의학박사 학위논문

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Effects of Environmental Factors on Chronic Kidney Disease

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이 논문을 의학 박사 학위논문으로 제출함
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박재윤의 의학 박사 학위논문을 인준함
2021년 2월

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Abstract

Background: Although management of the traditional risk factors for chronic kidney disease (CKD), such as diabetes mellitus, hypertension, dyslipidemia, smoking, and obesity, has advanced considerably for decades, the prevalence of CKD and its complications remain significant. Recently, environmental factors have recently emerged as a new risk factor for chronic diseases. However, the relationship between environmental factors and CKD is relatively unknown.

Objectives: The purpose of this study is to study the health problems caused by environmental factors, especially which affect the development of chronic kidney disease and the resulting mortality.

Method: For investigation of the effects of outdoor environmental factors on mortality of patients with end-stage renal disease, A total of 5,041 patients who started dialysis between 2008 and 2015 were prospectively enrolled in the Clinical Research Center for End-Stage Renal Disease (CRC-ESRD) cohort study. A daily mean concentration of air pollutants (PM_{10}, NO_2, and SO_2) was assigned to each participant. Time-varying Cox models were used to investigate the relationship between air pollutants and mortality in ESRD patients. To investigate the association of indoor environmental factors with kidney dysfunction, a total of 1,294 adults who participated in the Korean National Environmental Health Survey from 2015 to 2017 were enrolled. The association of major phthalates and their metabolites, bisphenol A and

parabens with albuminuria and renal dysfunction was examined.

Results: In the research estimating the association between clinical outcome and air pollution exposure, during the follow-up period (mean 4.18 years), 1475 deaths occurred among 5041 participants. A significant long-term relationship between mortality risk and PM_{10} (HR 1.33, CI 1.13–1.58), NO_2 (HR 1.46, CI 1.10–1.95), and SO_2 (HR 1.07, CI 1.03–1.11) was found. Elderly patients and patients who lived in metropolitan areas had an increased risk associated with PM_{10}. Elderly patients also had increased risks associated NO_2 and SO_2.

For the association between exposure to phthalates and environmental phenolics with markers of kidney function, regardless of correction method, urinary DEHP metabolites showed significant positive associations with albumin to creatinine ratio (ACR). Following covariate-adjusted standardization, urinary metabolites of other heavy molecular weight phthalates such MCOP and MCNP showed significant positive associations with ACR. For eGFR, conventional creatinine-correction resulted in positive associations with most of measured phthalate metabolites. However, following covariate-adjusted standardization, most of positive associations disappeared, and significant negative associations with eGFR were observed for MnBP, BPA, and EtP. Secondary analysis following stratification by CKD status and principal component analysis (PCA) generally support the observed associations.

Conclusion: Long-term exposure to air pollutants had negative effects on mortality in ESRD patients. These effects were prominent in elderly patients who lived in metropolitan areas, suggesting that ambient air pollution, in addition to traditional risk factors, is important for the survival of these patients. In addition, major phthalate metabolites exposed indoors increase the risk of chronic kidney disease in healthy adults. And this study highlights the importance of considering collider issues associated with the choice of dilution adjustment method, and provides better understanding on the association of major consumer chemicals with adverse kidney function among humans. Therefore, it is important to pay more attention to the health effects of outdoor and indoor environmental factors on CKD. This effort could reduce the risk of CKD, which has not been resolved by controlling traditional risk factors.

Keywords: Chronic Kidney Disease, End-Stage Renal Disease, Air Pollution, Phthalates

Student Number: 2014-31263

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Chapter 1. General Introduction

1.1 Study Background

According to the World Health Organization (WHO)'s report in 2016, 23% of global deaths (around 12.6 million) were attributable to environmental factors (e.g., air pollutants), which accounted for 22% of the global disease burden.[1] Environmental factors affect diseases of various organs, including kidneys, through exposure through various industrial products or disposable items that we consume in our daily life, or through air pollution.[2-8]

Chronic kidney disease (CKD) is a disease in which kidney function gradually worsens due to various causes, and can lead to other serious health consequences. Individuals with CKD are expected to exhibit approximately 10-fold higher mortality risk due to cardiovascular diseases than those without the kidney dysfunction.[9-11] Risk factors well-known for CKD include diabetes mellitus (DM), hypertension, dyslipidemia, smoking, and obesity.[10,12] Although decades of efforts to control these traditional risk factors, however, the socioeconomic and health burdens from CKD has been increasing.[13] Furthermore, despite the growing interest in health problems caused by the environmental factors, the correlation between environmental factors and chronic kidney disease is still not well known.

Environmental factors can be devided into daily changing ambient

enviroment such as air pollution (i.e., outdoor factors) and chemical substances through various industrial daily products such as personal hygiene products and cosmetics or disposable products consumed in daily life (i.e., indoor factors). Air pollution is one of the most important health issues in Korean society. The WHO announced that 7 million people died earlier than expected due to aerodynamic particulate matter (PM) in 2014. This is greater than premature deaths from smoking. According to the United States (US) Environmental Health Organization's institute for health impact, the average concentration of PM less than 2.5 μm ($PM_{2.5}$) in Korea was 29 $\mu g/m^3$, which is higher than the standard recommendation by the WHO of 10 $\mu g/m^3$. In addition, the concentration of PM in Korea is the second highest after Turkey among 35 Organization for Economic Co-operation and Development (OECD) countries, and the increase is 4 $\mu g/m^3$ in 5 years (2010-2015) which is top ranked.

Among consumer chemicals, lead and cadmium have traditionally been associated with kidney damage. Recently, phthalates, which are widely used as a plasticizer, and bisphenol A (BPA), which is used in the manufacture of coated paper, were reported that those were related to microalbuminuria. In addition, perfluoroalkyl acids (PFAs), which are used in the manufacture of heat-resistant and corrosion-resistant pipes frequently used in various industries and buildings, dioxins, which are often detected in herbicides and in waste incineration, and polycyclic aromatic hydrocarbons (PAHs), which are commonly generated during fossil fuel combustion, are emerging as novel

environmental risk factors. However, the previous reports are not consistent according to the population group (and mainly in Western societies) or the reporting period. Furthermore, research on the relationship between various consumer chemicals and CKD is limited. Therefore, it is necessary to examine the relationship in a sample cohort that is representative of the domestic population group.

1.2 Purpose of Research

The purpose of this study is to investigate the effects of outdoor and indoor environmental factors on the occurrence of chronic kidney disease and its mortality, by using air pollution indicators and daily chemical substances reported by the Korean National Institute of Environmental Research.

1.3. Ethical Aspects

The study protocol complied with the Declaration of Helsinki and received full approval from the institutional review board (IRB) of Seoul National University Hospital (H-1405-060-579).

Chapter 2. Effects of Outdoor Environment: Effects of Air Pollution on Mortality of Patients with End-Stage Renal Disease

2.1 Introduction

As industrialization progresses, the impact of air pollution on health is becoming a global issue. According to the WHO's recent statement, seven million premature deaths related to air pollution occur annually, particularly in the regions of southeastern Asia and the western Pacific.[14] Exposure to ambient air pollution contributes to the progression of cardiovascular (CV) diseases and respiratory diseases, such as chronic obstructive pulmonary disease and type 2 DM, malignancies, and even autoimmune diseases.[15-19]

The prevalence of CKD is increasing, and it has become one of the most important health problems worldwide. Individuals with CKD have an eight- to 10-fold higher risk of CV-related mortality than those without renal dysfunction.[20-21] DM, hypertension, dyslipidemia, smoking, old age, and male sex are well-established traditional risk factors for CKD.[22,23] However, recent reports have shown that air pollution, as well as traditional risk factors, play an important role in renal disease.[24-30]

Recent epidemiologic reports emphasized that aerodynamic PM less than 10 μm (PM_{10}) significantly increases the morbidity and mortality of various diseases, especially CV and pulmonary diseases.[15,16,31,32] Biologically,

PM was reported to contribute to the exacerbation of chronic diseases by promoting inflammatory or carcinogenic responses, and evidence suggests that the mechanism is mediated by both organic and inorganic components of PM.[33,34]

Although evidence from several experimental and clinical studies suggests that exposure to relatively high amounts of air pollution adversely affects kidney function,[24-27] few studies have reported the association between mortality in CKD patients and PM. In addition, few researchers have found an association between gaseous compounds, such as nitrogen dioxide (NO_2) and sulfur dioxide (SO_2), and kidney disease, although epidemiological studies have demonstrated the effect of long-term exposure to gaseous matter on general health.[35-37] Therefore, the impact of air pollutants on mortality in patients with end-stage renal disease (ESRD) was investigated in a nationwide, multicenter, prospective cohort in Korea.

2.2. Methods

2.2.1. Study Population

The Clinical Research Center for End-Stage Renal Disease (CRC-ESRD) cohort (Daegu, Republic of Korea) is a prospective cohort that has been continuously registered since July 2008 and includes those who have undergone dialysis previously. The number of hospitals contributing to the cohort was 31, which was advantageous because the characteristics of the majority of ESRD patients was able to be identified. Patients who started

dialysis between 2008 and 2015 and those who started dialysis prior to cohort registration were included. The data from the CRC-ESRD cohort included age, sex, body mass index (BMI), hemoglobin, Charlson comorbidity index (CCI), working status, marital status, education, social and family support, and insurance type. Social and family support were measured as percentages (%) of the degrees to which the patient was assisted by their family and society. Zero percent and 100% represented independent and full-support on society/family, respectively. Insurance was divided into five categories: (1) Medical protection (type 1): Those who received the National Basic Livelihood Security; (2) Medical protection (type 2): Those who received medical protection but not type 1; (3) Health insurance, working poor: Those in the potential low-income strata; (4) Health insurance, rare and incurable disease: Those with rare intractable diseases designated by country; and (5) Health insurance, general: Those who were normal subscribers of National Health Insurance. Working and marital status referred to the status at the time of cohort entry.

2.2.2. Data Collection

Air pollution data were collected from the National Institute of Environmental Research database (Incheon, Republic of Korea). This database provides the concentrations of PM_{10}, NO_2, and SO_2 from 274 stations on an hourly basis through the national Urban Atmospheric Monitoring Network. The whole country is classified into 17 provincial-level

regions, including major metropolitan cities (Seoul, Busan, Incheon, Daegu, Gwangju, Daejeon, and Ulsan). Daily mean concentrations of air pollutants were assigned to the 17 provincial-level regions (si-do) according to the locations of monitoring stations. The CRC-ESRD cohort data did not include the residential addresses of participants, but did include the province-level addresses of the hospitals in which the patients were treated. Therefore, exposures were assigned to the patients based on the province of the hospital where they received dialysis. Due to the characteristics of dialysis, the distance between the dialysis center and patient residence was likely not far because dialysis needs to be performed regularly,[38] in general, three times a week. In addition, the following province-level variables were obtained from the Korean Statistical Information Service (Daejeon, Republic of Korea) (1) Population density: Population divided by land area (km^2); (2) Economically active population: Mean population of economically active population aged over 15 years, including the number of employed and unemployed people per thousand people; and (3) Number of medical institutions: Mean number of institutions, including hospitals, clinics, public health agencies, and pharmacies. All province-level characteristics were matched to the enrollment year of the cohort.

2.2.3. Statistical Analysis

Time-varying Cox hazard models were used to investigate the relationship between mortality in ESRD patients who received dialysis and

long-term air pollutants. The fully adjusted model is described as follows:

$$\lambda(\mathrm{t}|\mathrm{Z}(\mathrm{t})) = \lambda_0(t)\exp\left(\beta' x + \gamma' X g(t)\right) \quad (1)$$

$$\mathrm{Z}(\mathrm{t}) = [x_1, x_2, \ldots, x_{14}, X_1 g(t)] \quad (2)$$

where λ0 (t) is the baseline hazard function and β'and γ' are the coefficients of time-independent and time-dependent covariates, respectively. The models were adjusted for potential confounding factors, including sex (male, female); age (continuous); smoking status (never, current, former); hemoglobin, BMI, and CCI (continuous); working status (unemployed, retired, employed); marital status (single, married); education (uneducated, elementary, middle, and high school; university/college; graduate school); insurance (medical protection (type 1 or 2), health insurance (working poor, rare and incurable disease, general)); and the duration of therapy, population density, economically active population, and the number of medical institutions (continuous). The enrollment year of ESRD patients was additionally adjusted since the entry dates of the patients were different. In addition, X1 g(t) was used to describe the annual average exposure to air pollutants from one year to seven years before the date of cohort enrollment. The exposure was used as a time-varying variable by updating each year. For example, one participant was enrolled in the cohort in 2008 and censored in 2011. To estimate the effect of six years of exposure on mortality, the mean concentrations of the 2002–2008, 2003–2009, 2004–2010, and 2005–2011 exposures were used. Long-term impacts for up to seven years could be

identified, since the National Institute of Environmental Research in Korea has provided the daily concentration of air pollutants across the country since 2001. Person-years of follow-up time were calculated from the start of follow-up (29 August 2008) until the end of follow-up (31 December 2015), censoring at death or the end of follow-up. A regression spline with two degrees of freedom was used to identify nonlinearity between mortality and air pollutants in the time-varying Cox proportional hazard model. The exposure period that yielded the smallest Akaike information criterion (AIC) was selected to conduct subgroup analyses.

The fully adjusted model was stratified by age (<65, ≥65), sex (male, female), social and family support (<50%, ≥50%), and habitation in a metropolitan area (no, yes). Metropolitan cities included seven major cities with populations of more than one million in Korea. The statistical significance of the subgroup differences was confirmed by the p-value for interaction. The results are presented as hazard ratios (HRs) and 95% confidence intervals (CIs) per interquartile range (IQR) increment of each air pollutant. All statistical analyses were performed with R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

2.2.4. Sensitivity Analysis

A time-independent baseline Cox model was constructed to identify the effect of PM_{10}, NO_2, and SO_2 on mortality in ESRD patients. The effects of exposure to air pollutants from one year to seven years before the

enrollment date of the cohort could be identified in the baseline model, although the time-varying model in which air pollutants were updated every year reflected the concentration of air pollutants over time. The trend p-value represents the linear trend of association considering the median value of each quartile as a continuous variable. In addition, a two-pollutant model with adjustments for other pollutants was constructed to identify the robustness of the association.

2.2.5. Validation Cohort

A validation cohort from Seoul National University Hospital (SNUH) was used from January 2001 to December 2017 to confirm the long-term association between mortality in ESRD patients and air pollutants (n = 8941). Patients who were enrolled in the cohort before 2008 were excluded to identify the seven-year long-term effect of air pollutants on mortality. Overall, 5910 participants were analyzed with a time-varying Cox model adjusted for seven-year air pollutants, sex, age, BMI, hemoglobin, alcohol consumption, smoking, population density, economically active population, the number of medical institutions, and the year of cohort enrollment. The average of air pollutants measured at monitoring stations within 3 km, 5 km, and 10 km of the residence was used since the SNUH cohort data provided the residence of the participants.

2.3. Results

2.3.1. Baseline Characteristics of the Subjects and Annual Trends of Air Pollutants

Table 1 shows the characteristics of the 5041 participants in the CRC-ESRD cohort. During the mean 4.18-year follow-up period, 1475 deaths (29.2%) occurred. The mean age of the ESRD patients was 60.48 years and 59% were male. Most of the subjects were nonsmokers or former smokers (90%) and 73% were unemployed. Nearly half of the participants responded that they received more than 50% support from their family and society. The concentration of air pollutants during 2001–2015 showed a tendency to decrease slightly over the study period (Figure 1). The means and standard deviations of the concentrations of PM_{10}, NO_2, and SO_2 measured seven years before the enrollment date of the cohort were 55.52 ± 5.28 μg/m^3, 28.13 ± 6.89 ppb, and 5.60 ± 0.88 ppb, respectively. The IQR increments of seven-year exposure to PM_{10}, NO_2, and SO_2 were 8.14 μg/m^3, 12.77 ppb, and 0.38 ppb, respectively. The average concentrations of air pollutants slightly increased as the duration of exposure increased from one year to seven years (Table 2).

Table 1. Descriptive characteristics of the Clinical Research Center for End-Stage Renal Disease (CRC-ESRD) cohort participants at baseline.

Characteristics		**Statistics**
No. of cohort participants		*n* = 5041
No. of deaths		1475 (29.2%)
Person-years of follow-up		4.18 ± 1.77
Hemodialysis		5041 (100%)
Primary causes of ESRD		
Hypertension		959 (19%)
Primary glomerulonephritis (GN)		660 (13.1%)
Diabetes		226 (4.5%)
Cystic, hereditary, congenital disease		141 (2.8%)
Secondary GN, vasculitis		65 (1.3%)
Interstitial nephritis		53 (1%)
Unknown		2821 (56%)
Miscellaneous conditions		116 (2.3%)
Duration of therapy		0.84 ± 2.04
Individual level		
Men		2963 (59%)
Age		60.48 ± 13.52
Hemoglobin (g/dL)		9.87 ± 1.67
Smoking status	Never	2915 (60%)
	Current	491 (10%)
	Former	1463 (30%)
CCI		5.09 ± 2.27
Comorbidities	Cerebrovascular disease	677 (13%)
	Diabetes	545 (10%)
	Coronary artery disease	319 (6%)
	Cancer	314 (6%)
	Congestive heart failure	186 (3%)
BMI		22.85 ± 3.38
Working status	Unemployed	3576 (73%)
	Retired	286 (6%)
	Employed	1012 (21%)
Marital status	Single	1148 (24%)
	Married	3562 (76%)
Education	Uneducated	205 (4%)
	Elementary school	738 (16%)
	Middle school	732 (16%)
	High school	1781 (38%)
	University/college	1104 (23%)
	Graduate school	151 (3%)
Social support	0%	986 (20%)
	<50%	1315 (27%)

	50–100%	2060 (42%)
	100%	579 (12%)
Family support	0%	577 (12%)
	<50%	1136 (23%)
	50–100%	2402 (49%)
	100%	825 (17%)
Insurance	Medical protection (1 type)	706 (14%)
	Medical protection (2 types)	48 (1%)
	Health insurance, working poor	144 (3%)
	Health insurance, rare & incurable disease	922 (19%)
	Health insurance, general	3131 (63%)
Enrollment year	2008–2009	1514 (30%)
	2010	1371 (27%)
	2011	988 (20%)
	2012	646 (13%)
	2013	357 (7%)
	2014–2015	165 (3%)
Province level		
Population density		6857.1 ± 6792.9
Economically active population		3235.9 ± 2254.7
Number of medical institutions (per 1000)		0.53 ± 0.02

Figure 1. Distribution (grey dot) and smoothing trend (blue line) of mean PM_{10} (A), NO_2 (B), and SO_2 (C) concentration from 2001 to 2015 in Korea.

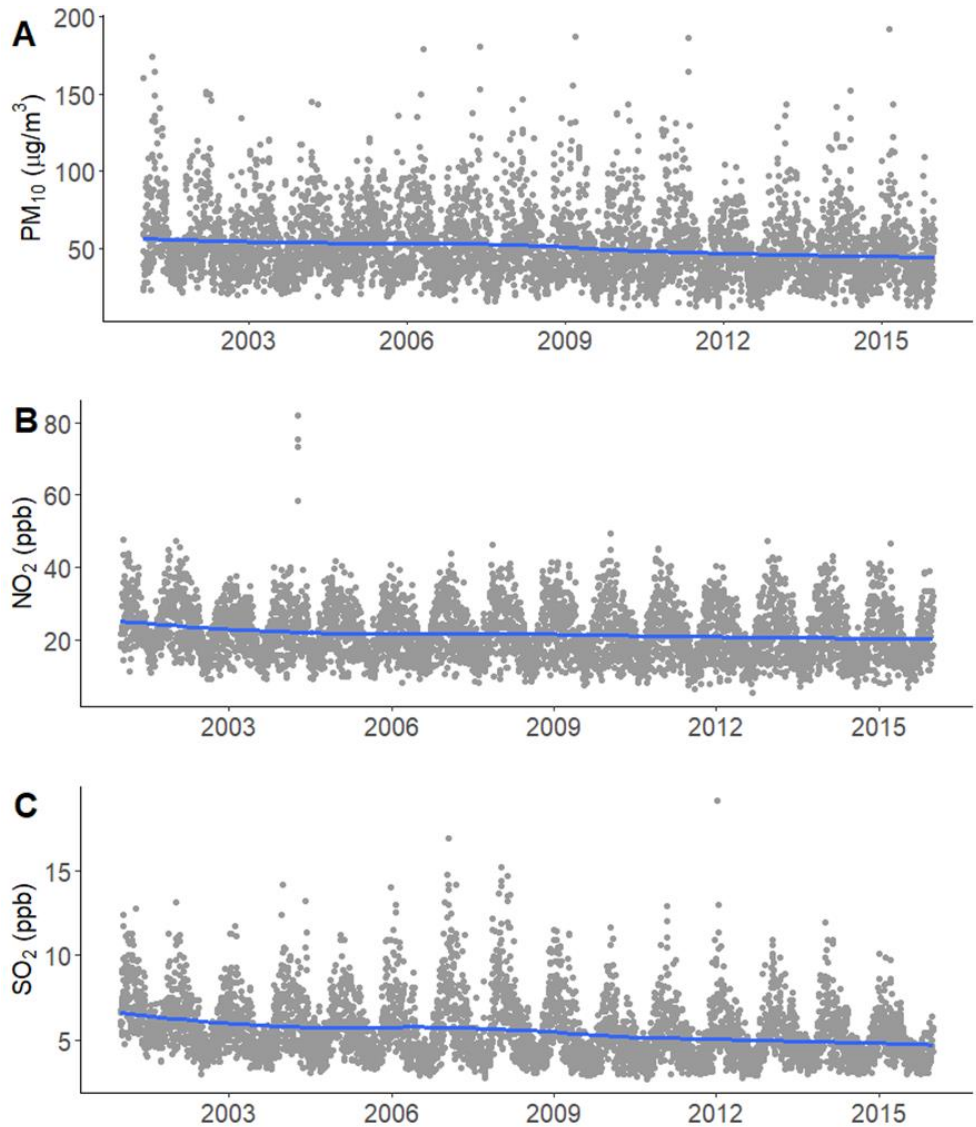


Table 2. Concentration of air pollutants from 1 year to 7 years ago on enrollment date of cohort participants

	Exposure years						
	1yr	2yr	3yr	4yr	5yr	6yr	7yr
PM_{10} ($\mu g/m^3$)							
IQR	7.54	6.65	7.6	6.91	6.92	7.23	8.14
Mean ± SD	50.38 ± 5.29	51.32 ± 4.95	52.33 ± 4.94	53.32 ± 4.96	54.05 ± 4.97	54.61 ± 5.02	55.22 ± 5.28
Min	33.81	35.69	38.43	40.01	41.01	40.83	41.71
25^{th}	46.63	47.99	48.89	50.32	50.5	50.92	51.26
50^{th}	50.54	51.33	52.19	53.04	53.51	54.15	55.11
75^{th}	54.18	54.64	56.49	57.22	57.42	58.15	59.41
Max	62.72	61.45	62.52	64.65	64.42	65.03	65.52
NO_2 (ppb)							
IQR	11.62	10.91	11.82	12.54	12.94	12.81	12.77
Mean ± SD	27.09 ± 6.66	27.5 ± 6.86	27.77 ± 6.98	27.85 ± 6.98	27.87 ± 6.93	28.03 ± 6.83	28.13 ± 6.89
Min	8.31	9.12	9.44	9.66	9.74	10.05	10.41
25^{th}	21.51	22.50	22.72	22.83	22.88	22.87	22.86
50^{th}	28.92	29.13	29.38	29.55	29.44	29.11	28.92
75^{th}	33.13	33.41	34.54	35.37	35.82	35.68	35.63
Max	36.90	37.61	37.48	37.02	36.62	36.05	36.78
SO_2 (ppb)							

IQR	0.50	0.68	0.81	0.67	0.53	0.39	0.38
Mean ± SD	5.21 ± 0.97	5.37 ± 0.98	5.5 ± 0.98	5.56 ± 0.94	5.6 ± 0.9	5.6 ± 0.88	5.6 ± 0.88
Min	2.09	2.20	2.33	2.44	2.49	2.51	2.62
25^{th}	4.93	5.02	5.11	5.21	5.38	5.51	5.49
50^{th}	5.27	5.33	5.52	5.68	5.70	5.60	5.52
75^{th}	5.43	5.70	5.92	5.88	5.91	5.90	5.87
Max	8.59	8.10	8.14	8.03	7.98	8.20	8.33

2.3.2. Association between Air Pollutants and Mortality of ESRD Patients in the CRC-ESRD Cohort

Figure 2 shows the association between mortality and the IQR increase in air pollutants. In the time-varying Cox model, the HRs per 7.54 μg/m3 increment in PM_{10} for one year (HR 1.10 CI 0.97–1.24), 6.65 μg/m^3 increment for two years (HR 1.09, CI 0.97–1.24), and 7.6 μg/m^3 increment for three years of exposure (HR 0.15, CI 0.99–1.34) were not statistically significant. However, long-term PM_{10} exposure, from four years to seven years, increased the mortality risk in ESRD patients from 15% to 33%. A similar risk for long-term exposure was estimated to NO_2 and SO_2. Seven years of exposure to NO_2 (HR 1.45, CI 1.09–1.94) further increased the HR compared with one year of exposure (HR 1.33, CI 1.05–1.69). SO_2 exposure was significantly associated with an increased mortality risk in ESRD patients when they were exposed to a 0.5-ppb increase for one year (HR 1.07, CI 1.03, 1.11) and a 0.38-ppb increase for seven years (HR 1.04, CI 1.01–1.07) before cohort enrollment. An exposure period of seven years for PM_{10} and NO_2 and one year for SO_2 was selected according to the AIC (Table 3). In addition, the association between mortality and air pollutants was investigated based on a natural spline with two degrees of freedom in a time-varying Cox model using seven-year exposure for PM_{10} and NO_2 and one-year exposure for SO_2. A significant linear association was confirmed (p-values for PM_{10} 0.0010, NO_2 0.0174, and SO_2 0.0003), although the effect of PM_{10} and NO_2 on mortality of ESRD patients showed a nonlinear tendency with decreased mortality at

high concentrations (Figure 3).

Figure 2. Hazard ratio and 95% confidence interval (CI) for end-stage renal disease (ESRD) mortality by duration of exposure to PM_{10} (A), NO_2 (B), and SO_2 (C) in a time-varying Cox model adjusted for sex, age, smoking status, hemoglobin, body mass index (BMI), Charlson comorbidity index (CCI), duration of therapy, working status, marital status, education, insurance, population density, and the number of medical institutions.

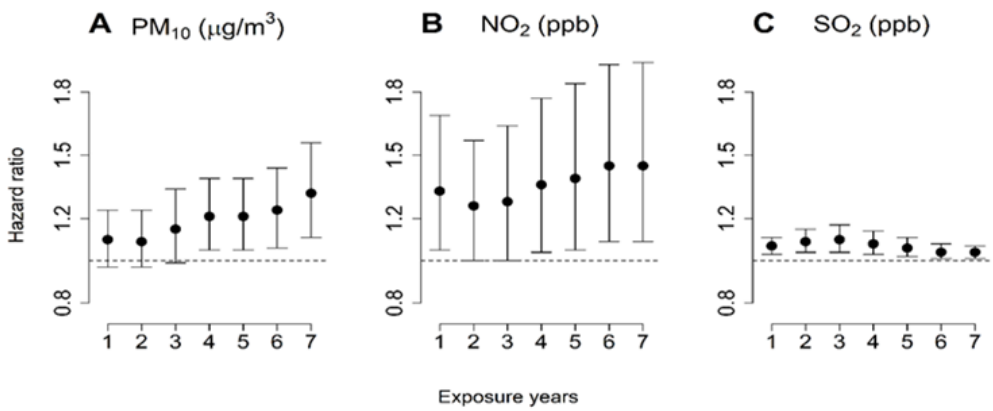
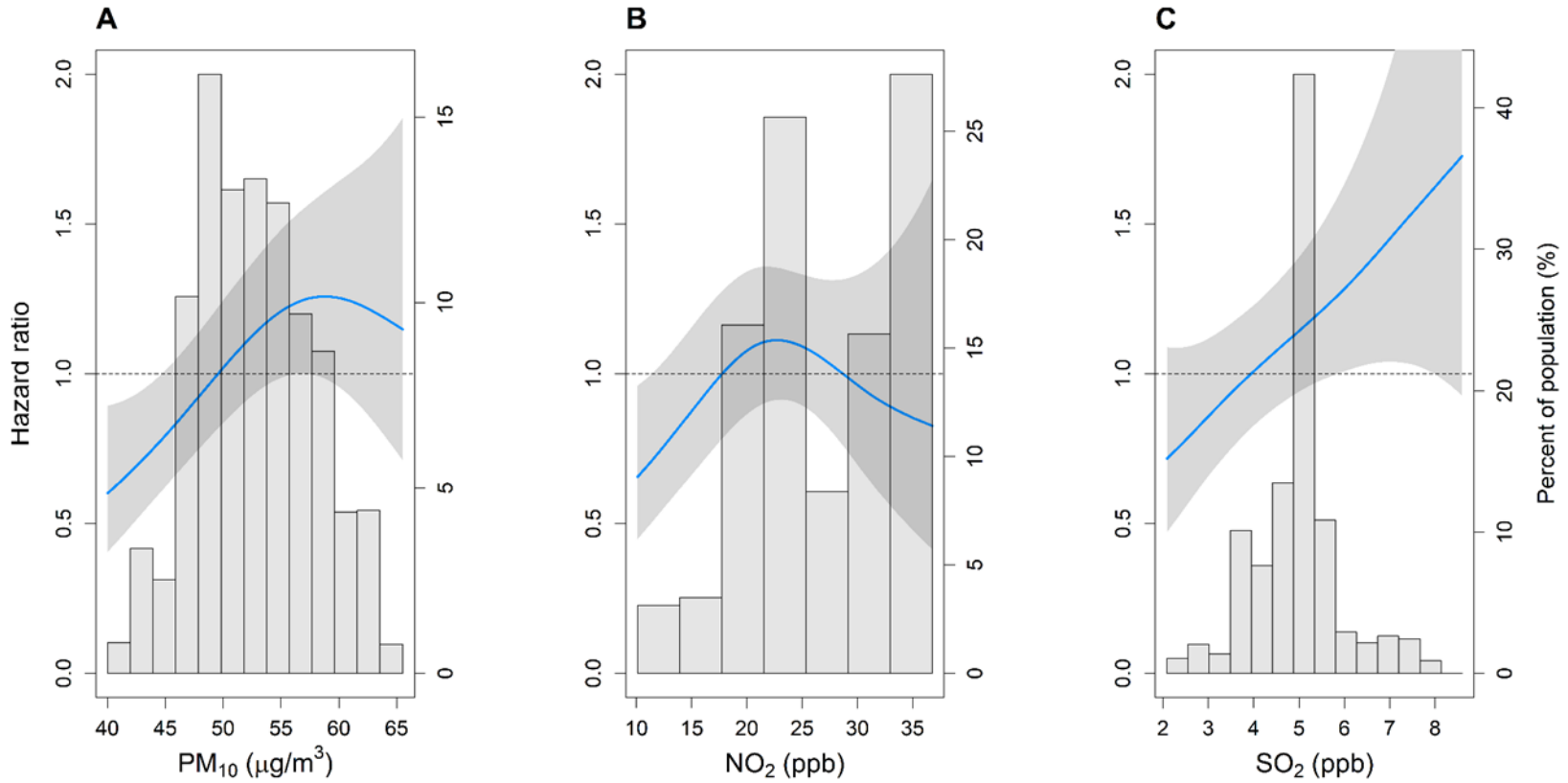


Table 3. Alkaike information criterion (AIC) of air pollutants by exposure years from 1-year to 7-year in time-varying model

	Exposure years						
	1yr	2yr	3yr	4yr	5yr	6yr	7yr
PM_{10} ($\mu g/m^3$)	18180	18180	18179	18175	18175	18175	18172
NO_2 (ppb)	18177	18178	18178	18177	18177	18176	18176
SO_2 (ppb)	18169	18171	18171	18173	18173	18174	18174

Figure 3. Concentration-mortality association (blue line) and 95% confidence interval (grey shadow) adjusted by natural spline with 2 degree of freedom in time-varying Cox model, with the percent distribution of population (histogram)



2.3.3. Stratified Analyses Considering Potential Confounders

Table 4 shows the HRs for IQR increases in average seven-year exposure to PM_{10} and NO_2 and one-year exposure to SO_2 in age-, sex-, family and social support-, and metropolitan-specific subgroups. Age had a significant effect on the association between air pollutants (PM_{10}: HR 1.34 (1.13, 1.59); NO_2: HR 1.52 (1.13–2.03); and SO_2: HR 1.07 (1.04–1.11)) and mortality in ESRD patients (p-value for interaction 0.02–0.03). The effect of PM_{10} (HR 1.48, CI 1.19–1.83) and SO_2 (HR 1.08, CI 1.03–1.14) on mortality was greater in females than males, but the differences were not significant (Pinteract = 0.09–0.43). However, males had a higher risk of mortality after NO_2 exposure than females (HR 1.49, CI 1.11–2.01). Increased risks were observed in those who received ≥50% social and family support, but the differences were not statistically significant, except for NO_2. In addition, the participants who lived in metropolitan areas had increased mortality risks associated with air pollution, but the differences were not significant, except for PM_{10}.

Table 4. The modification of association between interquartile range (IQR) increase of long-term exposure to air pollutants and mortality of end-stage renal disease (ESRD) patients by baseline characteristics among 5041 participants.

	PM_{10} ($\mu g/m^3$) [a]		NO_2 (ppb) [a]		SO_2 (ppb) [b]	
	HR (95% CI)	$P_{interact}$	HR (95% CI)	$P_{interact}$	HR (95% CI)	$P_{interact}$
Age						
<65	1.30 (1.10, 1.54)		1.37 (1.02, 1.84)		1.05 (1.01, 1.09)	
≥65	1.34 (1.13, 1.59)	0.03	1.52 (1.13, 2.03)	0.02	1.07 (1.04, 1.11)	0.02
Sex						
Female	1.48 (1.19, 1.83)		1.37 (0.99, 1.89)		1.08 (1.03, 1.14)	
Male	1.25 (1.04, 1.49)	0.09	1.49 (1.11, 2.01)	0.43	1.06 (1.02, 1.10)	0.39
Family support						
<50%	1.30 (1.10, 1.55)		1.42 (1.06, 1.90)		1.06 (1.02, 1.10)	
≥50%	1.32 (1.12, 1.56)	0.22	1.48 (1.11, 1.98)	0.13	1.07 (1.03, 1.11)	0.26
Social support						
<50%	1.30 (1.09, 1.54)		1.42 (1.06, 1.90)		1.06 (1.02, 1.10)	
≥50%	1.32 (1.11, 1.56)	0.08	1.51 (1.12, 2.02)	0.04	1.07 (1.03, 1.11)	0.12
Metropolitan						
No	1.27 (1.06, 1.52)		1.29 (0.78, 2.14)		1.04 (0.99, 1.09)	
Yes	1.33 (1.12, 1.59)	<0.01	1.37 (0.97, 1.95)	0.58	1.06 (1.02, 1.10)	0.12

[a] Seven-year average concentration before cohort enrollment; [b] one-year average concentration before cohort enrollment.

2.3.4. Sensitivity Analysis

Table 5 shows the hazard ratio of mortality for each air pollutant for each exposure period in the baseline Cox model. The years of exposure, from one to seven years, were separate exposure variables. Similar results in the time-varying Cox model were identified, suggesting a significant linear association between air pollutants and mortality, except for seven-year exposure to NO_2 and six-year exposure to SO_2. The highest mortality risks associated with PM_{10}, NO_2, and SO_2 were found for six years (HR 1.26, CI 1.07–1.47), seven years (HR 1.32, CI 1.00–1.75), and two years (HR 1.08, CI 1.03–1.13) of exposure, respectively. In addition, two-pollutant time-varying Cox models were constructed by including a second pollutant. Significant correlations were found between PM_{10} and SO_2 ($r = 0.65$), PM_{10} and NO_2 ($r = 0.56$), and SO_2 and NO_2 ($r = 0.74$) (Figure 4). SO_2 and NO_2 were not included in the two-pollutant model due to their high correlation. Robust associations were confirmed, although the statistical significance was not high in the two-pollutant model (Figure 5).

Table 5. Hazard ratio and 95% confidence interval of ESRD patients when exposed to air pollutants in baseline Cox model

	Exposure years						
	1yr	2yr	3yr	4yr	5yr	6yr	7yr
PM_{10} ($\mu g/m^3$)							
IQR increment	1.20 (1.06, 1.36)	1.17 (1.05, 1.31)	1.22 (1.06, 1.41)	1.21 (1.05, 1.40)	1.25 (1.08, 1.46)	1.26 (1.07, 1.47)	1.24 (1.06, 1.45)
Q2	1.26 (1.02, 1.55)	1.44 (1.16, 1.78)	1.57 (1.26, 1.96)	1.40 (1.13, 1.74)	1.11 (0.91, 1.35)	1.08 (0.89, 1.30)	1.09 (0.89, 1.32)
Q3	1.26 (1.01, 1.56)	1.09 (0.88, 1.35)	1.26 (0.99, 1.60)	1.20 (0.94, 1.54)	1.03 (0.77, 1.37)	1.06 (0.79, 1.43)	0.97 (0.76, 1.23)
Q4	1.58 (1.23, 2.03)	1.61 (1.25, 2.08)	1.62 (1.24, 2.14)	1.49 (1.13, 1.96)	1.48 (1.12, 1.95)	1.41 (1.06, 1.86)	1.47 (1.09, 1.97)
Trend p-value	<0.01	<0.01	<0.01	0.01	<0.01	<0.01	0.02
NO_2 (ppb)							
IQR increment	1.30 (1.02, 1.66)	1.24 (0.98, 1.57)	1.28 (0.99, 1.65)	1.31 (0.99, 1.75)	1.34 (0.99, 1.82)	1.28 (0.96, 1.70)	1.32 (1.00, 1.75)
Q2	0.99 (0.84, 1.17)	1.08 (0.91, 1.28)	1.07 (0.90, 1.26)	1.05 (0.89, 1.25)	1.00 (0.85, 1.19)	1.04 (0.88, 1.23)	1.05 (0.89, 1.25)
Q3	0.54 (0.35, 0.83)	0.46 (0.29, 0.73)	0.53 (0.34, 0.84)	0.48 (0.30, 0.77)	0.41 (0.23, 0.71)	0.40 (0.22, 0.71)	0.39 (0.21, 0.70)
Q4	0.47 (0.28, 0.78)	0.38 (0.22, 0.65)	0.43 (0.25, 0.74)	0.40 (0.23, 0.69)	0.34 (0.19, 0.62)	0.35 (0.19, 0.66)	0.33 (0.18, 0.63)
Trend p-value	0.03	0.05	0.06	0.03	0.02	0.06	0.15
SO_2 (ppb)							
IQR increment	1.06 (1.03, 1.10)	1.08 (1.03, 1.13)	1.08 (1.02, 1.14)	1.06 (1.01, 1.11)	1.04 (1.00, 1.08)	1.03 (1.00, 1.06)	1.03 (1.00, 1.06)
Q2	1.32 (1.09, 1.61)	0.95 (0.78, 1.16)	1.19 (0.96, 1.48)	1.20 (0.96, 1.49)	1.22 (0.97, 1.53)	1.35 (1.05, 1.75)	1.11 (0.85, 1.46)
Q3	1.39 (1.15, 1.68)	1.26 (1.04, 1.51)	1.23 (1.01, 1.50)	1.06 (0.86, 1.31)	1.21 (0.95, 1.54)	1.19 (0.97, 1.46)	1.24 (1.04, 1.49)
Q4	1.56 (1.28, 1.92)	1.27 (1.02, 1.57)	1.22 (0.98, 1.53)	1.37 (1.09, 1.73)	1.19 (0.97, 1.47)	1.17 (0.95, 1.44)	1.14 (0.92, 1.40)
Trend p-value	<0.01	0.02	0.04	0.06	0.06	0.10	0.05

Figure 4. Correlation between daily concentrations of air pollutants between 2001 and 2015

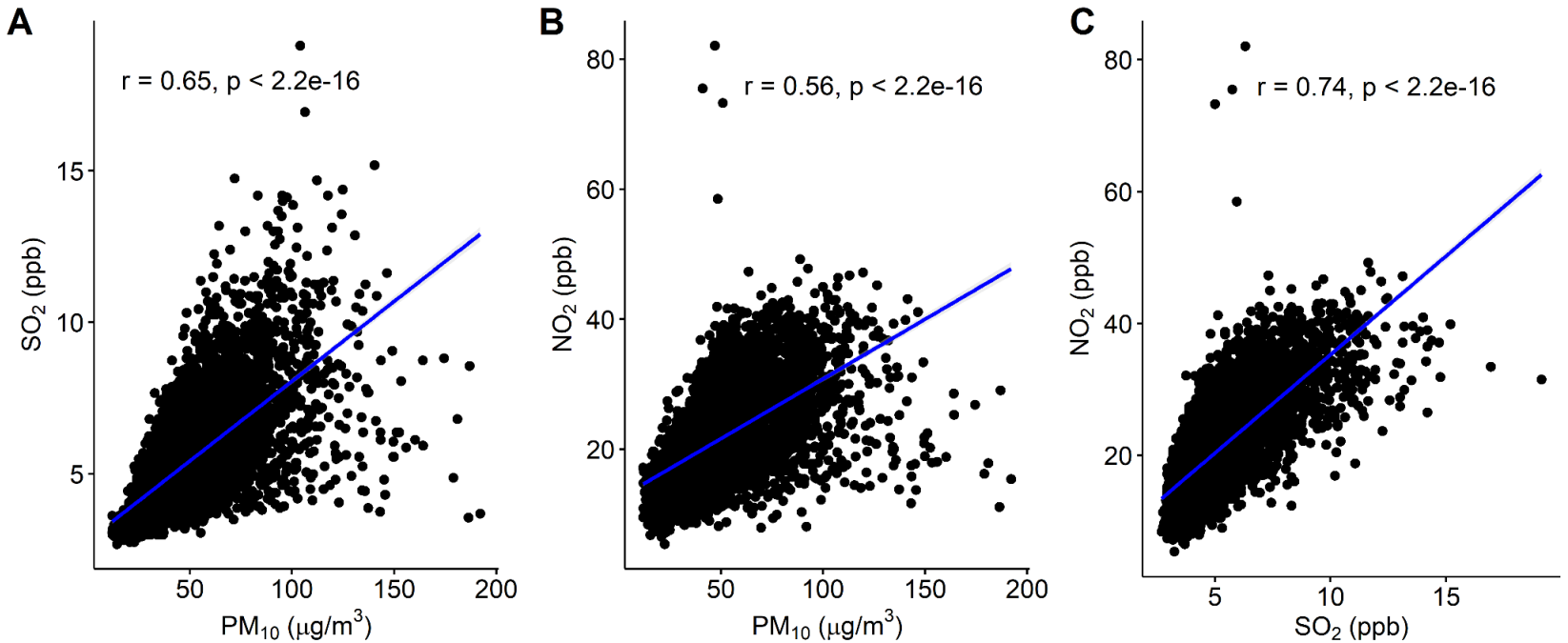
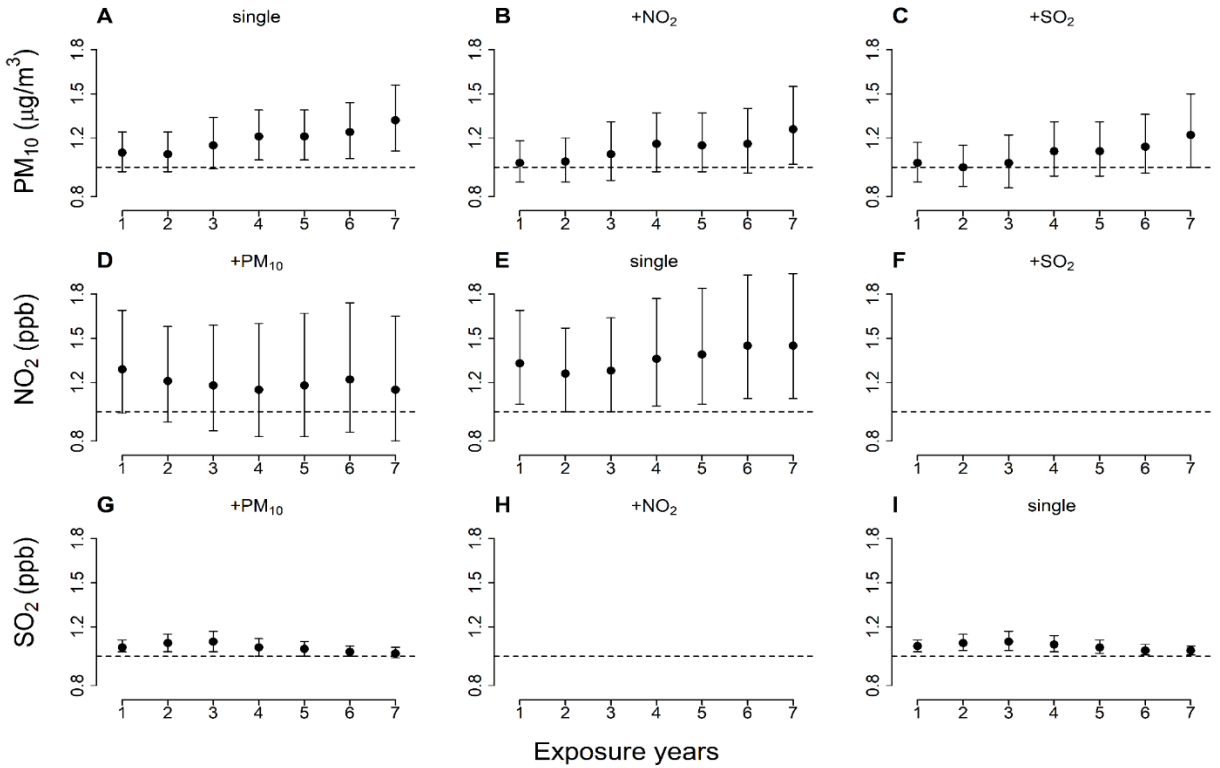


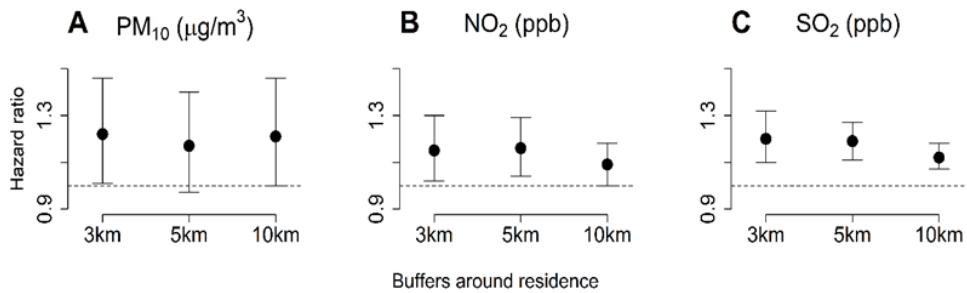
Figure 5. The association between mortality of ESRD patients and exposure to air pollutants in single- and two-pollutant models using time-varying (1yr-7yr) model



2.3.5. Association between Air Pollution and Mortality of ESRD Patients in the Validation Cohort

We analyzed the data of the ESRD cohort from the Seoul National University Hospital between 2008 and 2017. A total of 5910 patients with ESRD were enrolled, and 58.7% were male. During the follow-up period of a mean of 3.57 years, the mortality rate of the validation cohort was 29.6%. Exposure was determined by calculating the average concentration of air pollutants measured by the monitoring stations within the buffer regions of 3 km (n = 4627), 5 km (n = 5287), and 10 km (n = 5535). The HRs of PM_{10}, NO_2, and SO_2 measured at monitoring stations within 3 km of the residences of participants were 1.22 (1.01–1.46), 1.15 (1.02–1.30), and 1.20 (1.10–1.32), respectively, when the IQR unit was 8.13 μg/m^3 for PM_{10}, 4.73 ppb for NO_2, and 0.93 ppb for SO2 (Figure 6).

Figure 6. Hazard ratio and 95% CI per interquartile range (IQR) increase for air pollutants measured at monitoring stations within various buffer around the residence in validation cohort.



2.4. Discussion

In the present study, the long-term effects of air pollutants on the mortality of patients undergoing dialysis were evaluated using data obtained from a nationwide, multicenter, prospective cohort of ESRD patients. A linear association between air pollutants and mortality was found, although there was a decreased risk at high NO_2 concentrations, similar to other studies.[39,40] The results indicated that increased exposure to PM_{10} from one to seven years increased the mortality risk, and long-term exposure to SO_2 and NO_2 was a significant risk factor for ESRD morality regardless of the exposure period. The associations of these air pollutants remained robust in the baseline and two-pollutant models and were significant in the elderly patients.

Previously, epidemiological studies investigated the long-term effects of air pollutants on mortality. Hart, et al.[41] reported percent increases in all-cause mortality of 4.3%, 8.2%, and 6.9% for PM_{10} (6 $\mu g/m^3$), NO_2 (8 ppb), and SO_2 (4 ppb) in 53,814 men from U.S. trucking companies during 1985–2000. In addition, several studies confirmed the association between cause-specific morality and air pollutants.[42-44] Recently, a large population-based study demonstrated the effects of air pollutants on kidney disease. Kim, et al.[45] suggested that various air pollutants were related to the risk of kidney dysfunction in Korea. The researchers reported that a 10-$\mu g/m^3$ increase in PM_{10} and a 12-ppb increase in NO_2 were associated with decreases of 0.46 and 0.85, respectively, in estimated glomerular filtration rates (eGFRs). Although several studies have reported the relationship between air pollutant

exposure and the deterioration of renal function,[25-27,45] few studies have explored the direct relationship between air pollution and mortality in CKD patients.[28,30] A study that prospectively observed 256 elderly hemodialysis patients for two years reported that living in the Taipei Basin, which has relatively high levels of air pollutants, such as carbon monoxide, PM_{10}, and NO_2, is associated with protein-energy wasting and inflammation, as well as two-year mortality.[30] This study group further researched the impact of air pollution on the clinical outcomes of peritoneal dialysis (PD) patients.[28,29] They reported that high environmental $PM_{2.5}$ exposure was associated with an increased risk of one-year PD-related infection[29] and that high NO_2 exposure was associated with two-year mortality.[28] However, these studies enrolled a relatively small number of patients (maximum of 256 patients), and the observation periods were too short to evaluate the long-term effects of air pollution on clinical outcomes (maximum of two years).

Several hypotheses have been proposed to explain the biological effects of air pollutants on mortality. The mechanisms of inhaled particles causing renal function deterioration are similar to those proposed for CV diseases, such as inflammation and oxidative stress.[25,27,46] Evidence from laboratories has suggested that exposure to PM causes renal hemodynamic impairment and promotes oxidative stress, inflammation, and DNA damage in kidney tissue, which aggravates acute kidney injury and further progresses to chronic renal failure in murine models.[47,48] NO_2, mainly derived from the industrial burning of fuels and transportation, and SO_2 generated as industrial

byproducts have been associated with respiratory symptoms.[49,50] However, air pollutants might affect remote organs, such as the kidneys, through the bloodstream.[51,52]

In the subgroup analysis, elderly patients had significantly greater risks associated with various air pollutants than participants <65 years of age. These findings agree with previous evidence that older age groups are more vulnerable to air pollution than younger age groups.[53,54] In addition, the risks of sex-specific exposure differed by air pollutant, although the differences were not significant in our study. Several studies examining the relationship between air pollution and kidney disease have shown inconsistent sex-specific effects.[55,56] A distinct association between PM_{10} exposure and mortality was found in patients in metropolitan areas. These findings suggest that residence locations in rural or urban areas are potential confounders of the long-term effects of air pollutants.[57]

This study had several limitations. First, in some areas, the measurements of air pollutants might be inaccurate because the number of stations at the province level varied by region. The number of monitoring stations was sufficient to cover the entire area of the metropolitan cities with high population densities. However, there were only seven monitoring stations in large provinces, such as Gang-won, which has a relatively small population. In addition, there could be ambient air pollution measurement errors by the monitoring stations in time-series studies. Second, the unit of province-level exposure was larger than the unit of district-level exposure.

This study might suffer from exposure errors between ambient air pollution and actual exposure. Third, exposure values were assigned based on the addresses of hospitals because information on actual residence was not provided for the CRC-ESRD cohort. However, it could be assumed that there would be a similar degree of exposure because the distances between the actual residence of the patients and the dialysis centers were within the same daily life radius. To account for the province-level exposure unit of the dialysis hospital, we used detailed exposure values measured within various buffer diameters (3 km, 5 km, and 10 km), established by drawing circles around the actual residences of patients in the validation cohort, independent of the CRC-ESRD cohort. Long-term exposure to air pollutants was significantly associated with increased ESRD mortality regardless of the buffer size. Fourth, other socioeconomic status factors, such as income and occupation, acted as confounding factors on a small scale. Fifth, validation cohort was not entirely independent of the main cohort because one of the participating hospitals in the main cohort was SNUH. However, the two cohorts had some independent characteristics because of the different numbers of years tracked and the differences in participating hospitals. Sixth, it is impossible to estimate the hazard ratio separately for CV and non-CV disease because the number of fatalities caused by CV disease (n = 325) was not sufficient to estimate the coefficients. Last, $PM_{2.5}$ was not included in this study since it was measured nationwide from 2015. Although PM is simply a classification by particle size, most are less than 5 μm, and $PM_{2.5}$ is a subset

of PM_{10}, $PM_{2.5}$ pose the greatest risk to health. So, a follow-up study is warranted for the Seoul area, where $PM_{2.5}$ monitoring has been conducted since 2007.

2.5. Conclusion

Long-term exposure to air pollutants had negative effects on mortality in ESRD patients. These effects were prominent in elderly patients who lived in metropolitan areas, meaning that ambient air pollution, in addition to traditional risk factors, was important to the survival of these patients. Further biological studies are needed to confirm the specific pathophysiology of PM_{10} consisting of various organic and inorganic molecules, as well as NO_2 and SO_2.

Chapter 3. Effects of Indoor Environment: Association of Exposure to Phthalates and Environmental Phenolics with Markers of Kidney Function

3.1. Introduction

CKD is a disease in which kidney function gradually worsens due to various causes, and can lead to other serious health consequences. Individuals with CKD are expected to exhibit approximately 10-fold higher mortality risk due to cardiovascular diseases than those without the kidney dysfunction.[9-11] Due to growing socioeconomic and health burdens worldwide,[13] identifying risk factors for CKD is of great public health importance. Risk factors well-known for CKD include DM, hypertension, dyslipidemia, smoking, and obesity.[10,12] Although decades of efforts to control these traditional risk factors, however, the socioeconomic and health burdens from CKD has been increasing.[13] Recently, exposure to chemicals such as metals, and melamine has been suggested as among the potential risk factors for CKD.[58,59]

Increasing evidences support the involvement of the consumer chemicals such as phthalates and phenolic compounds in pathogenesis of CKD. Phthalates and phenolic compounds which are widely used in consumer chemicals, and hence have been frequently detected in humans worldwide.[60-62] In experimental studies, promotion of oxidative stress and proinflammatory responses has been suggested as mechanisms of action for

the pathogenesis of CKD by these consumer chemicals.[63-69] In human population, most association studies are limited to albuminuria, as measured as albumin to creatinine ratio (ACR) as a CKD outcome, and the observations are generally consistent. Among adult female population of Korea, urinary levels of monobutyl phthalate (MnBP) and benzophenone-1 were associated with increased ACR.[70] Bisphenol A (BPA) exposure caused an increase in low-grade albuminuria in healthy Chinese adults.[71] In a US children population, DEHP and BPA exposure were associated with elevated albuminuria.[72,73]

In contrast, the associations of consumer chemicals with estimated glomerular filtration rate (eGFR) generally did not support the observations with ACR. In adult population of US NHANES 2003-2006 (n=2573), high urinary BPA concentrations were associated with high eGFR.[74] In a children population with chronic kidney disease (n=538), urinary levels of low molecular weight phthalate metabolites were in a positive association with eGFR, while urinary BPA did not show any associations.[75] The reason for the opposite direction of association for eGFR could be found from chance of a reverse causation, as reduced GFR may decrease the urinary excretion of chemicals and therefore urinary chemical concentrations could underestimate the exposure level.[74] In addition, use of urine creatinine for adjusting urinary dilution may cause a collider problem in the association model for eGFR.[76,77]

In the present study, a subset of a nationally representative adult population participating in Korean National Environmental Health Survey

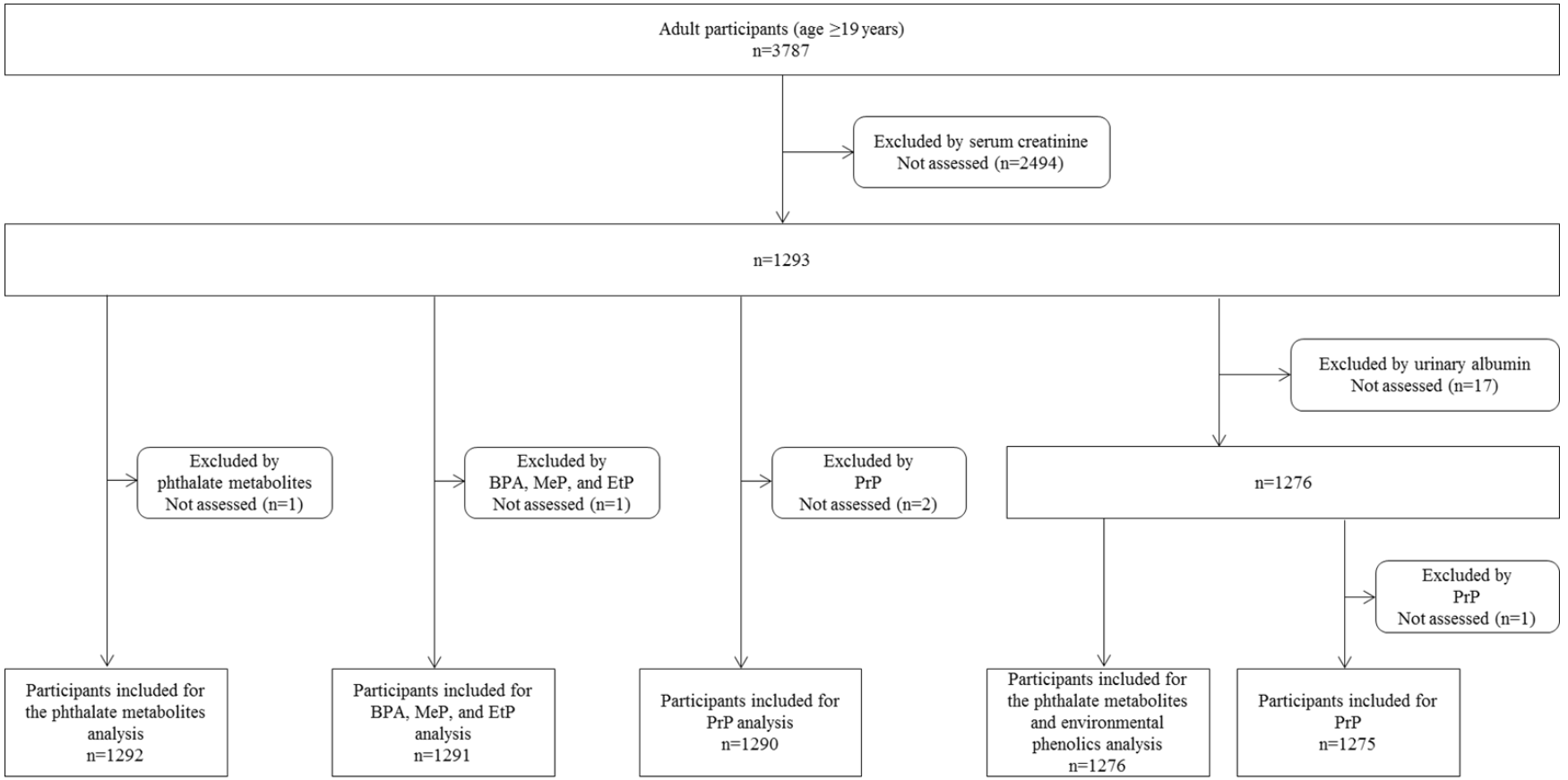
(KoNEHS) 2015-2017 was employed, and association of major phthalates and phenolic compounds with both eGRF and albuminuria was assessed. By employing a novel adjustment method for urinary dilution, this study intended to circumvent collider problem typically involved in the association study for a renal outcome. The present study will provide better understanding on the association of exposure to phthalates and phenolic compounds with markers of kidney function among the Korean adult population.

3.2. Methods

3.2.1. Study Population

KoNEHS is a nationally representative population-based cross-sectional study, which has begun since 2009 to assess current levels of environmental chemicals, demographic and behavioral factors, and several clinical markers of general Korean population.[78] In KoNEHS 2015-2017, adults (n=3787) were recruited throughout the country by two-stage proportionally stratified sampling design, based on sex, age, and geographical characteristics. A subset of adult population was randomly chosen after stratification by sex and age, and were measured for urinary albumin and serum creatinine. In restricting the study population to adults with information on urinary albumin and serum creatinine along with the urinary chemical measurement, initial sample size was reduced to 1292 (Figure 7).

Figure 7. Flow diagram showing final number of the study population for each analysis of association.



3.2.2. Measurement of Urinary Chemicals

On collection, spot urine samples were moved to the laboratory under cooling condition, and were stored at -20°C before analysis. Details of analytical procedures for phthalate metabolites and environmental phenolics in urine were described previously.[79] Briefly, target chemicals were measured by ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) equipped with eletrospray ionization (ESI). Quality control procedures for all analytes followed National Institute of Environmental Research of Korea protocol.[79]

Method detection limits (MDLs) for di-(2-ethylhexyl) phthalate (DEHP) metabolites, i.e., mono-(2-ethyl-5-oxohexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEHOP), and mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), a di-n-butyl phthalate (DBP) metabolite, i.e., mono-n-butyl phthalate (MnBP), a benzylbutyl phthalate (BzBP) metabolite, i.e., mono-benzyl phthalate (MBzP), a di-isononyl phthalate (DiNP) metabolite, i.e., mono-carboxy octyl phthalate (MCOP), a di-isodecyl phthalate (DiDP) metabolite, i.e., mono-carboxy nonyl phthalate (MCNP), a non-specific metabolite for di-n-octyl phthalate (DOP), di-n-butyl phthalate (DBP), and other high molecular weight phthalates, i.e., mono (3-carboxypropyl) phthalate (MCPP), bisphenol A (BPA), methyl paraben (MeP), and ethyl paraben (EtP) were 0.056, 0.048, 0.141, 0.04, 0.066, 0.048, 0.139, 0.078, 0.075, 0.108, and 0.107 μg/L, respectively.

3.2.3. Markers of Kidney Function

Urinary and serum creatinine were measured using Jaffe reaction method. Urinary creatinine was analyzed by the ADVIA 1800 Auto Analyzer (Siemens Medical Solutions Diagnotics, USA). Serum creatinine was measured by Hitachi Modular-DP analyzer (Roche Diagnostics, Switzerland). Urinary albumin was measured using Tina-quant albumin Gen.2 (Roche, Switzerland). The eGFR was derived from serum creatinine by using following equation:

$$eGFR_{CKD\text{-}EPI}\ (mL/min/m^2) = 141 \times \min(\frac{S_{cr}}{\kappa}, 1)^{\alpha} \times \max(\frac{S_{cr}}{\kappa}, 1)^{-1.209} \times 0.993^{Age} \times 1.018\ [\text{if female}]$$

Scr is serum creatinine (mg/dL). κ is 0.7 for females and 0.9 for males. α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

Participants with ACR >30 mg/g or eGFR <60 mL/min/1.73 m^2 were categorized as CKD patients.[80]

3.2.4. Adjustment of Urinary Dilution

For the adjustment for urinary dilution, urinary chemical concentrations were corrected by creatinine, i.e., chemical concentration in urine (μg/L) divided by urinary creatinine concentration (g/L). In addition, a covariate-adjusted standardization was used following approaches outlined previously.[76,77] For covariate-adjusted standardization, a model for the ln-

transformed creatinine was fitted with covariates and eGFR, which can predict urinary creatinine.[76] Ln-transformed urinary creatinine was regressed on the significant variables among the total study population, and then exponentiated. To derive predicted urinary creatinine level for each subject, age, sex, BMI, and eGFR were used (n=1292, Table 6). Then, the ratio between the measured creatinine level and the predicted creatinine level was obtained for each participant, and the urinary levels of each chemical were divided by the ratio to adjust urinary dilution.[77]

Table 6. Results of linear regression model for predicting ln-transformed urinary creatinine concentration (g/L) (n=1292).

	β (95% CI)	**p-value**
Intercept	1.316 (0.781, 1.850)	<0.001
eGFR (mL/min/1.73 m^2, continuous)	-0.007 (-0.010, -0.004)	<0.001
Age (year, continuous)	-0.013 (-0.019, -0.009)	<0.001
Sex (male: 1, female:2)	-0.298 (-0.374, -0.223)	<0.001
BMI (kg/m^2, continuous)	0.013 (0.002, 0.023)	0.017

3.2.5. Statistical Analysis

For examining the relationship between urinary chemicals, the Spearman's correlation between urinary chemicals was assessed and visualized using R package 'corrplot'. Only chemicals detected in > 80% of samples were included for statistical analysis. For these chemicals, non-detects were substituted with method detection limit (MDL) divided by $\sqrt{2}$. Due to right skewness, chemical concentrations and ACR were natural log (ln)-transformed. Linear regression models were used to assess association between urinary chemicals and markers of kidney function. The covariates that were adjusted in the statistical models were chosen based on previous studies which reported associations of urinary chemicals with markers for kidney function or risk factors for CKD.[70,10,81,12,82] These covariates included age (years), sex (male and female), BMI (kg/m^2), cigarette smoking (never smoker, former smoker, and current smoker), alcohol drinking (never drinker and drinker), monthly household income (<840; 840-1,680; 1,680-2,520; 2,520-4,200; 4,200-5,880; ≥5,880 US dollars; unknown income), and medication for diabetes mellitus (no and yes), and hypertension (no and yes).

As secondary analyses, participants were stratified based on CKD status to further explore CKD modification, because markers of kidney function have been reported to be related to urinary excretion of chemicals.[83,84] In addition, a principal component analysis (PCA) with varimax rotation was used to reduce number of variables and to identify the principal components. For PCA, ln-transformed urinary chemicals were included in the analytical

model following covariate-adjusted standardization. Factors which accounted for >70% of the total variance were retained,[85] and were fitted with a linear regression model. Both single-factor model with each factor included in each adjusted model, and multiple-factor model with factors mutually adjusted in the same adjusted model were developed.

The differences in markers of kidney function by potential covariates were tested using t-test or one-way analysis of variance, and all the chosen covariates showed statistical significance ($p<0.05$) with ACR or eGFR. All analyses except Spearman's correlation analysis were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

3.3. Results

3.3.1. Characteristics of Study Population and Markers of Kidney Function

Demographic and lifestyle characteristics of study participants are summarized in Table 1. For phthalate metabolites, 1276 and 1292 participants were included in association analyses with ACR and eGFR, respectively. For environmental phenolics, 1275 and 1291 (except for PrP (n=1290)) participants were included in association analyses with ACR and eGFR, respectively (Figure 1). Compared to females, males showed lower ACR and eGFR. In older population, ACR tended to increase, and eGFR, decrease. Higher BMI was correlated with higher ACR and lower eGFR (Table 7).

Table 7. Demographic and lifestyle characteristics of the study participants, and observed ACR and eGFR

	N	ACR (mg/g)	*p*-value	N	eGFR (mL/min/1.73 m^2)	*p*-value
Total	1276	4.6 (2.1, 9.2)	-	1292	102.9 (92.2, 114.4)	-
Sex						
Male	632	3.8 (1.6, 7.8)	<0.001	638	100.8 (90.7, 111.7)	<0.001
Female	644	5.4 (2.6, 10.6)		654	105.5 (93.3, 116.9)	
Age[a]						
19-29	184	3.6 (1.7, 6.1)	<0.001	186	124.0 (114.7, 130.1)	<0.001
30-39	272	3.7 (1.8, 6.7)		275	114.1 (106.2, 119.0)	
40-49	265	4.9 (2.7, 8.3)		266	107.1 (100.6, 111.9)	
50-59	247	5.6 (2.1, 11.5)		251	99.4 (92.6, 103.2)	
60-69	201	5.1 (1.8, 11.9)		205	91.0 (82.2, 95.5)	
≥70	107	7.4 (3.4, 14.4)		109	84.8 (72.0, 90.0)	
BMI (kg/m^2)[b]						
<18.5	37	4.4 (2.4, 8.1)	0.036	37	115.6 (105.6, 124.6)	<0.001
18.5-22.9	450	4.3 (2.0, 8.0)		456	107.8 (95.0, 118.7)	
23-25	323	4.6 (2.1, 9.0)		326	102.4 (92.4, 111.8)	
25-30	386	4.7 (2.2, 11.7)		392	98.2 (89.4, 109.6)	
≥30	80	5.8 (2.6, 10.9)		81	102.9 (93.3, 113.2)	
Smoking status						
Never smoker	779	5.1 (2.5, 10.5)	0.003	793	104.3 (92.9, 116.4)	<0.001
Former smoker	238	3.7 (1.5, 8.1)		239	95.6 (87.7, 106.2)	
Current smoker	259	3.8 (1.7, 6.7)		260	106.3 (95.3, 115.0)	
Drinking status						
Never drinker	206	5.6 (2.2, 11.6)	0.214	210	97.7 (87.4, 107.8)	<0.001
Drinker	1070	4.4 (2.1, 8.6)		1082	104.5 (93.3, 115.4)	
Monthly household income (US$)						
<840	149	6.6 (3.2, 15.4)	0.001	151	90.4 (82.4, 98.0)	<0.001
840-1680	209	5.0 (2.3, 9.8)		209	100.6 (89.5, 113.8)	
1680-2520	271	4.6 (2.1, 8.6)		275	105.5 (94.3, 116.7)	
2520-4200	389	4.4 (2.2, 8.4)		396	106.0 (94.5, 115.4)	
4200-5880	165	4.1 (1.8, 8.3)		165	106.7 (97.9, 116.4)	
≥5880	86	3.2 (1.1, 6.8)		88	103.7 (96.6, 114.8)	
Unknown	7	2.1 (1.9, 13.0)		8	107.0 (89.9, 113.6)	
Hypertension[c]						
No	1083	4.3 (2.0, 8.2)	<0.001	1095	106.1 (94.6, 116.3)	<0.001
Yes	193	8.0 (3.1, 14.8)		197	90.7 (78.8, 98.7)	
Diabetes[c]						
No	1192	4.4 (2.0, 8.6)	<0.001	1204	103.8 (93.0, 115.3)	<0.001

Yes	84	10.3 (4.0, 35.1)	88	89.3 (74.0, 99.2)

[a]47.0±15.3 (mean±SD) years old.
[b]24.3±3.5 (mean±SD) kg/m^2.
[c]Hypertension and diabetes status were defined by self-reported use of hypertension medication and diabetes medication, respectively.

3.3.2. Urinary chemicals and associations with markers of kidney function

Among the measured chemicals in urine, all eight phthalate metabolites and four phenolic compounds were detected in >90% samples (Table 8). Similar associations between urinary chemicals were observed regardless of adjustment of urine dilution, i.e., those without adjustment of dilution, with traditional creatinine correction, and with covariate-adjusted standardization (Figure 8). Among measured chemicals, phthalate metabolites showed moderate to high correlations. In contrast, MeP and EtP showed weak correlation with phthalate metabolites.

Following creatinine correction for urinary dilution, urinary DEHP metabolites, i.e., MEOHP, MECPP, and ΣDEHPm, showed significant positive associations with ACR. In contrast, MnBP showed a significant negative association with ACR (Table 9). When stratified by sex, similar direction of associations was observed in adult male population. With ACR, MECPP and ΣDEHPm showed positive associations, and MnBP showed a negative association.

The covariate-adjusted standardization method resulted in generally similar patterns of association with ACR, except for MCOP and MCNP in female adults (Table 9). DEHP metabolites and MnBP showed the same directions of association with ACR, in both total and male populations. Following the covariate-adjusted standardization, MCOP and MCNP showed

significant positive associations with ACR, in female population only, but the estimates were similar with those obtained following creatinine correction.

For eGFR, following the creatinine-correction for urinary dilution, several phthalate metabolites in urine including MEHHP, MECPP, ΣDEHPm MBzP, MCOP, MCNP, and MCPP showed significant positive associations (Table 10). Similar pattern of positive associations was also observed in both male and female populations. However, following the covariate-adjusted standardization method, most positive associations disappeared. Instead, MnBP, BPA, and EtP in urine showed significant negative associations with eGFR in total population. The only exception was MECPP in female population, which showed a significant positive association.

When stratified by CKD status, effect estimates were generally greater among CKD patients, compared with non-CKD participants, while more chemicals were identified to be significant among the non-CKD subjects (Tables 11 and 12).

Table 8. Detection frequencies and distribution of phthalate metabolites and environmental phenolics in the study population (ng/mL).

			Total		Male		Female	
		DF (%)[a]	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)
Parent compounds of phthalate metabolites								
DEHP	**MEHHP**	99.8	1292	14.07 (6.89, 27.29)	638	14.18 (7.16, 26.11)	654	13.90 (6.44, 28.62)
	MEOHP	99.7	1292	10.70 (5.03, 21.37)	638	10.36 (5.09, 20.25)	654	11.17 (4.92, 22.93)
	MECPP	100	1292	21.68 (11.80, 44.88)	638	21.15 (12.48, 43.98)	654	22.07 (11.05, 46.20)
	ΣDEHPm[b]	-	1292	48.43 (26.18, 92.29)	638	46.47 (27.41, 88.93)	654	49.74 (24.39, 95.41)
DBP	**MnBP**	98.9	1292	26.44 (13.04, 54.21)	638	27.34 (13.36, 56.38)	654	26.11 (12.70, 52.99)
BBZP	**MBzP**	98.1	1292	2.00 (0.92, 4.39)	638	2.21 (1.03, 4.82)	654	1.81 (0.88, 4.04)
DiNP	**MCOP**	99.5	1292	1.04 (0.57, 1.94)	638	1.03 (0.59, 1.98)	654	1.05 (0.55, 1.91)
DiDP	**MCNP**	91.1	1292	0.50 (0.23, 0.77)	638	0.51 (0.23, 0.76)	654	0.48 (0.24, 0.77)
A non-specific metabolite for DOP and DBP, and other HMW phthalate metabolites	**MCPP**	99.6	1292	1.02 (0.68, 1.82)	638	0.99 (0.67, 1.88)	654	1.04 (0.69, 1.81)
Environmental phenolics								
	BPA	98.8	1291	1.31 (0.51, 2.72)	638	1.50 (0.56, 3.12)	653	1.15 (0.47, 2.42)
	MeP	99.9	1291	37.99 (9.50, 138.63)	638	23.83 (7.47, 111.88)	653	53.36 (15.39, 164.19)
	EtP	99.0	1291	36.20 (8.48, 142.70)	638	39.64 (9.85, 142.26)	653	34.12 (7.41, 145.59)
	PrP	95.7	1290	2.69 (0.53, 23.08)	638	1.40 (0.37, 11.55)	652	5.22 (0.83, 41.27)

[a]Total population; [b]Sum of DEHP metabolites

Figure 8. Pairwise Spearman correlation coefficients of urinary concentrations of phthalate metabolites (n=1292) and environmental phenolics (n=1291, except for PrP (n=1290)).

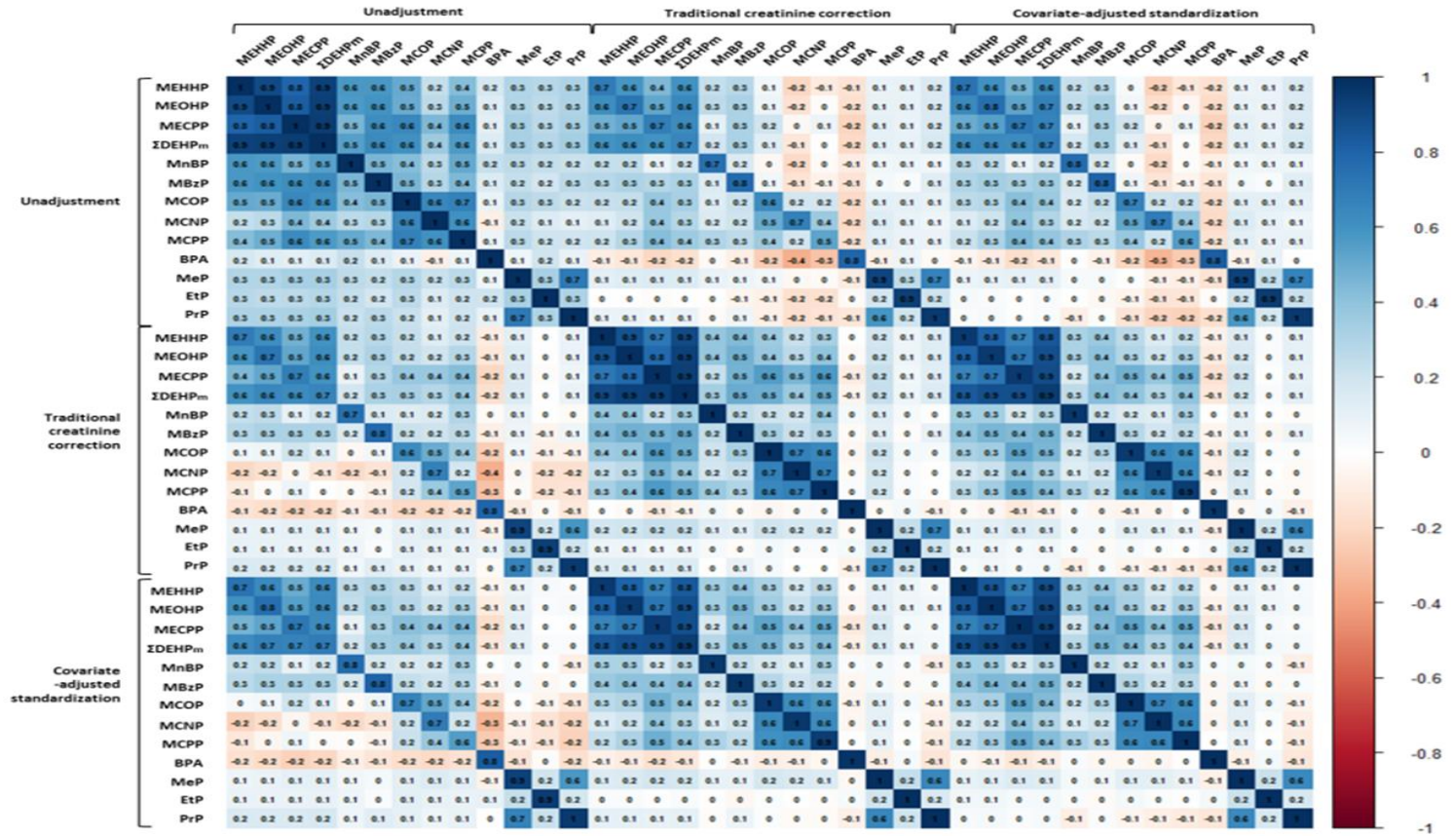


Table 9. Associations of urinary phthalate metabolites and environmental phenolics with ACR.

	Total[a] (n=1276)		Male[b] (n=632)		Female[b] (n=644)	
	β (95% CI)	**p-value**	**β (95% CI)**	**p-value**	**β (95% CI)**	**p-value**
Traditional creatinine correction						
MEHHP	0.09 (0.00, 0.18)	0.050	0.11 (-0.03, 0.25)	0.125	0.08 (-0.04, 0.21)	0.170
MEOHP	**0.09 (0.00, 0.17)**	**0.048**	0.10 (-0.03, 0.23)	0.129	0.07 (-0.04, 0.19)	0.196
MECPP	**0.12 (0.02, 0.22)**	**0.017**	**0.20 (0.05, 0.35)**	**0.011**	0.05 (-0.08, 0.17)	0.438
ΣDEHPm	**0.13 (0.02, 0.23)**	**0.018**	**0.20 (0.03, 0.36)**	**0.020**	0.07 (-0.07, 0.20)	0.318
MnBP	**-0.07 (-0.14, -0.01)**	**0.028**	**-0.11 (-0.21, -0.01)**	**0.037**	-0.03 (-0.12, 0.05)	0.451
MBzP	-0.03 (-0.10, 0.04)	0.385	0.01 (-0.10, 0.12)	0.846	-0.06 (-0.16, 0.03)	0.177
MCOP	0.08 (-0.01, 0.18)	0.085	0.04 (-0.11, 0.18)	0.626	0.12 (0.00, 0.24)	0.056
MCNP	0.05 (-0.03, 0.14)	0.214	-0.01 (-0.13, 0.12)	0.888	0.10 (0.00, 0.21)	0.061
MCPP	-0.02 (-0.12, 0.08)	0.656	-0.11 (-0.26, 0.04)	0.147	0.06 (-0.08, 0.19)	0.402
BPA	0.00 (-0.07, 0.07)	0.991	-0.04 (-0.14, 0.06)	0.428	0.04 (-0.05, 0.12)	0.426
MeP	-0.02 (-0.07, 0.03)	0.378	-0.03 (-0.10, 0.04)	0.433	-0.01 (-0.08, 0.06)	0.769
EtP	-0.02 (-0.06, 0.02)	0.316	-0.01 (-0.08, 0.05)	0.701	-0.03 (-0.08, 0.02)	0.280
PrP	0.01 (-0.03, 0.04)[c]	0.614	0.03 (-0.03, 0.08)	0.321	-0.01 (-0.05, 0.04)[d]	0.746
Covariate-adjusted standardization						
MEHHP	**0.10 (0.01, 0.19)**	**0.034**	0.11 (-0.03, 0.25)	0.124	0.10 (-0.02, 0.22)	0.105
MEOHP	**0.09 (0.01, 0.18)**	**0.035**	0.10 (-0.03, 0.23)	0.128	0.09 (-0.03, 0.20)	0.129
MECPP	**0.13 (0.03, 0.23)**	**0.010**	**0.20 (0.05, 0.35)**	**0.011**	0.07 (-0.06, 0.19)	0.297

ΣDEHPm	**0.14 (0.03, 0.24)**	**0.011**	**0.20 (0.03, 0.36)**	**0.019**	0.09 (-0.05, 0.22)	0.200
MnBP	**-0.07 (-0.13, 0.00)**	**0.037**	**-0.11 (-0.21, -0.01)**	**0.038**	-0.03 (-0.11, 0.06)	0.560
MBzP	-0.03 (-0.10, 0.04)	0.450	0.01 (-0.10, 0.12)	0.846	-0.06 (-0.15, 0.04)	0.240
MCOP	0.09 (0.00, 0.19)	0.058	0.04 (-0.11, 0.18)	0.624	**0.14 (0.01, 0.26)**	**0.029**
MCNP	0.06 (-0.02, 0.14)	0.165	-0.01 (-0.13, 0.12)	0.888	**0.12 (0.01, 0.23)**	**0.035**
MCPP	-0.01 (-0.12, 0.09)	0.777	-0.11 (-0.26, 0.04)	0.145	0.07 (-0.06, 0.21)	0.268
BPA	0.00 (-0.06, 0.07)	0.922	-0.04 (-0.14, 0.06)	0.428	0.04 (-0.04, 0.13)	0.334
MeP	-0.02 (-0.07, 0.03)	0.425	-0.03 (-0.10, 0.04)	0.428	-0.01 (-0.07, 0.06)	0.877
EtP	-0.02 (-0.06, 0.02)	0.351	-0.01 (-0.08, 0.05)	0.702	-0.03 (-0.08, 0.03)	0.331
PrP	0.01 (-0.03, 0.05) [c]	0.576	0.03 (-0.03, 0.08)	0.320	-0.01 (-0.05, 0.04)[d]	0.815

Bold numbers indicate $p<0.05$.

Concentrations of all urinary chemicals (both traditional and covariate-adjusted standardization) and ACR were ln-transformed.

[a]Adjusted for age, sex, BMI, smoking status, drinking status, monthly household income, hypertension, and diabetes mellitus.

[b]Adjusted for age, BMI, smoking status, drinking status, monthly household income, hypertension, and diabetes mellitus.

[c]n=1275.

[d]n=643.

Table 10. Associations of urinary phthalate metabolites and environmental phenolics with eGFR.

	Total[a] (n=1292)		**Male[b] (n=638)**		**Female[b] (n=654)**	
	β (95% CI)	**p-value**	**β (95% CI)**	**p-value**	**β (95% CI)**	**p-value**
Traditional creatinine correction						
MEHHP	**1.09 (0.34, 1.83)**	**0.004**	**1.46 (0.31, 2.62)**	**0.013**	0.94 (-0.01, 1.90)	0.052
MEOHP	0.55 (-0.13, 1.24)	0.114	0.83 (-0.22, 1.89)	0.121	0.42 (-0.46, 1.30)	0.348
MECPP	**2.09 (1.30, 2.87)**	**<0.001**	**1.91 (0.65, 3.17)**	**0.003**	**2.37 (1.40, 3.33)**	**<0.001**
ΣDEHPm	**1.76 (0.91, 2.61)**	**<0.001**	**1.97 (0.60, 3.33)**	**0.005**	**1.77 (0.72, 2.82)**	**0.001**
MnBP	-0.21 (-0.74, 0.33)	0.448	-0.53 (-1.37, 0.31)	0.214	0.17 (-0.50, 0.84)	0.622
MBzP	**1.08 (0.50, 1.66)**	**<0.001**	0.87 (-0.04, 1.79)	0.062	**1.32 (0.59, 2.04)**	**<0.001**
MCOP	**1.85 (1.08, 2.62)**	**<0.001**	**1.80 (0.61, 2.99)**	**0.003**	**1.93 (0.96, 2.90)**	**<0.001**
MCNP	**1.54 (0.87, 2.21)**	**<0.001**	**1.35 (0.32, 2.38)**	**0.011**	**1.73 (0.88, 2.58)**	**<0.001**
MCPP	**1.54 (0.72, 2.35)**	**<0.001**	**1.47 (0.21, 2.72)**	**0.022**	**1.67 (0.64, 2.71)**	**0.002**
BPA	-0.02 (-0.56, 0.52)[c]	0.945	0.39 (-0.45, 1.23)	0.363	-0.44 (-1.13, 0.25)[d]	0.208
MeP	0.10 (-0.31, 0.51)[c]	0.634	0.21 (-0.39, 0.81)	0.498	0.06 (-0.49, 0.61)[d]	0.837
EtP	-0.25 (-0.58, 0.09)[c]	0.153	-0.44 (-0.98, 0.09)	0.102	0.01 (-0.42, 0.43)[d]	0.973
PrP	0.16 (-0.12, 0.45)[e]	0.258	0.39 (-0.04, 0.82)	0.076	-0.03 (-0.40, 0.34)[f]	0.863
Covariate-adjusted standardization						
MEHHP	-0.24 (-0.99, 0.51)	0.533	-0.09 (-1.26, 1.07)	0.875	-0.15 (-1.10, 0.81)	0.765
MEOHP	-0.57 (-1.25, 0.12)	0.106	-0.47 (-1.53, 0.59)	0.387	-0.50 (-1.38, 0.38)	0.262
MECPP	0.60 (-0.20, 1.40)	0.142	0.04 (-1.24, 1.32)	0.949	**1.24 (0.25, 2.23)**	**0.014**
ΣDEHPm	0.02 (-0.85, 0.88)	0.969	-0.22 (-1.60, 1.16)	0.754	0.43 (-0.64, 1.50)	0.427

MnBP	**-0.88 (-1.41, -0.35)**	**0.001**	**-1.33 (-2.16, -0.50)**	**0.002**	-0.37 (-1.04, 0.30)	0.281
MBzP	0.28 (-0.31, 0.86)	0.357	-0.11 (-1.03, 0.81)	0.818	0.69 (-0.04, 1.43)	0.065
MCOP	0.43 (-0.35, 1.21)	0.276	0.13 (-1.08, 1.34)	0.830	0.79 (-0.20, 1.78)	0.117
MCNP	0.47 (-0.21, 1.15)	0.175	0.10 (-0.94, 1.14)	0.848	0.86 (-0.01, 1.73)	0.053
MCPP	-0.04 (-0.86, 0.78)	0.916	-0.38 (-1.65, 0.88)	0.552	0.39 (-0.66, 1.44)	0.463
BPA	**-0.71 (-1.25, -0.17)**[c]	**0.010**	-0.43 (-1.27, 0.41)	0.314	**-0.99 (-1.67, -0.31)**[d]	**0.004**
MeP	-0.30 (-0.70, 0.11)[c]	0.155	-0.21 (-0.82, 0.39)	0.487	-0.30 (-0.85, 0.25)[d]	0.283
EtP	**-0.51 (-0.85, -0.18)**[c]	**0.003**	**-0.77 (-1.30, -0.24)**	**0.004**	-0.21 (-0.63, 0.22)[d]	0.340
PrP	-0.03 (-0.31, 0.26)[e]	0.849	0.17 (-0.26, 0.61)	0.428	-0.19 (-0.56, 0.17)[f]	0.303

Concentrations of all urinary chemicals (both traditional and covariate-adjusted standardization) were ln-transformed.
[a]Adjusted for age, sex, BMI, smoking status, drinking status, monthly household income, hypertension, and diabetes mellitus.
[b]Adjusted for age, BMI, smoking status, drinking status, monthly household income, hypertension, and diabetes mellitus.
[c]n=1291.
[d]n=653.

Table 11. Associations of urinary phthalate metabolites and environmental phenolics with ACR after stratification by CKD status.

	Total[a]			Male[b]			Female[b]		
	n	**β (95% CI)**	**p-value**	**n**	**β (95% CI)**	**p-value**	**n**	**β (95% CI)**	**p-value**
No CKD									
MEHHP	1178	0.04 (-0.05, 0.12)	0.413	581	0.05 (-0.08, 0.18)	0.425	597	0.02 (-0.09, 0.13)	0.723
MEOHP		0.05 (-0.03, 0.12)	0.242		0.06 (-0.05, 0.18)	0.290		0.03 (-0.07, 0.13)	0.615
MECPP		**0.11 (0.02, 0.20)**	**0.022**		**0.16 (0.02, 0.30)**	**0.028**		0.05 (-0.07, 0.16)	0.410
ΣDEHPm		0.08 (-0.01, 0.18)	0.087		0.15 (-0.01, 0.30)	0.064		0.03 (-0.10, 0.15)	0.664
MnBP		**-0.08 (-0.14, -0.02)**	**0.008**		**-0.10 (-0.19, -0.01)**	**0.028**		-0.05 (-0.12, 0.03)	0.229
MBzP		-0.04 (-0.10, 0.03)	0.298		0.00 (-0.10, 0.10)	0.989		-0.06 (-0.15, 0.02)	0.145
MCOP		0.07 (-0.01, 0.16)	0.101		0.06 (-0.08, 0.19)	0.421		0.09 (-0.02, 0.20)	0.121
MCNP		0.03 (-0.04, 0.11)	0.398		0.00 (-0.12, 0.12)	0.998		0.06 (-0.04, 0.16)	0.260
MCPP		-0.04 (-0.13, 0.05)	0.388		-0.09 (-0.23, 0.05)	0.211		0.01 (-0.11, 0.13)	0.905
BPA		-0.01 (-0.07, 0.06)	0.838		-0.02 (-0.11, 0.08)	0.753		0.00 (-0.08, 0.08)	0.985
MeP		-0.02 (-0.06, 0.03)	0.459		-0.02 (-0.08, 0.05)	0.604		-0.01 (-0.07, 0.05)	0.711
EtP		0.00 (-0.04, 0.03)	0.823		0.00 (-0.06, 0.06)	0.923		-0.01 (-0.06, 0.04)	0.703
PrP		0.01 (-0.02, 0.04)	0.562		0.03 (-0.02, 0.07)	0.300		-0.22 (-0.56, 0.13)	0.217
CKD									
MEHHP	98	0.34 (-0.02, 0.71)	0.066	51	0.43 (-0.18, 1.04)	0.159	47	0.26 (-0.11, 0.63)	0.169
MEOHP		0.17 (-0.17, 0.51)	0.318		0.28 (-0.23, 0.79)	0.275		0.02 (-0.40, 0.44)	0.919
MECPP		0.14 (-0.23, 0.51)	0.442		0.37 (-0.31, 1.05)	0.279		0.01 (-0.32, 0.33)	0.956
ΣDEHPm		0.22 (-0.18, 0.63)	0.276		0.43 (-0.25, 1.11)	0.212		0.04 (-0.36, 0.45)	0.827
MnBP		-0.16 (-0.42, 0.10)	0.228		-0.48 (-1.04, 0.08)	0.091		0.09 (-0.12, 0.30)	0.397
MBzP		-0.10 (-0.35, 0.16)	0.457		-0.05 (-0.55, 0.45)	0.848		-0.10 (-0.31, 0.11)	0.348
MCOP		0.10 (-0.23, 0.43)	0.541		0.10 (-0.47, 0.66)	0.736		0.20 (-0.11, 0.50)	0.200

MCNP	0.08 (-0.21, 0.37)	0.579	0.20 (-0.38, 0.77)	0.492	0.05 (-0.19, 0.28)	0.690
MCPP	-0.03 (-0.42, 0.36)	0.878	0.14 (-0.61, 0.89)	0.706	0.02 (-0.36, 0.39)	0.919
BPA	-0.07 (-0.29, 0.14)	0.502	-0.09 (-0.49, 0.30)	0.638	-0.04 (-0.23, 0.16)	0.720
MeP	0.01 (-0.19, 0.21)	0.952	-0.13 (-0.52, 0.26)	0.515	0.15 (-0.01, 0.31)	0.069
EtP	0.00 (-0.16, 0.15)	0.972	-0.15 (-0.53, 0.24)	0.445	0.07 (-0.03, 0.18)	0.168
PrP	0.07 (-0.08, 0.21)[c]	0.355	0.07 (-0.19, 0.34)	0.590	0.011 (-0.02, 0.24)[d]	0.100

Bold numbers indicate $p<0.05$.

Concentrations of all urinary chemicals (covariate-adjusted standardization) and ACR were ln-transformed.

Only participants with information on both urinary albumin and serum creatinine were included.

[a]Adjusted for age, sex, BMI, smoking status, drinking status, monthly household income, hypertension, and diabetes mellitus.

[b]Adjusted for age, BMI, smoking status, drinking status, monthly household income, hypertension, and diabetes mellitus.

[c]n=97.

[d]n=46.

Table 12. Associations of urinary phthalate metabolites and environmental phenolics with eGFR after stratification by CKD status.

	Total[a]			Male[b]			Female[b]		
	n	**β (95% CI)**	**p-value**	**n**	**β (95% CI)**	**p-value**	**n**	**β (95% CI)**	**p-value**
Non-CKD									
MEHHP	1178	-0.19 (-0.88, 0.50)	0.582	581	-0.39 (-1.45, 0.68)	0.478	597	0.22 (-0.66, 1.11)	0.622
MEOHP		-0.48 (-1.11, 0.15)	0.139		-0.84 (-1.82, 0.14)	0.092		0.02 (-0.79, 0.83)	0.962
MECPP		0.63 (-0.11, 1.37)	0.096		-0.24 (-1.41, 0.92)	0.682		**1.56 (0.64, 2.48)**	**0.001**
ΣDEHPm		0.13 (-0.67, 0.92)	0.750		-0.57 (-1.84, 0.70)	0.378		0.93 (-0.06, 1.92)	0.065
MnBP		**-0.51 (-1.00, -0.03)**	**0.038**		-0.73 (-1.48, 0.02)	0.055		-0.22 (-0.85, 0.40)	0.485
MBzP		0.49 (-0.05, 1.04)	0.076		0.10 (-0.75, 0.95)	0.814		**0.91 (0.22, 1.60)**	**0.010**
MCOP		0.58 (-0.14, 1.31)	0.114		0.18 (-0.94, 1.31)	0.748		**0.97 (0.05, 1.88)**	**0.038**
MCNP		0.60 (-0.03, 1.23)	0.063		0.23 (-0.73, 1.19)	0.634		**0.93 (0.11, 1.75)**	**0.026**
MCPP		0.23 (-0.52, 0.98)	0.550		-0.19 (-1.34, 0.95)	0.741		0.68 (-0.30, 1.65)	0.174
BPA		**-0.54 (-1.04, -0.03)**	**0.037**		-0.50 (-1.28, 0.28)	0.206		-0.61 (-1.26, 0.03)	0.062
MeP		-0.31 (-0.68, 0.07)	0.106		-0.16 (-0.70, 0.39)	0.570		-0.40 (-0.90, 0.11)	0.127
EtP		**-0.38 (-0.69, -0.08)**	**0.015**		**-0.57 (-1.05, -0.10)**	**0.018**		-0.13 (-0.53, 0.27)	0.530
PrP		-0.09 (-0.36, 0.17)	0.482		0.05 (-0.34, 0.45)	0.796		0.00 (-0.04, 0.04)	0.932
CKD									
MEHHP	98	1.59 (-3.66, 6.85)	0.548	51	2.93 (-4.48, 10.34)	0.430	47	-3.79 (-12.76, 5.17)	0.397
MEOHP		0.05 (-4.75, 4.85)	0.984		2.57 (-3.56, 8.70)	0.403		-8.18 (-17.77, 1.42)	0.093
MECPP		1.80 (-3.46, 7.06)	0.498		3.08 (-5.12, 11.27)	0.453		-0.11 (-7.81, 7.59)	0.977
ΣDEHPm		0.93 (-4.83, 6.70)	0.748		2.63 (-5.60, 10.86)	0.523		-3.46 (-13.07, 6.16)	0.471
MnBP		**-3.79 (-7.47, -0.11)**	**0.044**		**-10.08 (-16.21, -3.94)**	**0.002**		-0.38 (-5.48, 4.72)	0.882
MBzP		-0.62 (-4.24, 3.01)	0.736		-1.94 (-7.87, 4.00)	0.514		0.82 (-4.21, 5.85)	0.744
MCOP		0.98 (-3.68, 5.65)	0.677		-0.15 (-6.95, 6.65)	0.965		3.32 (-3.98, 10.62)	0.363

MCNP	0.79 (-3.32, 4.89)	0.705	-0.80 (-7.67, 6.06)	0.815	2.01 (-3.52, 7.53)	0.467
MCPP	-2.92 (-8.44, 2.59)	0.295	-5.61 (-14.40, 3.17)	0.204	1.43 (-7.49, 10.34)	0.747
BPA	-1.98 (-5.07, 1.12)	0.207	-0.72 (-5.44, 4.00)	0.760	-2.68 (-7.30, 1.94)	0.248
MeP	-0.96 (-3.81, 1.88)	0.503	-1.92 (-6.55, 2.71)	0.406	0.68 (-3.33, 4.68)	0.735
EtP	**-2.91 (-5.00, -0.81)**	**0.007**	**-4.67 (-9.04, -0.29)**	**0.037**	-2.09 (-4.61, 0.44)	0.103
PrP	0.35 (-1.68, 2.39)[c]	0.731	1.39 (-1.77, 4.55)	0.380	-0.44 (-3.71, 2.83)[d]	0.788

Bold numbers indicate $p<0.05$.

Concentrations of all urinary chemicals (covariate-adjusted standardization) were ln-transformed.

[a]Adjusted for age, sex, BMI, smoking status, drinking status, monthly household income, hypertension, and diabetes mellitus.

[b]Adjusted for age, BMI, smoking status, drinking status, monthly household income, hypertension, and diabetes mellitus.

[c]n=97.

[d]n=46.

3.3.3. Principal Component Analysis (PCA)

Using PCA on twelve urinary chemicals, five factors that accounted for greater than 70% of the total variance were generated. Detailed information on varimax-rotated factor loadings is shown in Table 13. In total population, factor 1 is highly loaded with DEHP metabolites and MBzP. Factor 2 is highly loaded with by MCOP, MCNP, and MCPP. Factor 3 is highly loaded with MeP and PrP. Factor 4 is highly loaded with BPA and EtP, and factor 5 is highly loaded with MnBP. Factor patters in males and females were similar with those in total population except EtP and MnBP.

In the multiple-factor model, factor 1 was significantly positively associated with ACR, but factor 5 was significantly negatively associated with ACR (Table 14). Factors 4 and 5 were significantly negatively associated with eGFR. In males, factor 4 was significantly negatively associated with ACR and eGFR. In females, factor 2 was significantly positively associated with eGFR, and factor 4 was significantly negatively associated with eGFR. Results from the single-factor model were similar to the results from the multiple-factor model.

Table 13. Varimax-rotated factor loadings of of phthalate metabolites and environmental phenolics in PCA.

		Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
Total (n=1290)	**MEHHP**	**0.89**	0.05	0.03	0.02	0.19
	MEOHP	**0.91**	0.07	0.04	0.02	0.13
	MECPP	**0.81**	0.38	0.06	-0.05	-0.12
	MnBP	0.20	0.10	-0.02	0.02	**0.96**
	MBzP	**0.57**	0.17	0.00	-0.06	0.06
	MCOP	0.24	**0.82**	0.04	0.03	0.01
	MCNP	0.07	**0.89**	0.02	-0.02	-0.02
	MCPP	0.22	**0.83**	-0.03	0.03	0.17
	BPA	-0.07	0.02	-0.20	**0.85**	-0.03
	MeP	0.05	0.15	**0.88**	0.02	0.03
	EtP	0.02	0.02	0.44	**0.57**	0.09
	PrP	0.03	-0.12	**0.88**	-0.09	-0.07
Male (n=638)	**MEHHP**	**0.91**	0.10	0.01	0.04	0.01
	MEOHP	**0.90**	0.10	0.04	-0.03	0.04
	MECPP	**0.72**	0.45	-0.01	-0.25	0.15
	MnBP	0.47	0.05	0.07	**0.53**	-0.45
	MBzP	**0.56**	0.20	0.03	0.03	-0.04
	MCOP	0.23	**0.82**	-0.01	0.03	0.06
	MCNP	0.06	**0.89**	0.04	-0.06	0.00
	MCPP	0.28	**0.79**	0.03	0.13	-0.11
	BPA	-0.12	0.04	-0.10	**0.81**	0.21
	MeP	0.04	0.16	**0.89**	0.04	0.12
	EtP	0.10	-0.02	0.19	0.17	**0.84**
	PrP	0.03	-0.11	**0.89**	-0.13	0.06
Female (n=652)	**MEHHP**	**0.91**	0.03	0.02	0.03	0.13
	MEOHP	**0.93**	0.07	0.01	0.04	0.11
	MECPP	**0.84**	0.35	0.05	-0.03	-0.09
	MnBP	0.18	0.10	-0.01	-0.02	**0.95**
	MBzP	**0.54**	0.18	0.05	-0.24	0.10
	MCOP	0.22	**0.83**	0.08	-0.01	0.00
	MCNP	0.06	**0.89**	-0.01	0.00	0.00
	MCPP	0.18	**0.86**	-0.05	0.04	0.15

BPA	-0.06	0.03	-0.15	**0.87**	-0.07
MeP	0.07	0.13	**0.86**	-0.05	0.00
EtP	-0.03	0.04	**0.51**	0.47	0.25
PrP	0.03	-0.14	**0.87**	-0.12	-0.07

Factors derived from PCA with loading >0.5 are shown in bold print.
For dilution adjustment, covariate-adjusted standardization was used, and then ln-transformed.

Table 14. Associations of urinary phthalate metabolites and environmental phenolics component scores (covariate-adjusted standardization) with markers of kidney function.

			Single-factor		Multiple-factor	
			β (95% CI)	**p-value**	**β (95% CI)**	**p-value**
Total[a]	**Ln-ACR (n=1275)**	**Factor 1[c]**	**0.09 (0.01, 0.17)**	**0.023**	**0.09 (0.01, 0.17)**	**0.025**
		Factor 2[d]	0.03 (-0.05, 0.11)	0.441	0.03 (-0.05, 0.11)	0.450
		Factor 3[e]	-0.02 (-0.10, 0.06)	0.696	-0.02 (-0.10, 0.06)	0.690
		Factor 4[f]	-0.01 (-0.09, 0.07)	0.803	-0.01 (-0.09, 0.07)	0.788
		Factor 5[g]	**-0.12 (-0.20, -0.04)**	**0.003**	**-0.12 (-0.20, -0.04)**	**0.003**
	eGFR (n=1290)	**Factor 1[c]**	-0.05 (-0.70, 0.60)	0.885	-0.06 (-0.71, 0.58)	0.844
		Factor 2[d]	0.43 (-0.21, 1.06)	0.192	0.45 (-0.19, 1.08)	0.168
		Factor 3[e]	-0.45 (-1.10, 0.20)	0.174	-0.44 (-1.09, 0.20)	0.180
		Factor 4[f]	**-1.19 (-1.83, -0.55)**	**<0.001**	**-1.18 (-1.82, -0.55)**	**<0.001**
		Factor 5[g]	**-1.17 (-1.81, -0.54)**	**<0.001**	**-1.18 (-1.81, -0.55)**	**<0.001**
Male[b]	**Ln-ACR (n=632)**	**Factor 1[c]**	0.09 (-0.03, 0.21)	0.122	0.09 (-0.03, 0.21)	0.126
		Factor 2[d]	-0.03 (-0.15, 0.09)	0.593	-0.03 (-0.15, 0.09)	0.610
		Factor 3[e]	-0.03 (-0.15, 0.09)	0.668	-0.03 (-0.15, 0.09)	0.660
		Factor 4[h]	**-0.16 (-0.28, -0.04)**	**0.008**	**-0.16 (-0.28, -0.04)**	**0.008**
		Factor 5[i]	0.08 (-0.04, 0.20)	0.194	0.07 (-0.05, 0.19)	0.222
	eGFR (n=638)	**Factor 1[c]**	-0.51 (-1.50, 0.47)	0.309	-0.51 (-1.49, 0.47)	0.308
		Factor 2[d]	0.15 (-0.84, 1.13)	0.771	0.16 (-0.83, 1.14)	0.756
		Factor 3[e]	-0.13 (-1.12, 0.86)	0.802	-0.14 (-1.13, 0.85)	0.781

		Factor 4[h]	**-1.46 (-2.44, -0.48)**	**0.004**	**-1.47 (-2.45, -0.49)**	**0.003**
		Factor 5[i]	-0.53 (-1.52, 0.47)	0.300	-0.54 (-1.54, 0.45)	0.282
Female[b]	**Ln-ACR (n=643)**	**Factor 1[c]**	0.06 (-0.05, 0.17)	0.276	0.05 (-0.05, 0.16)	0.325
		Factor 2[d]	0.09 (-0.01, 0.20)	0.072	0.09 (-0.01, 0.20)	0.074
		Factor 3[j]	-0.03 (-0.13, 0.08)	0.623	-0.03 (-0.13, 0.08)	0.599
		Factor 4[k]	0.04 (-0.06, 0.15)	0.409	0.04 (-0.06, 0.15)	0.408
		Factor 5[l]	-0.07 (-0.17, 0.03)	0.181	-0.07 (-0.17, 0.03)	0.171
	eGFR (n=652)	**Factor 1[c]**	0.07 (-0.77, 0.92)	0.865	0.03 (-0.81, 0.86)	0.950
		Factor 2[d]	0.81 (0.00, 1.62)	0.051	**0.82 (0.02, 1.63)**	**0.046**
		Factor 3[j]	-0.52 (-1.33, 0.30)	0.215	-0.54 (-1.35, 0.27)	0.189
		Factor 4[k]	**-1.18 (-1.99, -0.38)**	**0.004**	**-1.19 (-1.99, -0.38)**	**0.004**
		Factor 5[l]	-0.55 (-1.35, 0.26)	0.185	-0.56 (-1.37, 0.24)	0.168

Concentrations of all urinary chemicals (covariate-adjusted standardization) were ln-transformed.
[a]Adjusted for age, sex, BMI, smoking status, drinking status, monthly household income, hypertension, and diabetes mellitus.
[b]Adjusted for age, BMI, smoking status, drinking status, monthly household income, hypertension, and diabetes mellitus.
[c]Factor 1 is highly loaded with MEHHP, MEOHP, MECPP, and MBzP.
[d]Factor 2 is highly loaded with MCOP, MCNP, and MCPP.
[e]In total and male population, factor 3 is highly loaded with MeP and PrP.
[f]In total population, factor 4 is highly loaded with BPA and EtP.
[g]In total population, factor 5 is highly loaded with MnBP.
[h]In males, factor 4 is highly loaded with MnBP and BPA.
[i]In males, factor 5 is highly loaded with EtP.
[j]In females, factor 3 is highly loaded with MeP, EtP, and PrP.
[k]In females, factor 4 is highly loaded with BPA.

[l]In females, factor 5 is highly loaded with MnBP.

3.4. Discussion

This study clearly shows that the use of urinary creatinine correction to adjust urinary dilution status might confound the association of urinary chemicals with eGFR. Following covariate-adjusted standardization, significant positive associations between major phthalate metabolites and eGFR which were observed by the creatinine-correction disappeared, and MnBP, BPA, and EtP in urine exhibited significant negative associations with eGFR (Table 10). Because of the influence of covariates such as age, sex, and BMI, the use of creatinine to adjust hydration status may cause a collider problem in an association model depending on target health outcomes.[86,77] In order to handle such issue, a covariate-adjusted standardization method has been suggested.[77] For this purpose, because urinary creatinine concentration was influenced not only by age, sex, and BMI, but also by eGFR in the present population (Table 6), eGFR was included in the model to predict urinary creatinine for each individual, and derived the ratio between measured creatinine levels and the predicted creatinine levels. The ratio was confirmed not to be associated with eGFR (data not shown). Following the covariate-adjusted standardization, several chemical risk factors for decreased eGFR could be identified in the current population (Table 10).

When the conventional creatinine-adjustment was applied for correction of urinary dilution, the positive association was observed between phthalates and eGFR (Table 10). This observation suggests renal-protective effects of

these chemicals, and are different from those which suggested increased risk of CKD in terms of ACR, for these chemicals.[70,71,73] Indeed, several previous studies have also reported positive associations of phthalates and BPA with eGFR.[74,75] One possible explanation for the positive associations might be due to urinary dilution adjustment method, and therefore previous studies were compared according to the urinary dilution method. In an adult population of US NHANES 2003-2006 (n=2573), high urinary BPA concentrations were associated with high eGFR.[74] In a child population with chronic kidney disease (n=451), urinary levels of low molecular weight phthalate metabolites were in a positive association with eGFR, while urinary BPA did not show any associations.[75] In previous studies, seemingly protective or positive associations reported between urinary chemicals and eGFR were explained by a hypothesis of reverse causation.[75,83] For instance, reduced eGFR may lower the urinary excretion of chemicals, which may mistakenly lead to a conclusion of positive associations between urinary chemicals and eGFR.[74,83,84] In addition, the use of urinary creatinine to adjust urinary chemical concentrations may contribute to the observations of positive associations between urinary chemicals and eGFR, because the urinary creatinine concentration is influenced by serum creatinine level, which is a key determinant of eGFR. Our observation indicates that by applying the covariate-adjusted standardization, one can more clearly identify chemical risk factors of CKD (Table 10). Recently, Kang et al. demonstrated that significant negative associations of several

organophosphate esters with eGFR only appeared after employing the covariate-adjusted standardization method, in adult population of US NHANES 2013-2014.[76]

Following the covariate-adjusted standardization, DEHP metabolites in urine showed positive association with ACR; and urinary MnBP, BPA, and EtP showed negative associations with eGFR (Tables 9 and 10). Sex different effects on the associations were observed. This might be due to biological difference between them, which can be supported by studies on sex differences in chronic kidney disease. Several phthalates have been associated with CKD in other populations as well. In Chinese adults (n=1663), urinary DEHP metabolites and MnBP, following creatinine adjustment, showed significant positive and negative associations with ACR, respectively.[87] Higher DEHP metabolites and sum of high molecular weight phthalate metabolites were related with increased ACR in the child and adolescent subjects (between 6 and 19 years old, n=667) of the 2009-2010 NHANES, in an association model with urinary creatinine included as a covariate.[73] Similar results were also observed in Taiwanese children (aged ≤10 years, n=184), which reported a positive association between daily intake of DEHP and urinary ACR.[88] In experimental models, treatment with DEHP induced renal fibrosis or tubular degeneration in renal tubular cells,[89] and in animals.[89,90] Meanwhile, discrepancy with findings of this study also exists. In a pre-menopausal adult women population, urinary DEHP metabolites (creatinine-adjusted) were not associated with ACR, but the

fasting urine samples (>9 h) were collected and hence levels and detection frequencies of urinary chemicals including phthalate metabolites were much lower than those observed in the present population.[70]

The significant negative association of urinary EtP with eGFR (Tables 10 and 14) is noteworthy. This is the first report that suggest potential association between EtP exposure and reduced kidney function, and therefore should be replicated in other population studies. EtP has been associated with oxidative stress in both experimental and epidemiological studies.[63,64] Parabens could significantly increase H_2O_2 and lipid peroxidation in the liver and kidney homogenates,[63] and induce lipid peroxidation in the liver of female adult albino mice.[64] Oxidative stress has been suggested as one of major mechanisms of chemical induced CKD.[65] The reason why only EtP, among three measured parabens, exhibited significant negative association with eGFR is not clear and warrants further study. EtP has been detected at relatively high levels among Korean populations,[60,91,92] and used as a preservative in condiments in Korea.[91] While a possibility of confounding which was not considered in this study cannot be ruled out, potential roles of EtP in pathogenesis of CKD warrants follow up studies.

Significant negative associations observed for MnBP with both ACR and eGFR (Tables 9 and 10) are interesting and warrant discussion. In fact, MnBP was associated with ACR in the pre-menopausal adult women population of Korea, but the direction of association was the opposite.[70]

Generally, elevated ACR is considered as one of the early signs of CKD, and the CKD stage depends on the degree of decrease of eGFR.[93] While eGFR could be decreased without increasing ACR for certain kidney diseases like diabetic kidney disease (DKD) without proteinuria,[94] further investigations are warranted to confirm the observed association of MnBP with CKD in the present study.

This study has several limitations. As a cross-sectional study, the associations observed in the present study do not support causal links with CKD. While a third of random samples were chosen from the nationally representative population of KoNEHS 2015-2017, weights could not be assigned to the study population and therefore the current population could not represent general Korean adults. In addition, interactions among measured chemicals could not be considered in the statistical models. Jaffe method used for measurement of serum creatinine, while being widely employed due to its automated process and cost-effectiveness, has a limitation in that it measures nonchromogen creatinine which may underestimate the actual glomerular filtration by 10-20%. However, this study employed a reasonable number of adult subjects, and applied a novel covariate-adjusted standardization method to address collider issues in the association studies for kidney outcomes and to identify chemical risk factors for CKD.

3.5. Conclusion

The observations on the general adult population of Korea (n=1292) show that the choice of adjusting method for urinary chemical dilution could influence the conclusion of the association studies on CKD. By use of the covariate-adjusted standardization, we identified that MnBP, BPA, or EtP is associated with lower eGFR in the general Korean adult population. In addition, among the measured urinary chemicals, several high molecular weight phthalate metabolites are associated with ACR. Further studies are warranted to confirm our findings in human populations and experimental studies.

Chapter 4. General Discussion

4.1. Key Findings

This thesis investigated the health effects of outdoor and indoor environments on CKD, respectively in Korea. Long-term exposure to air pollutants had negative effects on mortality in ESRD patients. These effects were prominent in elderly patients who lived in metropolitan areas, meaning that ambient air pollution, in addition to traditional risk factors, was important to the survival of these patients. Also, we identified that MnBP, BPA, or EtP is associated with lower eGFR in the general Korean adult population. In addition, among the measured urinary chemicals, several high molecular weight phthalate metabolites are associated with ACR.

4.2. Public Health Implications

This thesis suggested the negative effects of outdoor and indoor environmental factors to CKD. Although traditional risk factors for CKD, such as diabetes, hypertension and dyslipidemia, have been controlled for decades, the prevalence and complications following CKD are increasing. Therefore, it is necessary to find and control new risk factors. Investigation for the effects of environmental factors such as air pollution and household chemicals on CKD is expected to reduce the complications and socio-economic burdens caused by CKD. By uncovering new risks from air

pollution, it is expected that urban planning and industrialization plans could be affected. Also, a new light on the risks of household chemicals would provide the basis for a new guideline for the management of hazardous substances in consumer goods used in our daily lives.

4.3. Recommendation for Future Developments

Further biological studies are needed to confirm the specific pathophysiology of PM_{10} consisting of various organic and inorganic molecules, as well as NO_2 and SO_2. Also, further studies are warranted to confirm the findings through the analyses of environmental chemicals in human populations and experimental studies.

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환경요인이 만성콩팥병에 미치는 영향

서울대학교 대학원

의학과 법의학전공

박 재 윤

연구배경

만성콩팥병의 전통적인 위험인자인 당뇨병과 고혈압, 고지혈증, 흡연, 비만 등에 대한 치료를 수십년간 지속해왔음에도 오히려 만성콩팥병은 세계적으로 그 유병률이 증가하고 있고, 그에 따르는 합병증의 위험 및 사회경제적인 부담 역시 증가하고 있어 최근 환경요인이 만성 질환의 새로운 위험요인으로 부상하고 있다. 그러나 환경요인과 만성콩팥병과의 상관관계는 상대적으로 잘 알려지지 않은 부분이 많다.

연구목표

본 학위 논문은 국립환경과학원 (Korean National Institute of Environmental Research)에서 보고한 대기오염 지표와 생활화학물질 지표를 이용하여 다양한 환경인자들에 의한 건강문제, 그 중

에서 특히 환경인자가 만성콩팥병의 발생 및 그에 따른 사망에 미치는 영향에 대해 연구하고자 하였다.

연구방법

실외 환경인자가 말기신부전 환자의 사망에 미치는 영향을 알아보기 위해, 2008년부터 2015년까지 말기신부전으로 투석을 시작한 5,041 명의 CRC-ESRD (Clinical Research Center for End-Stage Renal Disease) 코호트 연구 참여자를 대상으로 하였다. 국립과학원으로부터 동 기간 매일 측정된 대기오염인자, 즉, PM_{10} 및 NO_2, SO_2를 각 참여자에 할당하였다. Time-varying Cox 모델을 이용하여 시간의 흐름에 따라 변화하는 각 대기오염인자와 말기신부전 환자의 사망의 연관성을 분석하였다.

실내 환경인자가 신기능에 미치는 영향을 알아보기 위해, 2015년부터 2017년까지의 국민환경보건조사 (KoNEHS, Korean National Environmental Health Survey)에 참여한 1,294 명을 대상으로 하였다. 주요 프탈레이트와 그 대사체, 비스페놀 A, 파라벤과 알부민뇨 (urine albumin-creatinine ratio 30 mg/g 이상) 및 신기능 감소 (eGFR 60 mL/min/1.73m^2 미만) 와의 연관성을 살펴보았다.

연구결과

대기오염 노출과 말기신부전 환자의 사망률 사이의 연관성을 살펴본 연구에서는, 5041명의 대상자들을 평균 4.18년 관찰하였고 그 중에서 1475명이 사망하였다. PM_{10} (HR 1.33, CI 1.13–1.58)과 NO_2 (HR 1.46, CI 1.10–1.95), SO_2 (HR 1.07, CI 1.03–1.11)가 말기신부전 환자의 사망률과 유의한 상관관계를 보였다. 또한 65세 이상의 노인 인구와 대도시 주변 거주자가 특히 PM_{10}에 의한 사망 위험이 높았다.

프탈레이트 및 환경성 페놀릭과 신장기능 사이의 연관성을 보면, 요중 화학물질의 농도 보정법의 종류와 관계없이 요중 DEHP 대사체가 ACR 과 양의 상관관계를 보였다. 보정법으로 Covariate-adjusted standardization 을 이용하였을 때 MCOP 및 MCNP 와 같은 고분자량 프탈레이트의 요중 대사체도 ACR 과 양의 상관관계를 보였다. 통상적인 크레아티닌을 이용한 농도보정법을 이용하였을 때, eGFR은 대부분의 프탈레이트 대사체와 양의 상관관계를 보였다. 그러나 보정법으로 covariate-adjusted standardization 을 이용하였을 때, 그러한 양의 상관관계의 유의성은 사라졌고, MnBP 및 BPA, EtP 가 음의 상관관계를 보였다. 층화분석과 주성분 분석 (principal component analysis, PCA) 을 통한 이차 분석 결과도 비슷한 결과를 보였다.

결론

실외에서 대기오염에 장기간 노출되면 말기신부전 환자의 사망률이 높아지고, 이러한 현상은 노인과 대도시 거주자에게 두드러졌다. 또한 실내에서 노출되는 주요 프탈레이트 대사체는 건강한 성인에서 만성콩팥병의 위험을 높였다. 프탈레이트 대사체 연구를 통해서 요중 화학물질의 농도 보정법의 선택이 주요 소비재 화학물질과 신기능의 상관관계를 살펴보는 연구에서 결과의 해석에 중요한 영향을 미친다는 것을 강조한다. 결론적으로, 전통적인 위험인자들 뿐만 아니라, 실외 및 실내 환경인자의 조절이 신장질환의 발생 및 그에 따른 사망의 위험을 낮추는데 역할을 할 수 있다.

주요어: 만성콩팥병, 말기신부전, 대기오염, 프탈레이트

학번: 2014-31263