level and method of payment, with higher levels of nicotine among those subjects insured by Medicaid. The geometric mean (SD) for hair nicotine for subjects insured by Medicaid was -0.123 (0.632) ($n = 71$) versus -0.694 (0.70) ($n = 62$) for subjects with private insurance ($P < .0001$).

Bivariate Relationships with s-ICAM1

In addition to the relationship with hair nicotine, there was a strong inverse relationship with EPC count. There was a weak but significant relationship between BMI and s-ICAM1. There were small but significant negative relationships between systolic and diastolic blood pressure, and VLDL and s-ICAM1. There was no relationship between gender, age, and method of payment for medical care (Medicaid vs private insurance), lipid profile (except VLDL), insulin, glucose and HOMA levels, and s-ICAM1.

Regression Analysis

We performed stepwise regression analysis using s-ICAM1 as the dependent variable. In the final model (Table 4), hair nicotine, EPC prevalence, mean blood pressure, age, triglycerides, BMI, and VLDL were independent predictors of s-ICAM1. This model accounted for 42% of the variance in s-ICAM1 ($R^2 = 0.42$, $P < .0001$). BMI and hair nicotine level were positively correlated to s-ICAM1, while mean blood pressure, VLDL, age, and EPC prevalence were inversely correlated with s-ICAM1. The joint (interaction) effect of BMI and hair nicotine was not significant. Additionally, we performed stepwise regression analyses using EPC count (log 34–35 count) as the dependent variable. The only significant variable in this model was hair nicotine, with an inverse relationship to EPC count (F ratio 5.585, $R^2 = 0.04$, $P < .0196$).

Discussion

We found that secondhand smoke exposure, as measured by hair nicotine, was linked to both vascular endothelial stress (s-ICAM1) and to decreased endothelial repair (EPC prevalence), and that it had a weak relationship with one marker of anti-inflammation. This research adds to the literature regarding the cardiovascular effects of tobacco smoke exposure during childhood and adolescence. Although others have found links between secondhand smoke exposure and inflammation,¹⁴ endothelial dysfunction^{12,29} during childhood and adolescence, and increased intima media thickness during adulthood,^{13,30} to our knowledge, this is the first work to show a relationship between a biomarker of tobacco smoke exposure and endothelial stress and repair in children.

This study extends information regarding the positive relationship between tobacco smoke exposure in nonsmokers and s-ICAM1 found in adults^{31,32} to children and youth. Although s-ICAM1 has been reported to be elevated in the bronchoalveolar lavage fluid of tobacco-exposed children,¹⁵ our work is novel in that it found this relationship in the serum of children. Our findings regarding the inverse relationship between smoke exposure and endothelial repair is new information in pediatrics. In the adult literature, a brief experimental exposure to tobacco smoke in nonsmokers results in increased EPCs in the bloodstream.²² Our work measured chronic exposure, and therefore our findings may differ from the findings in adults after short experimental exposures.

Our study had several limitations. We used a convenience sample, not a random or epidemiologically based sample. However, we have no reason to believe that the relationships between secondhand smoke exposure and outcomes of interest would be different because of the sampling technique. Also, this was a cross-sectional study, from which we can infer correlation but not causation. Although we did examine BMI as a contributor in our multivariate model, there may be other unmeasured variables that contribute to endothelial stress. This is first step toward understanding these relationships, and longitudinal studies are needed.

Another limitation is that we did not interview adolescents separately regarding their own personal tobacco use, so it is possible that there were active smokers who did not reveal their smoking status in front of their parents. This could skew the data in the sense that we would

misattribute the results of secondhand exposure to what would actually be active smoking. However, this is unlikely. There was no relationship detected between hair nicotine level and age of subject. Furthermore, we obtained serum cotinine levels for 37 of 54 subjects over 14 years old, and none had levels consistent with active smoking.

Another limitation is that because we were studying children and teens, we used proxy measures of cardiovascular disease in adults. The key challenge in such work is to find meaningful markers of cardiovascular insult because during this time period, adult-onset heart disease is in the pre-clinical phase. We believe that we selected 3 measures that are meaningful in adult heart disease and that measure an important domain: endothelial stress, inflammation, and endothelial repair.

It is counterintuitive that traditional markers of cardiovascular risk, such as BP and VLDL, were inversely correlated with s-ICAM1. It is possible that in this younger population, these factors are not elevated enough to have relationships with vascular endothelial stress. We did not note a relationship between hsCRP and secondhand smoke exposure, as others have done,¹⁴ but in this sample, children with persistent asthma were excluded, so we may have biased our sample against children with chronic inflammation.

This investigation begins to define the effect of 2 simultaneous risk factors, secondhand smoke exposure and elevated BMI, which were both significant independent factors in our final model of endothelial stress. Our work corresponds to that of Laitinen et al,³³ who performed a longitudinal analysis of risk factors for adult cardiovascular health. Both parental smoking and elevated BMI were independent factors in their models (among others) of poor cardiovascular status in adulthood. Our cross-sectional study provides additional evidence of relationships between tobacco smoke exposure, BMI, and endothelial stress. Clinicians recognize that risk factors do not exist singularly. Our work has demonstrated that both secondhand smoke exposure and elevated BMI are independent contributors to endothelial stress and represent an overlay of health risks and potential related health disparities.

In summary, this work demonstrates that in a cohort of healthy 9- to 18-year-olds with no overt cardiovascular disease, objectively measured secondhand smoke exposure was related to both increased endothelial stress and decreased endothelial repair. In addition to the cumulative effects of years of exposure, these youth have a greater risk of becoming active smokers as a result of parental modeling of smoking behavior.³⁴ Therefore, these findings have important implications in understanding the potential lifetime burden of cardiovascular disease starting with smoke exposure during childhood.

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What's New

Secondhand smoke exposure, measured objectively by hair nicotine, was a significant predictor in a model for endothelial stress and was the only significant variable in a model predicting endothelial repair. These findings add to our knowledge that cardiovascular effects of tobacco smoke exposure begin in childhood, long before clinical cardiovascular disease is evident.

Table 1**Demographic Data**

Characteristic	Value
Total no. of subjects	145
Male	69 (47.6%)
Age, y	
Mean (SD)	12.5 (2.5)
Range	9–19
Age distribution	
9–11 y	40 (37%)
12–13 y	37 (26%)
14–15 y	34 (24%)
16–19 y	20 (13%)
Race	
African American	45 (31.0%)
White	66 (45.5%)
Asian	2 (1.4%)
Multiracial and other	32 (22.1%)
Family income	
<\$10,000	17 (11.7%)
\$10,000–\$20,000	24 (16.6%)
\$20,000–\$30,000	20 (13.8%)
\$30,000–\$40,000	22 (15.1%)
>\$40,000	56 (38.6%)
Not answered	6 (4.1%)
Maternal education	
Less than high school	10 (6.9%)
Graduated high school	29 (20.0%)
Some college or technical school	53 (36.6%)
Graduated college	51 (35.2%)
Not answered	2 (1.4%)
Subject insurance status	
Medicaid	74 (51.0%)
Private insurance	64 (44.1%)
Self-pay	2 (1.4%)
Other	5 (3.5%)

Table 2

Secondhand Smoke Exposure in 145 Subjects

Exposure	Value
Live with smoker	66 (45.5%)
No. of smokers exposed to in past 24 h	
0	69 (47.6%)
1	31 (21.4%)
2 or more	44 (30.3%)
Not answered	1 (0.7%)
Hair nicotine, ng/mg hair	
Mean (SD)	1.541 (4.044)
Median	0.42
Range	0.004–35.24
Hair nicotine (log) vs self-report correlation	
No. of smokers lived with, Pearson <i>r</i>	0.5232 (<i>P</i> < .0001)
No. of smokers exposed to in past 24 h, Pearson <i>r</i>	0.4816 (<i>P</i> < .0001)

Table 3**Bivariate Analyses**

Variable	Correlation	Count	P
Correlation with log hair nicotine (with $P < .05$)			
Log(133_34_45count)	−0.2690	136	.0015
Log(34_45count)	−0.2002	136	.0195
BMI	0.1756	145	.0346
Adiponectin	−0.1529	145	.0663
Log(CRP)	0.1320	145	.1135
Correlation with log s-ICAM1 (with $P < .25$)			
log(hair nicotine)	0.4090	145	<.0001
log(34_45count)[EPC]	−0.3816	136	<.0001
log(133_34_45count)	−0.3639	136	<.0001
log(VLDL)	0.2443	139	.0038
Mean BP	−0.2099	145	.0113
Diastolic BP	−0.1930	145	.0200
log(CRP/ADIP [adiponectin])	0.1872	145	.0242
age(y)	−0.1860	145	.0251
log(CRP)	0.1851	145	.0258
Systolic BP	−0.1583	145	.0572
BMI	0.1572	145	.0590
log(HOMA-IR)	0.1485	144	.0757
log(insulin)	0.1427	145	.0868
log(TGL/HDL)	0.1273	145	.1272
log(TGL)	0.1238	145	.1379
Adiponectin	−0.1124	145	.1783

EPC indicates endothelial progenitor cell; BMI, body mass index; CRP, C-reactive protein; s-ICAM1, soluble intercellular adhesion molecule 1; VLDL, very low-density lipoprotein; BP, blood pressure; BMI, body mass index; HOMA-IR, homeostatic model assessment–insulin resistance; TRGS/HDL, triglycerides/high-density lipoprotein; and TGL, triglyceride.

Table 4Final Predictive Model for log(s-ICAM1) Using Stepwise Method^{*}

Term	Slope Estimate	Standard Error	<i>t</i> Ratio	<i>P</i>	Sequential <i>R</i> ²
Log 34_35 count(EPC)	−0.2570	0.0621	−4.14	<.0001	0.1590
Log hair nicotine	0.1627	0.0413	3.94	.0001	0.2594
Log(VLDL)	0.2661	0.1212	2.2	.0300	0.3023
Mean BP	−0.0329	0.0099	−3.33	.0012	0.3502
BMI	0.0292	0.0088	3.31	.0012	0.3764
Age (y)	−0.0855	0.0290	−2.94	.0039	0.4172

EPC indicates endothelial progenitor cell; VLDL, very low-density lipoprotein; BP, blood pressure; and BMI, body mass index.

^{*}*R*² = 0.42, *P* < .0001.