

## Secondhand Smoke and CKD

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### Abstract

**Background and objectives** Active smoking is associated with higher risk of various diseases. However, the risk of CKD development in nonsmokers exposed to secondhand smoke is not well elucidated. We aimed to investigate the association between secondhand smoke exposure and the risk of CKD development among never-smokers.

**Design, setting, participants, & measurements** A total of 131,196 never-smokers with normal kidney function, who participated in the Korean Genome and Epidemiology Study from 2001 to 2014, were analyzed. The participants were classified into three groups on the basis of frequency of secondhand smoke exposure, assessed with survey questionnaires; no exposure, <3 days per week, and ≥3 days per week. The association between secondhand smoke and CKD, defined as eGFR <60 ml/min per 1.73 m<sup>2</sup>, was examined in the cross-sectional analysis. In addition, the risk of incident CKD development was analyzed in a longitudinal cohort of 1948 participants without CKD at baseline, which was a subset of the main cohort.

**Results** The mean age of participants was 53 years, and 75% were women. Prevalent CKD was observed in 231 (1.8%), 64 (1.7%), and 2280 (2.0%) participants in the ≥3 days per week, <3 days per week, and no exposure groups. The odds ratio (OR) of prevalent CKD was significantly higher in the groups exposed to secondhand smoke than the no exposure group (<3 days per week: OR, 1.72; 95% confidence interval [95% CI], 1.30 to 2.27; and ≥3 days per week: OR, 1.44; 95% CI, 1.22 to 1.70). During a mean follow-up of 104 months, CKD occurred in 319 (16%) participants. Multivariable Cox analysis revealed that the risk for CKD development was higher in participants exposed to secondhand smoke than the no exposure group (<3 days per week: hazard ratio, 1.59; 95% CI, 0.96 to 2.65; and ≥3 days per week: hazard ratio, 1.66; 95% CI, 1.03 to 2.67).

**Conclusions** Exposure to secondhand smoke was associated with a higher prevalence of CKD as well as development of incident CKD.

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### Introduction

The number of patients with CKD is rapidly increasing worldwide (1–3). CKD has become a global health problem because of its association with poorer quality of life and higher mortality risk for patients (4,5). Considering that established CKD is an irrecoverable condition, identifying modifiable factors and applying early interventions are crucial to reducing the burden of CKD.

Cigarette smoking is associated with a higher risk of various diseases, including cancer, lung diseases, and cardiovascular diseases (6–8). Reports on the association of smoking with CKD have shown mixed results. Several investigations failed to find a significant relationship between cigarette smoking and kidney function decline (9–11). However, a large population-based study of 65,589 participants showed that smoking was a significant risk factor for future kidney failure. In addition, a recent analysis of 15 cohort studies showed that cigarette smoking is independently associated with CKD (12). These recent investigations support the hypothesis that active smoking may be a notable risk factor for kidney function decline.

Because of these adverse effects, legislative actions have been taken to prohibit smoking in public areas and workplaces. Nonetheless, despite these measures, the prevalence of secondhand smoke exposure is still increasing in some countries. The Korea National Health and Nutrition Examination Survey reported that the prevalence of secondhand smoke exposure in the workplace has steadily increased between 2005 and 2013 (13). Exposure to secondhand smoke has been reported to be associated with a higher risk of several types of cancer and cardiovascular disease (14,15). In addition, recent data have shown that side-stream smoke, which is the main component of secondhand smoke, comprises more toxic substances than those found in mainstream smoke, postulating that secondhand smoke exposure could also cause serious harm (16).

Unfortunately, despite the potential toxic effect of secondhand smoke, the association between secondhand smoke exposure and the risk of CKD development has not been well elucidated. Therefore, this study aimed to investigate the association between secondhand smoke exposure and the risk of CKD

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development in never-smoking adults by using a large community-based cohort comprising participants with normal kidney function.

## Materials and Methods

### Study Design and Participants

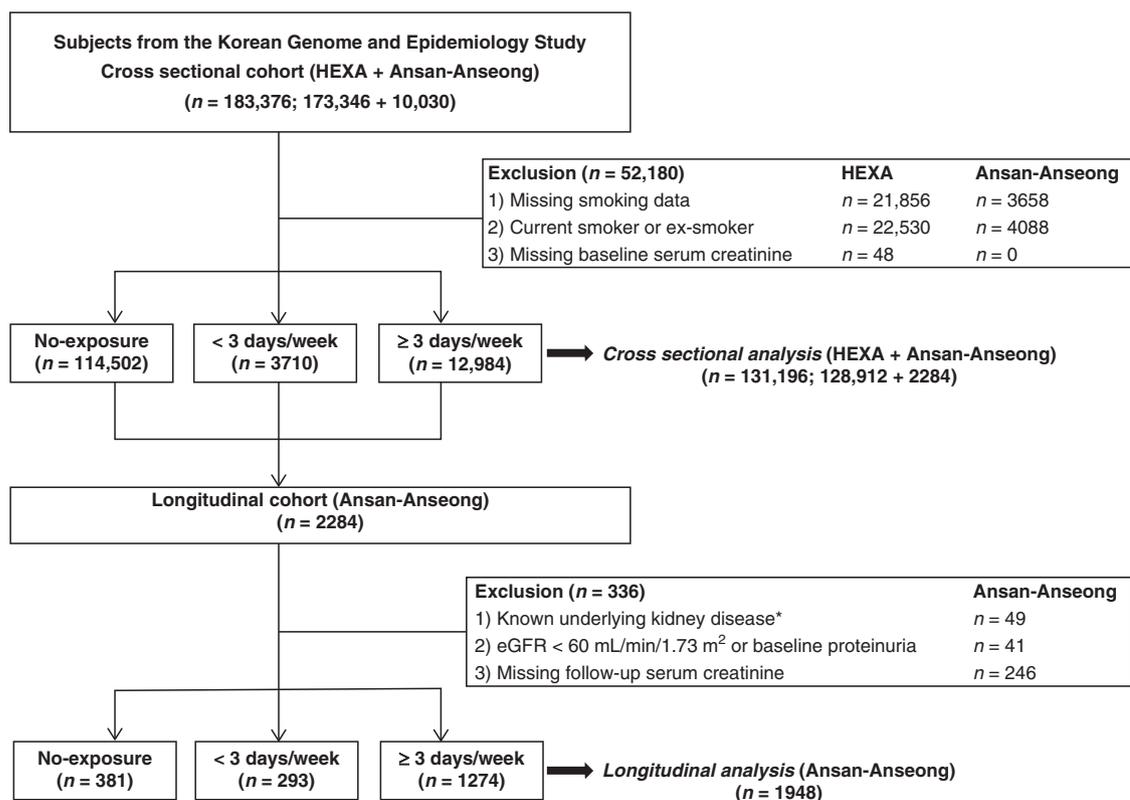
This study used data from the Korean Genome and Epidemiology Study (KoGES), a community-based cohort study. The detailed profile and methods concerning the development of KoGES has been described previously (17). The KoGES study is composed of two geographically distinctive cohorts, the KoGES\_health examinees (KoGES\_HEXA) study and the KoGES\_Anсан-Anseong study (17). The KoGES\_HEXA study includes participants residing in metropolitan cities of Korea. The participants of the KoGES\_Anсан-Anseong study are from a medium-sized city (Ansan) and a rural area (Anseong) near Seoul, Korea. For the cross-sectional analysis, baseline data from the KoGES\_HEXA study and the KoGES\_Anсан-Anseong study were used. The KoGES\_Anсан-Anseong study data were used for the longitudinal analysis. A total of 183,376 participants (173,326 from the KoGES\_HEXA study and 10,030 from the KoGES\_Anсан-Anseong study) aged 40–69 years were initially screened. For the cross-sectional analysis, participants with information on smoking history were initially screened. Those with missing smoking data or serum creatinine levels, and those who were current or ex-smokers were excluded. A total of 131,196 participants were included in the final analysis (Figure 1). Participants included in the KoGES\_Anсан-Anseong study underwent serial health

examinations and surveys biennially from 2001 to 2014. After excluding those whose baseline eGFR was  $<60$  ml/min per  $1.73$  m<sup>2</sup>, those with underlying kidney disease or positive for proteinuria, and those without follow-up creatinine data, a total of 1948 individuals were analyzed for the longitudinal analysis. The presence of underlying kidney disease was surveyed by a questionnaire asking whether the participants had been previously diagnosed with CKD. All participants were enrolled in the study voluntarily, and informed consent was obtained in all cases. This study was carried out in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the Yonsei University Health System Clinical Trial Center (approval no. 4–2016–0900).

### Smoking and Secondhand Smoke Assessments

Smoking status was assessed with the following questions: “Have you ever smoked?” and “Do you currently smoke?”. If a participant answered that they currently smoke, they were categorized as “current smokers.” If a participant answered that they do not currently smoke but had a history of ever smoking, they were classified as “ex-smokers.” If a participant answered that they do not currently smoke and have never had a history of smoking, they were classified as “never-smokers.”

Among never-smokers, exposure to secondhand smoke was surveyed with the question “Have you been exposed to cigarette smoke from other smokers?”. Never-smokers who were not exposed to secondhand smoke were



**Figure 1.** | Study participants were grouped according to secondhand smoke exposure frequency. \*Presence of underlying kidney disease was surveyed through a questionnaire asking whether the participants had been previously diagnosed with CKD.

allocated as the no exposure group. The frequency of secondhand smoke exposure was defined by the answers to the question “How many days per week have you been exposed to cigarette smoke?”. Participants were to select from the given choices of none, <3 days per week,  $\geq 3$  days per week, or every day. According to the answers, participants were classified into three groups: no exposure, <3 days per week, or  $\geq 3$  days per week. The overall response rate of the smoking status assessment survey was 86%.

### Study Outcome

For the cross-sectional analysis, the association between secondhand smoke exposure and prevalent CKD was evaluated. For the longitudinal analysis, the primary end point was incident CKD development. CKD was defined as eGFR <60 ml/min per 1.73 m<sup>2</sup>. Serum creatinine level was measured by Jaffe assay. The samples were analyzed in two KoGES central laboratories and the intra- and interlaboratory reliability of the serological parameters have been previously confirmed (18). eGFR was calculated by the CKD Epidemiology Collaboration equation (19). In the longitudinal cohort, serum creatinine levels were measured biennially. The dipstick urine test was done, and proteinuria was classified on the basis of a color scale that quantified proteinuria as absent, trace, 1+, 2+, or 3+. This scale correlates approximately with urine protein levels of <10, 10–20, >30, >100, and >500 mg/dl, respectively (18). Proteinuria was determined as present if the results of the dipstick urine test were higher than trace levels. For detailed methods, see Supplemental Material.

### Statistical Analyses

All statistical analyses were performed with IBM SPSS software for Windows, version 23.0 (IBM Corporation, Armonk, NY). Each variable was tested for normality before the statistical analysis, using the Kolmogorov–Smirnov test with Lilliefors correction and the Shapiro–Wilk test. Adjusted mean values of eGFR were produced by general linear models adjusted for age, sex, body mass index, systolic BP, history of hypertension, and diabetes. Multivariable logistic regressions were used to analyze the association of secondhand smoke exposure with CKD. The cumulative kidney survival rates were estimated with Kaplan–Meier analysis and a log-rank test. Survival time was defined as the interval between baseline and outcome or the last follow-up. Individuals who were lost to follow-up or death were censored at the date of the last examination. Cox proportional hazards analyses were performed to determine the independent association of secondhand smoke with the development of incident CKD. Proportional hazards assumptions were confirmed using Schoenfeld residuals (Supplemental Figure 1). Multivariable models were constructed with adjustment for confounding factors. Variables that showed statistical significance in univariable regression analyses were selected for the multivariable model. The causal diagram model included variables that have been selected from a “causal diagram,” which was used to choose variables with appropriate directional association (Supplemental Figure 2) (20). When dealing with missing covariate values, the pairwise deletion method was applied (21). Missing serum creatinine data in the longitudinal analysis were imputed with the values of the last observation. The

missing data rates were <5% for the variables in the cross-sectional analysis. For the longitudinal analysis, expected and observed creatinine values were counted. For all analyses, a *P* value of <0.05 was considered statistically significant.

## Results

### Baseline Characteristics

The baseline characteristics of the participants are described in Table 1. The mean age was 53±8 years and 75% were women. The average eGFR was 92±14 ml/min per 1.73 m<sup>2</sup>. A total of 114,502 (74%) participants were included in the no exposure group. Among those exposed to secondhand smoke, 12,984 (78%) participants were exposed to secondhand smoke  $\geq 3$  days per week, and 3710 (22%) participants were exposed <3 days per week. Participants were more often exposed to secondhand smoke at home (*n*=12,683, 76%) than at work (*n*=6674, 40%). Total duration of secondhand smoke exposure tended to be significantly longer in the secondhand smoke  $\geq 3$  days per week (22±13 years) than <3 days per week (17±12 years) group. The secondhand smoke exposure groups tended to be younger, include more female participants, and have higher body mass index than those in the no exposure group.

### Baseline eGFR According to Frequency of Secondhand Smoke Exposure

When the mean baseline eGFR adjusted for confounding factors was compared among the secondhand smoke exposure frequency groups, the mean eGFR was 88 (95% CI, 77–88), 89 (95% CI, 88–89), and 91 (95% CI, 90–93) ml/min per 1.73 m<sup>2</sup> in the <3 days per week,  $\geq 3$  days per week, and no exposure groups, respectively.

### Association between Secondhand Smoke Frequency and Prevalent CKD

To examine the association between prevalent CKD and secondhand smoke exposure frequency, logistic regression analyses were performed. Prevalent CKD was observed in 231 (1.8%), 64 (1.7%), and 2280 (2.0%) cases in the  $\geq 3$  days per week, <3 days per week, and no exposure groups, respectively. The adjusted odds ratio (OR) for prevalent CKD was significantly higher in participants with secondhand smoke exposure than those without exposure (OR, 1.48; 95% confidence interval [95% CI], 1.25 to 1.74). When participants were stratified by frequency of secondhand smoke exposure, the <3 days per week (OR, 1.72; 95% CI, 1.30 to 2.27) group and  $\geq 3$  days per week (OR, 1.44; 95% CI, 1.22 to 1.70) group were associated with higher ORs compared with the no exposure group (Table 2). A similar association was found when CKD was defined as a composite of eGFR <60 ml/min per 1.73 m<sup>2</sup> and/or development of proteinuria (Supplemental Table 1).

In an additional analysis of 125,371 participants for whom secondhand smoke exposure duration information was available, prevalent CKD was significantly associated with lifetime secondhand smoke exposure duration when the duration was longer than 10 years. In addition, a dose-response relationship was found with increasing exposure duration (Supplemental Table 2).

**Table 1. Baseline characteristics of participants in the Korean Genome and Epidemiology study**

Characteristics	Total, n=131,196	Secondhand Smoke Frequency		
		No Exposure, n=114,502	<3 d/wk, n=3710	≥3 d/wk, n=12,984
<b>Secondhand smoke exposure</b>				
Location, %				
<i>At home only</i>		N/A	1924 (52)	8096 (62)
<i>At work only</i>		N/A	1367 (37)	2644 (21)
<i>At both home and work</i>			419 (11)	2244 (17)
Total duration, yr <sup>a</sup>		N/A	17±12	22±13
<b>Demographic data</b>				
Age, yr	53±8	54±8	51±8	52±8
Women	115,082 (75)	86,790 (76)	2963 (80)	11,576 (89)
BMI, kg/m <sup>2</sup>	24±3	24±3	24±3	24±3
Waist-to-hip ratio	0.9±0.1	0.9±0.1	0.9±0.1	0.9±0.1
Alcohol status, ever	67,464 (44)	45,358 (40)	1750 (48)	5253 (41)
Physical activity, yes	77,756 (52)	58,586 (53)	1801 (55)	5426 (48)
Married, yes	125,737 (88)	93,783 (88)	2871 (88)	9936 (89)
Education status				
≤Elementary	30,355 (20)	22,393 (20)	817 (22)	3985 (31)
Middle–high school	84,137 (55)	61,490 (55)	2018 (55)	7094 (55)
≥College	37,793 (25)	28,964 (26)	841 (23)	1776 (14)
Income				
Low	17,046 (13)	13,152 (13)	385 (12)	1834 (17)
Intermediate	57,227 (43)	41,534 (42)	1366 (44)	4871 (46)
High	57,828 (44)	43,287 (44)	1356 (44)	3945 (37)
Systolic BP, mm Hg	122±16	122±16	121±16	122±17
Diastolic BP, mm Hg	76±10	76±10	76±10	77±11
<b>Comorbidities</b>				
Hypertension	29,486 (19)	22,534 (20)	581 (16)	2314 (18)
Diabetes	9731 (6)	7411 (7)	204 (6)	707 (6)
Dyslipidemia	13,756 (9)	10,339 (9)	241 (7)	828 (7)
Cardiovascular events	3485 (2)	2717 (2)	34 (1)	118 (1)
<b>Laboratory data</b>				
eGFR, ml/min per 1.73 m <sup>2</sup>	91±13	91±14	90±14	90±14
Proteinuria <sup>b</sup>	7866 (6)	5994 (6)	137 (5)	447 (5)
Hemoglobin, g/dl	13.6±1.5	13.6±1.4	13.3±1.5	13.2±1.3
Albumin, g/dl	4.6±0.3	4.6±0.2	4.6±0.3	4.6±0.3
Glucose, mg/dl	94±21	95±21	93±21	93±22
Hemoglobin A1c, %	5.7±0.7	5.7±0.7	5.7±0.8	5.7±0.9
Total cholesterol, mg/dl	198±36	198±36	197±35	198±36
Triglyceride, mg/dl	123±86	123±85	129±94	120±81
HDL cholesterol, mg/dl	54±13	54±13	54±13	55±13
LDL cholesterol, mg/dl	119±33	119±33	117±33	119±32
hs-CRP, mg/dl	0.1 [0.0–0.1]	0.1 [0.0–0.1]	0.1 [0.0–0.1]	0.1 [0.0–0.1]

Data are presented as mean±SD, median [interquartile range], or n (%). N/A, not applicable; BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein.

<sup>a</sup>The information of total duration of secondhand smoke exposure during lifetime was examined in 125,371 out of 131,196 (95%) participants.

<sup>b</sup>Proteinuria was determined as present if the results of the dipstick urine test were higher than trace levels.

### Association of Secondhand Smoke Frequency with Incident CKD Development

To further validate the association between kidney function and secondhand smoke exposure, the risk of secondhand smoke exposure on incident CKD development was evaluated in a longitudinal subgroup of 1948 individuals. In this subgroup, 1567 (80%) of participants were exposed to secondhand smoke. During a mean follow-up duration of 104±52 months, CKD newly developed in 319 (16%) individuals. The numbers of expected and observed serum creatinine values were 5.5 and 5.2 per participant, respectively. When multivariable Cox proportional hazards regression analysis was performed, the risk for incident CKD development was significantly higher in those exposed to secondhand smoke than those

without exposure (hazard ratio [HR], 1.64; 95% CI, 1.03 to 2.60). Furthermore, those exposed to secondhand smoke <3 days per week (HR, 1.59; 95% CI, 0.96 to 2.65) or ≥3 days per week (HR, 1.66; 95% CI, 1.03 to 2.67) were associated with higher risk for incident CKD compared with those not exposed to secondhand smoke (Table 3). The proportional hazards assumption held reasonably for secondhand smoke exposure (Supplemental Figure 2). Factors associated with CKD in the univariable analyses are shown in Supplemental Table 3. Kaplan–Meier plots showed that the time to incident CKD development was significantly longer in the no exposure group than in groups exposed to secondhand smoke, regardless of exposure frequency (Figure 2).

**Table 2. Relative risk for the prevalence of CKD at baseline according to frequency of secondhand smoke**

Variables	No. (%) with CKD	Multivariable Model	Causal Diagram Model
		OR (95% CI)	OR (95% CI)
<b>Secondhand smoke (yes versus no)</b>			
No exposure	2280 (2.0)	1.00 (Reference)	1 (Reference)
Exposure	295 (1.8)	1.44 (1.23 to 1.68)	1.48 (1.25 to 1.74)
<b>Secondhand smoke frequency</b>			
No exposure	2280 (2.0)	1.00 (Reference)	1 (Reference)
<3 d/wk	64 (1.7)	1.65 (1.22 to 2.22)	1.72 (1.30 to 2.27)
≥3 d/wk	231 (1.8)	1.38 (1.16 to 1.65)	1.44 (1.22 to 1.70)

Multivariable model: adjustment for age, sex, body mass index, systolic BP, history of hypertension, history of diabetes, alcohol status, education levels, income levels, marital status, hemoglobin, and serum albumin. Causal diagram model: adjustment for age, sex, history of hypertension, history of diabetes, education levels, income levels, and marital status. OR, odds ratio; 95% CI, 95% confidence interval.

## Discussion

In this study, the prevalence of secondhand smoke exposure among nonsmokers was surveyed and the association with CKD development was investigated in individuals with normal eGFR. Despite public health regulations prohibiting smoking in public places, a considerable proportion of the nonsmoking population was found to be exposed to secondhand smoke. Baseline eGFR was lower and the relative risk for the prevalence of CKD was significantly higher in those with secondhand smoke exposure. In addition, secondhand smoke was significantly associated with higher risk of incident CKD development, and this risk was evident even in individuals with less frequent secondhand smoke exposure.

To our knowledge, this is the first study to demonstrate a significant association between secondhand smoke and CKD development. Previously, in a cross-sectional analysis of 15,535 patients with hypertension, a history of secondhand smoke exposure was found to be associated with presence of albuminuria (22). In addition, another small investigation showed that serum cotinine, a nicotine metabolite, and urine albumin levels were higher in passive smokers compared with nonsmokers, suggesting that glomerular function could be affected by secondhand smoke

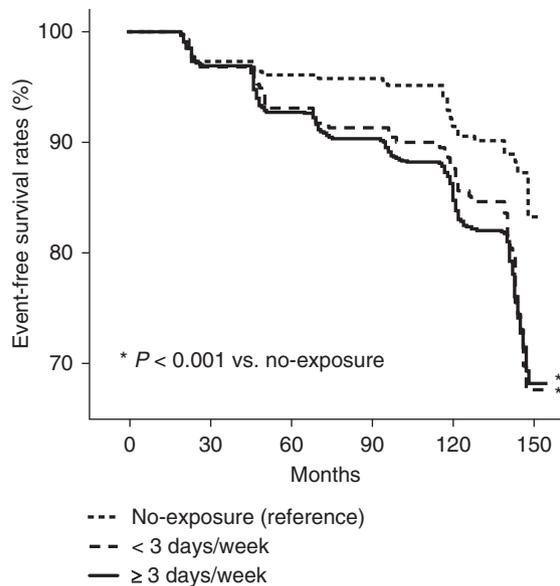
exposure (23). Although these investigations have raised suspicion that exposure to secondhand smoke could have an influence on kidney function, the direct relationship has not been evaluated in a prospective observation of a large-scale cohort.

The proportion of participants who were exposed to secondhand smoke was considerably high (almost half of the nonsmoking individuals). Worldwide, the estimated proportions of men and women exposed to secondhand smoke in 2004 were 33% and 35%, respectively (24). The proportions of secondhand smoke exposure differ among countries because of different cultural background and policies regarding smoke-free areas (25–29). The regional variation of secondhand smoke exposure rate is known to range from <15% in Africa to >50% in the European and Western Pacific regions (24). As extensive legislative restrictions to prohibit smoking in public areas have been enacted in Korea since 2007, there is a possibility that the secondhand smoke exposure rate could have decreased recently. Nonetheless, the fact that most of the secondhand smoke exposure was household-oriented rather than from the workplace reduces the likelihood that these policies may not have had a large effect in lowering the rate of secondhand smoke exposure. In addition to legal restrictions, education

**Table 3. Relative risk for incident CKD according to secondhand smoke exposure**

Variables	No. of Cases (%)	Number at Risk	Multivariable Model	Causal Diagram Model
			HR (95% CI)	HR (95% CI)
<b>Secondhand smoke (yes versus no)</b>				
No exposure	35 (9)	381	1.00 (Reference)	1.00 (Reference)
Exposure	319 (16)	1948	1.61 (1.02 to 2.59)	1.64 (1.03 to 2.60)
<b>Secondhand smoke frequency</b>				
No exposure	35 (9)	381	1.00 (Reference)	1.00 (Reference)
<3 d/wk	54 (18)	293	1.58 (0.94 to 2.66)	1.59 (0.96 to 2.65)
≥3 d/wk	230 (18)	1274	1.62 (1.03 to 2.63)	1.66 (1.03 to 2.67)

Multivariable model: adjustment for age, sex, body mass index, systolic BP, history of hypertension, history of diabetes, alcohol status, education levels, income levels, marital status, hemoglobin, and serum albumin. Causal diagram model: adjustment for age, sex, history of hypertension, history of diabetes, education levels, income levels, and marital status. HR, hazard ratio; 95% CI, 95% confidence interval.



**Figure 2. | Time to CKD development was longer in secondhand smoke non-exposed than exposed participants.** Kaplan–Meier plot of incident CKD development according to secondhand smoke exposure frequency in 1948 participants with follow-up data.

and efforts to increase community consciousness should be provided to reduce household smoking rates.

In a previous meta-analysis of 15 cohort studies, the relative risk of CKD development in ever-smokers was 1.27 compared with nonsmokers (12). This higher risk in ever-smokers is comparable with the relative risk associated with secondhand smoke exposure found in this study. In addition, the OR for CKD prevalence in participants exposed to secondhand smoke in this study was also similar to that of ever-smokers (1.37; 95% CI, 1.22 to 1.53; Supplemental Table 4). These findings suggest that the association of CKD with secondhand smoke exposure could be at least similar to its relationship with active smoking. Although active smoking is an intermittent activity, nonsmokers are commonly exposed to secondhand smoke from multiple smokers. Therefore, some nonsmokers exposed to secondhand smoke could be exposed to a similar dose of cigarette smoke to active smokers. However, a subgroup analysis stratified by location of exposure showed a lack of association between secondhand smoke exposure and CKD in those exposed  $\geq 3$  days per week at work (Supplemental Table 5). The fact that those exposed at work were younger, had less comorbidities, and were exposed for a shorter total duration could account for this finding (Supplemental Table 6). Supporting this possibility, a clear dose-response relationship between CKD prevalence and lifetime secondhand smoke exposure duration was presented. These findings suggest that exposure duration than frequency could be a more considerable factor associated with kidney function. Nevertheless, further studies with more information on secondhand smoke exposure frequency or dose would be worthwhile. Interestingly, secondhand exposure rate was higher in the longitudinal analysis than in the cross-sectional analysis. Because of the geographic distinction, socioeconomic characteristics were also found to be different between

the two cohorts (Supplemental Table 7). The participants from KoGES\_Ansan-Anseong study were likely to be less educated and had lower income levels compared with the participants of the KoGES\_HEXA study. Because the KoGES\_HEXA study participants make up most of the cross-sectional cohort, the characteristics of the cross-section cohort are represented by those of the KoGES\_HEXA study. Therefore, the geographic and demographic difference could have resulted in the observed secondhand smoke exposure difference between the cross-sectional and prospective cohort. This possibility is supported by a previous report showing that secondhand smoke exposure could vary depending on the characteristics of the society (30).

Several mechanisms are suspected to contribute to secondhand smoke-induced kidney function decline. There is evidence suggesting that exposure to environmental tobacco smoke decreases the serum antioxidant defense and impairs endothelial function in nonsmokers (31–34). Animal studies have shown that the amount of reactive oxygen species in kidney tissue significantly increased in mice exposed to cigarette smoke compared with mice not exposed to cigarette smoke (35). As inflammation and oxidative stress in the lungs have been found to affect the circulatory system, resulting in an increase in systemic oxidative stress (36), there is a possibility that secondhand smoke-induced respiratory reactive oxidative species could have resulted in kidney damage. In addition, a recent study showing that nicotine directly causes apoptosis of podocytes through the induction of oxidative stress suggested that the toxins in secondhand smoke could directly act on the kidney (34).

This study has a number of limitations. First, the exposure amount of secondhand smoke was not directly measured, but was on the basis of answers from questionnaires surveying the exposure frequency. Because most individuals are exposed to secondhand smoke at irregular intervals, unlike in active smoking, the amount of secondhand smoke exposure is difficult to quantify. Second, information regarding medication was not available. Relevant renoprotective medications that block the renin-angiotensin-aldosterone system, and potential harmful medications such as nonsteroidal anti-inflammatory drugs, would have had effect on kidney function. Future investigations including medication history would be necessary. Third, direct measurements of the accumulation of secondhand smoke-related toxic substances were not done. To more directly demonstrate the association between secondhand smoke and its adverse kidney effect, further investigations on serum cotinine or nicotine levels are needed.

In conclusion, exposure to secondhand smoke was significantly associated with higher risk of CKD development. Lowering the risk of secondhand smoke exposure by enhancing public smoking restriction policies and educating the public about the potential harm of household tobacco use could reduce the risk of CKD development in the nonsmoking population with normal kidney function.

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## Disclosures

None.

## Supplemental Material

This article contains the following supplemental material online at <http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.09540818/-/DCSupplemental>.

Supplemental Table 1. The prevalence of CKD on the basis of eGFR and proteinuria definition.

Supplemental Table 2. Relative risk for the prevalence of CKD according to lifetime total duration of secondhand smoke.

Supplemental Table 3. Univariable associations between clinical factors and CKD in cross-sectional and prospective analysis.

Supplemental Table 4. Relative risk for the prevalence of CKD according to ever-smoker versus never-smoker.

Supplemental Table 5. Relative risk for the prevalence of CKD according to frequency of secondhand smoke exposure at home and work.

Supplemental Table 6. Baseline characteristics according to exposure location.

Supplemental Table 7. Baseline characteristics according to two different cohort datasets.

Supplemental Figure 1. Graphical evaluation of the proportional hazards assumption.

Supplemental Figure 2. Causal diagram showing assumed associations between baseline secondhand smoke, CKD, and baseline characteristics.

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## **Secondhand Smoke and Chronic Kidney Disease**

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## **SUPPLEMENTAL METHODS**

### **Anthropometric and laboratory data**

All subjects received a comprehensive health examination, and filled out questionnaires on health and lifestyle at the time of study entry. Demographic and socioeconomic data, including age, sex, level of education and income, marital status, smoking status, alcohol intake, degree of physical activity, and medical histories were also collected. Anthropometric parameters such as height, body weight, and waist and hip circumferences were measured by skilled study workers following standard methods while the subjects were wearing light clothes. Body mass index (BMI) and waist-to-hip ratio were calculated as the weight divided by height squared ( $\text{kg}/\text{m}^2$ ) and the waist circumference divided by the hip circumference, respectively. The level of education was divided into three groups: low, lower than middle school; middle, middle school; high, higher than middle school. The level of income was divided into three groups: low,  $< \$850$  per month; middle,  $\$850$  to  $\$1,700$  per month; high,  $\geq \$1,700$  per month. Physical activities were expressed as the metabolic equivalent of task. Subjects who had a history of hypertension, with a blood pressure of  $\geq 140/90$  mm Hg, or were taking antihypertensive agents were considered hypertensive. Those who had a medical history of diabetes, blood glucose levels  $\geq 126$  mg/dL in an 8-h fasting status, postload glucose levels  $\geq 200$  mg/dL after a 75-g oral glucose tolerance test, HbA1c  $\geq 6.5\%$ , or were receiving oral medication and/or insulin treatment for hyperglycemia were considered as having diabetes. Subjects with a medical history of dyslipidemia or taking medication for lipid control were considered as having dyslipidemia. Cardiovascular disease was defined as the composite of myocardial infarction, congestive heart failure, coronary artery disease, peripheral artery disease, and/or cerebrovascular accident.

The following biochemical data were determined by using fasting blood samples: concentrations of sodium, blood urea nitrogen, creatinine, hemoglobin, glucose, HbA1c, albumin, total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and C-reactive protein. LDL-C was calculated by using the Friedewald formula (1). Urine samples were collected in the morning after the first voiding. Fresh urine samples were analyzed by using URISCAN Pro II (YD Diagnostics Corp., Seoul, Korea).

### **Reference**

1. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 18(6): 499-502, 1972.

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**Supplemental Table 1.** The prevalence of CKD based on eGFR and proteinuria definition\*

	Case (%)	Model 1		Model 2		Model 3		Model 4	
		OR (96% CI)	P						
<b>Secondhand smoke (yes vs. no)</b>	358/16,694 (2)	1.23 (1.10-1.38)	<0.001	1.45 (1.27-1.66)	<0.001	1.37 (1.19-1.58)	<0.001	1.44 (1.26-1.65)	<0.001
<b>Secondhand smoke frequency</b>									
No-exposure	2,627/114,502 (2)	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
<3 days/week	80/3,710 (2)	1.34 (1.07-1.69)	0.01	1.74 (1.35-2.25)	<0.001	1.59 (1.21-2.10)	0.001	1.72 (1.33-2.22)	<0.001
≥3 days/week	278/12,984 (9)	1.20 (1.06-1.36)	0.01	1.37 (1.17-1.60)	<0.001	1.31 (1.11-1.54)	0.001	1.37 (1.17-1.60)	<0.001

**Note:** \*CKD was defined as eGFR < 60 mL/min/1.73 m<sup>2</sup> or having higher than trace level proteinuria according to dipstick test results.

**Model 1:** Adjustment for age and sex

**Model 2:** Model 1 + demographic factors including BMI, systolic BP, history of hypertension, history of diabetes, alcohol status, education levels, income levels, and marital status

**Model 3:** Model 2 + laboratory factors including hemoglobin and serum albumin

**Model 4:** Adjustment for age, sex, history of hypertension, history of diabetes, alcohol status, education levels, income levels, and marital status

**Abbreviations:** CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; OR, odds ratio; CI, confidence; BMI, body mass index

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**Supplemental Table 2.** Relative risk for the prevalence of CKD according to life-time total duration of secondhand smoke (n = 125,371)\*

	Case (%)	Model 1		Model 2		Model 3		Model 4	
		OR (96% CI)	P						
<b>Secondhand smoke exposure duration</b>									
No-exposure	2,274/114,502 (2)	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
<10 years	40/3,018 (1)	1.09 (0.79-1.50)	0.61	1.22 (0.86-1.74)	0.26	1.09 (0.75-1.58)	0.66	1.19 (0.84-1.69)	0.34
10-19 years	42/3,022 (1)	1.43 (1.04-1.95)	0.03	1.46 (1.02-2.09)	0.04	1.28 (0.87-1.87)	0.21	1.47 (1.03-2.08)	0.03
≥20 years	144/4,829 (3)	1.52 (1.28-1.82)	<0.001	1.65 (1.34-2.03)	<0.001	1.62 (1.30-2.01)	<0.001	1.61 (1.31-2.00)	<0.001

**Note:** \*Analysis was done in 125,371 subjects who had full information regarding life-time total secondhand smoke exposure duration.

**Model 1:** Adjustment for age and sex

**Model 2:** Model 1 + demographic factors including BMI, systolic BP, history of hypertension, history of diabetes, alcohol status, education levels, income levels, and marital status

**Model 3:** Model 2 + laboratory factors including hemoglobin and serum albumin

**Model 4:** Adjustment for age, sex, history of hypertension, history of diabetes, education levels, income levels, and marital status

**Abbreviations:** CKD, chronic kidney disease; OR, odds ratio; CI, confidence; BMI, body mass index; SBP, systolic blood pressure

**Supplemental Table 3.** Univariable associations between clinical factors and CKD in cross-sectional and prospective analysis

	Cross-sectional analysis		Prospective analysis	
	OR (95% CI)*	P	HR (95% CI)†	P
Age (per 1 year)	1.16 (1.15-1.17)	<0.001	1.12 (1.10-1.14)	<0.001
Sex (female vs. male)	1.60 (1.47-1.74)	<0.001	1.45 (1.01-2.08)	0.04
BMI (per 1 kg/m <sup>2</sup> )	1.11 (1.10-1.13)	<0.001	1.08 (1.04-1.11)	<0.001
SBP (per 1 mmHg)	1.02 (1.01-1.03)	<0.001	1.02 (1.01-1.03)	<0.001
Alcohol status (yes vs. no)	0.80 (0.77-0.84)	<0.001	0.74 (0.65-0.84)	<0.001
Education levels				
≤Elementary	reference		reference	
Middle–high school	0.48 (0.44-0.53)	<0.001	0.44 (0.35-0.55)	<0.001
≥College	0.48 (0.43-0.53)	<0.001	0.42 (0.26-0.68)	<0.001
Income levels				
Low	reference		reference	
Intermediate	0.51 (0.46-0.57)	<0.001	0.52 (0.40-0.68)	<0.001
High	0.31 (0.27-0.34)	<0.001	0.48 (0.34-0.68)	<0.001
Marital status (yes vs. no)	0.57 (0.51-0.63)	<0.001	0.52 (0.36-0.74)	<0.001
Hypertension (yes vs. no)	4.91 (4.54-5.31)	<0.001	2.62 (1.82-3.77)	<0.001
Diabetes (yes vs. no)	4.34 (3.94-4.78)	<0.001	2.31 (1.78-2.99)	<0.001
Hemoglobin (per 1 g/dL)	0.89 (0.86-0.91)	<0.001	1.09 (1.01-1.18)	0.03
Albumin (per 1 g/dL)	0.72 (0.62-0.83)	<0.001	0.55 (0.37-0.81)	0.01
eGFR (per 1 mL/min/1.73m <sup>2</sup> )	N/A		0.95 (0.94-0.96)	<0.001
Total cholesterol (per 1 mg/dL)	1.00 (0.99-1.01)	0.40	1.01 (1.00-1.02)	<0.001

**Note:** \*Univariable logistic regression analysis was performed with CKD and each clinical factor.

†Univariable Cox analysis was performed for incident CKD and each clinical factor.

**Abbreviations:** BMI, body mass index; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; N/A, not applicable

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**Supplemental Table 4.** Relative risk for the prevalence of CKD according to ever smoker vs. never smoker (n\* = 157,814)

Case (%)	Model 1		Model 2		Model 3		Model 4		
	OR (96% CI)	P	OR (96% CI)	P	OR (96% CI)	P	OR (96% CI)	P	
<b>Smoking status</b>									
Never smoker	2,575/131,196 (2)	1.00 (reference)							
Ever smoker	731/26,618 (3)	1.35 (1.23-1.49)	<0.001	1.35 (1.21-1.51)	<0.001	1.32 (1.18-1.48)	<0.001	1.37 (1.22-1.53)	<0.001

**Note:** \*Non-smokers (131,196) plus current or ex-smokers who were initially excluded from the main analysis (26,618), Ever smokers include current and ex-smokers.

**Model 1:** Adjustment for age and sex

**Model 2:** Model 1 + demographic factors including BMI, systolic BP, history of hypertension, history of diabetes, alcohol status, education levels, income levels, and marital status

**Model 3:** Model 2 + laboratory factors including hemoglobin and serum albumin

**Model 4:** Adjustment for age, sex, history of hypertension, history of diabetes, education levels, income levels, and marital status

**Abbreviations:** CKD, chronic kidney disease; OR, odds ratio; CI, confidence; BMI, body mass index; SBP, systolic blood pressure

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**Supplemental Table 5.** Relative risk for the prevalence of CKD according to frequency of secondhand smoke exposed at home and work

	At home		At work	
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
<b>Secondhand smoke frequency</b>				
No-exposure	1.00 (reference)		1.00 (reference)	
<3 days/week	1.83 (1.18-2.84)	0.01	1.63 (1.11-2.40)	0.01
≥3 days/week	1.66 (1.35-2.04)	<0.001	1.02 (0.74-1.39)	0.38

Models were adjustment for age, sex, history of hypertension, history of diabetes, education levels, income levels, and marital status

**Abbreviations:** CKD, chronic kidney disease; OR, odds ratio; CI, confidence; BMI, body mass index; BP, blood pressure

**Supplemental Table 6.** Baseline characteristics according to exposure location

<b>Characteristics</b>	<b>At home only (n = 10,020)</b>	<b>At work only (n = 4,011)</b>
<b>Secondhand smoke exposure</b>		
Total duration (year)	24 ± 12	14 ± 12
<b>Demographic data</b>		
Age (years)	52 ± 8	50 ± 7
Female	9,819 (98.0)	2,428 (58.2)
BMI (kg/m <sup>2</sup> )	24 ± 3	24 ± 3
Alcohol status (ever)	6,178 (62.0)	1,650 (39.7)
Physical activity (yes)	4,136 (49.2)	1,949 (51.9)
Married (yes)	7,584 (90.4)	3,149 (84.1)
Education status		
≤Elementary	3,380 (34.1)	801 (19.4)
Middle–high school	5,249 (52.9)	2,382 (57.6)
≥College	1,288 (13.0)	950 (23.0)
Income		
Low	1,636 (20.0)	340 (9.6)
Intermediate	3,714 (45.3)	1,594 (44.8)
High	2,846 (34.7)	1,625 (45.7)
Systolic BP (mm Hg)	121.5 ± 16.9	121.7 ± 15.6
Diastolic BP (mm Hg)	76.4 ± 10.5	77.3 ± 10.5
<b>Comorbidities</b>		
Hypertension	1,844 (18.4)	663 (15.9)
Diabetes	573 (5.7)	225 (5.4)
Dyslipidemia	655 (7.8)	247 (6.6)
Cardiovascular events	94 (1.1)	37 (1.0)
<b>Laboratory data</b>		
eGFR (mL/min/1.73 m <sup>2</sup> )	90.1 ± 14.4	90.0 ± 13.9
Hemoglobin (g/dL)	13.0 ± 1.2	13.8 ± 1.5
Albumin (g/dL)	4.6 ± 0.3	4.7 ± 0.3
Glucose (mg/dL)	94 ± 23	94 ± 19
HbA1c (%)	5.7 ± 0.9	5.7 ± 0.9
Total cholesterol (mg/dL)	199 ± 36	195 ± 35
Triglyceride (mg/dL)	120 ± 80	120 ± 82
HDL-C (mg/dL)	55 ± 12	54 ± 13
LDL-C (mg/dL)	120 ± 32	117 ± 31
hs-CRP (mg/dL)	0.1 [0.0-0.2]	0.1 [0.0-0.1]

**Note:** Data are presented as mean ± standard deviation, median [interquartile range], or number (%).

**Abbreviations:** BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein

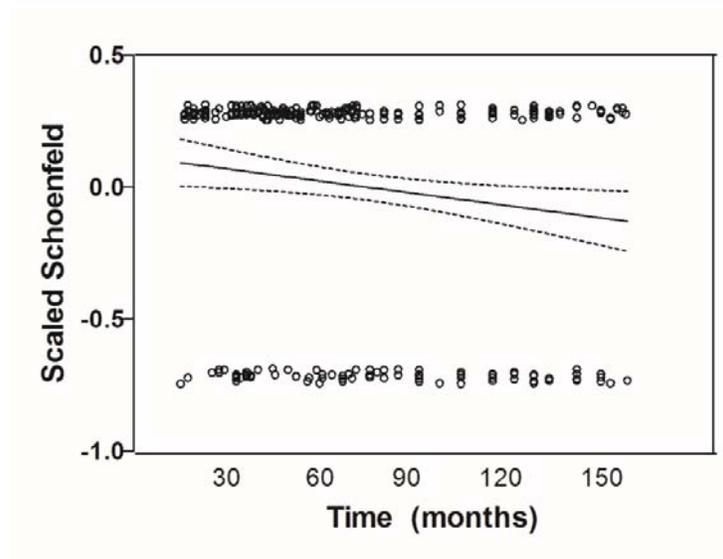
**Supplemental Table 7.** Baseline characteristics according to two different cohort datasets

Characteristics	KoGES_HEXa study (n = 128,912)	KoGES_Ansan-Anseong study (n = 1,948)
<b>Demographic data</b>		
Age (years)	54 ± 8	52 ± 9
Female	99,262 (77)	1,626 (84)
BMI (kg/m <sup>2</sup> )	24 ± 3	25 ± 3
Alcohol status (ever)	51,564 (40)	662 (34)
Physical activity (yes)	67,034 (52)	1,363 (70)
Married (yes)	109,575 (85)	1,714 (88)
Education status		
≤Elementary	24,493 (19)	1,227 (63)
Middle–high school	70,901 (55)	681 (35)
≥College	33,517 (26)	38 (2)
Income		
Low	14,180 (11)	720 (37)
Intermediate	46,408 (36)	896 (46)
High	48,986 (38)	292 (15)
Systolic BP (mm Hg)	122 ± 16	121 ± 19
Diastolic BP (mm Hg)	76 ± 10	80 ± 12
<b>Comorbidities</b>		
Hypertension	25,782 (20)	311 (16)
Diabetes	7,734 (6)	117 (6)
Dyslipidemia	11,602 (9)	37 (2)
Cardiovascular events	1,289 (1)	19 (1)
<b>Laboratory data</b>		
eGFR (mL/min/1.73 m <sup>2</sup> )	91 ± 14	95 ± 14
Hemoglobin (g/dL)	13.6 ± 1.4	12.8 ± 1.4
Albumin (g/dL)	4.6 ± 0.3	4.5 ± 0.3
Glucose (mg/dL)	94 ± 21	91 ± 21
HbA1c (%)	5.7 ± 0.8	5.7 ± 0.7
Total cholesterol (mg/dL)	198 ± 36	198 ± 36
Triglyceride (mg/dL)	121 ± 83	139 ± 98
HDL-C (mg/dL)	55 ± 13	51 ± 12
LDL-C (mg/dL)	119 ± 32	120 ± 33
hs-CRP (mg/dL)	0.1 [0.0-0.2]	0.1 [0.1-0.2]

**Note:** Data are presented as mean ± standard deviation, median [interquartile range], or number (%).

**Abbreviations:** BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein

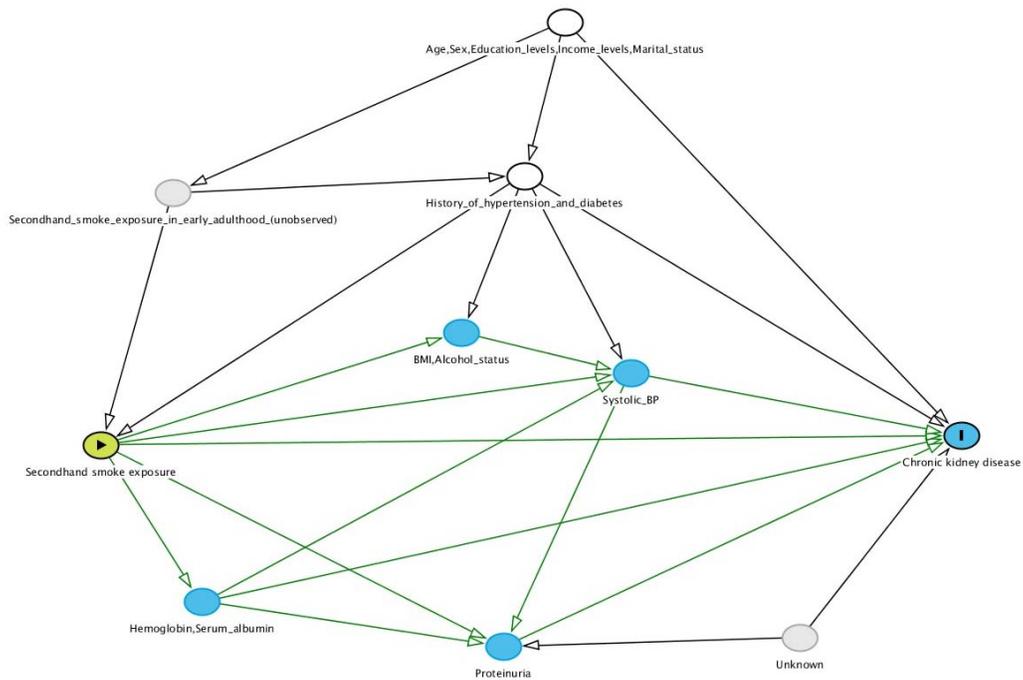
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**Supplemental Figure 1.** Graphical evaluation of the proportional hazards assumption using scaled Schoenfeld residuals in univariable Cox proportional hazards models for the association of chronic kidney disease with the frequency of secondhand smoke exposure

**Note:**  $P$ -value for slope = 0.93. Dots represents Schoenfeld residuals. Solid line is a smoothing spline fit to the plot with the dashed lines representing a 2-standard error band around the fit.

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**Supplemental Figure 2.** Causal diagram showing assumed associations between baseline secondhand smoke, chronic kidney disease, and baseline characteristics. Variables with white circles are considered to be confounders and those with blue circles are considered to be effect mediator.

**Note:** Constructed with <http://www.dagitty.net>.

**Abbreviations:** BP, blood pressure