Master's Thesis of Public Health

The impact of sunlight exposure on mortality of ESRD patients:
Comparison of the results using case-crossover study design

일조시간이 말기신부전(ESRD) 환자의 사망에 미치는 영향:
Case-crossover design을 이용한 결과비교

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Abstract

Background

Recent data suggest that reduced sunlight exposure is associated with increased mortality in the general population. To date, the association between sunlight exposure and mortality in dialysis patients has not been examined.

Objective

Among 134,478 dialysis patients in the Korean end-stage renal disease (ESRD) cohort from 2001 to 2014, 31,291 patients were enrolled from seven metropolitan cities, and data were analyzed using bi-directional case-crossover design. We examined the association between short-term sunlight exposure and mortality in ESRD patients. We adjusted for temperature, humidity, and daily concentrations of nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), carbon monoxide (CO), and particle matter (PM_{10}) as confounders.

Method

Among 134,478 dialysis patients in the Korean end-stage renal

disease (ESRD) cohort from 2001 to 2014, 31,291 patients were enrolled from seven metropolitan cities, and data were analyzed using bi-directional case-crossover design. We examined the association between short-term sunlight exposure and mortality in ESRD patients. We adjusted for temperature, humidity, and daily concentrations of nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), carbon monoxide (CO), and particle matter (PM_{10}) as confounders.

Result

The characteristics of the study population included age (65.6 ± 12.26 (mean ± standard deviation [SD]) years), sex (male, 59.96%; female, 41.04%), comorbidity (diabetes, 53.58%; hypertension, 40.5%), and kidney dialysis type (hemodialysis, 73.02%; peritoneal dialysis, 26.98 %). The mean ± SD follow-up time was 4.68 ± 4.37 years. The daily sunlight exposure was significantly decreased in the case group compared with the control group (P=0.004). Sunlight exposure was associated with all-cause death overall (ORs [95%CI]: 0.99 [0.98-0.99], P=0.042) in a fully adjusted model. Patients with diabetes (ORs [95%CI]: 0.98 [0.97-0.99], P=0.016) or aged higher than 75 years (ORs [95%CI]; 0.97

[0.96 – 0.99], P=0.020) had higher risks of mortality than patients without diabetes or aged below 75 years, respectively.

Conclusion

These findings suggest that sunlight exposure is inversely correlated with all-cause mortality in dialysis patients, especially in high-risk patients with diabetes and older adults.

Keyword : sunlight exposure, mortality, end stage renal disease, ESRD, sunshine vitamin, vitamin D

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Table of Contents

Abstract 2

Chapter 1. Introduction... 7

Chapter 2. Method... 9

2.1. Study population... 9

2.2. Weather and air pollution data 10

2.3. Study design 10

2.4. Statistical analysis..12

Chapter 3. Result 15

3.1. Descriptive results 15

3.2. Effect modification by meteological and
air pollution factors 21

3.3. Difference in daily levels of environmental variables
Between case and control periods(2001-2014)..................22

3.4. Effect of sunlight exposure on ESRD death 24

3.5. Comparison of the results in Case-crossover
designs...26

Chapter 4. Discussion 30

Reference 36

List of Tables

Table 1. Baseline characteristics 16

Table 2. City-specific descriptive information on the study period, ESRD death, and the levels of environmental variables 18

Table 3. Sunlight hour descriptive statistics by cities

....19

Table 4. Difference in daily levels of environmental variables between case and control periods(2001-2014) 24

Table 5. Effect modification of association between ESRD death and sunlight exposure with environmental confounders in conditional logistic regression model..................................25

Table 6. Comparison the results of control selection in the Case-crossover design...27

List of Figures

Figure 1. Bi-directiona sampling of control time in the case crossover study 11

Figure 2. Daily weather and five major air pollutants from 2001 to 2014..20

Figure 3. The trend of ESRD mortality and sunlight.............21

Figure 4. Percent decrease in odds ratios of sunlight exposurefor ESRD death..28

Figure 5. Penalized spline terms on exposure......................29

Abstract in Korean...44

Chapter 1. Introduction

There is a lively debate about avoidance of sunlight is a major risk factor for public health. Although high-intensity ultraviolet radiation could be a carcinogen to the skin, there is growing scientific evidence that avoidance of sunlight exposure, is a major risk factor for various diseases and ultimately death. Vitamin D is the "sunshine vitamin", synthesized primarily in the skin during sunlight exposure, especially by ultraviolet B (UVB) radiation. In addition to observational studies, many randomized trials have demonstrated the inverse associations of circulating vitamin D with risks of cancer, cardiovascular diseases, infectious diseases, metabolic disorders as well as mortality. Prevalence of vitamin D deficiency is high in patients with chronic kidney disease (CKD) including end-stage renal disease (ESRD) patients undergoing dialysis. In patients with CKD, conversion of serum 25-hydroxyvitamin D [25(OH)D] to 1,25(OH)$_2$D, the active form of vitamin D, is insufficient due to the loss of 1alpha-hydroxylase activity.

Low circulating 25(OH)D concentration leads to mineral bone disease (MBD) such as secondary hyperparathyroidism, which is critically correlated with increased risks of coronary arterial calcification, atherosclerosis, and endothelial cell dysfunction, which results in cardiovascular events and mortality. Although, it is known that vitamin D supplementation improves serum 25(OH)D levels, there is still debate on whether this results in improved mortality .

Until recently, there were few studies on the relationship between sunlight exposure and clinical prognosis in patients with ESRD, who undergo renal replacement therapy, such as hemodialysis and peritoneal dialysis. Given this concern, this study was conducted to investigate the relationship of sunlight exposure and death in dialysis patients.

Chapter 2. Method

2.1. Study population

The Korean Society of Nephrology (KSN) end-stage renal disease (ESRD) registry was established in 1985. All KSN members contribute voluntarily to the 'Insan Prof. Byung-Suk Min Memorial ESRD Patient Registry. The KSN ESRD Registry Committee has been collecting data on dialysis through the internet online program that was opened in 2001 and revised in 2013. The Korean ESRD registry covers about two-thirds of all dialysis patients in Korea because the enrollment is voluntarily. The present study enrolled patients who died from KSN data from 2001 through 2014. The study protocol complies with the Declaration of Helsinki and received full approval from the institutional review board at the Seoul National University Boramae Medical Center (10-2018-50-051). Clinical information, including the date of death, age, sex, body mass index (BMI), comorbidities (hypertension and diabetes mellitus) and type of kidney dialysis (peritoneal dialysis and hemodialysis), the causes of ESRD and the cause of death were obtained from the registry.

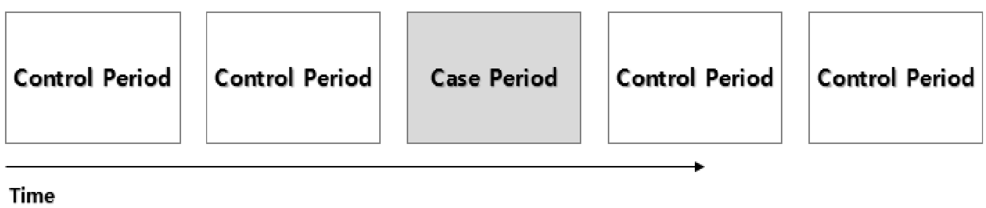
2.2. Weather and air pollution data

The seven metropolitan cities in Korea were selected as our study area and the study period, 2001 to 2014 was chosen. We obtained hourly data on ambient temperature, relative humidity, and sunlight hour from the Korea Meteorological Administration. To adjust for potential confounding, we also obtained the daily (24-hour) concentrations of nitrogen dioxide (NO_2), sulfur dioxide (SO_2), ozone (O_3), carbon monoxide (CO), and particulate matter (PM_{10}) measured at 89 monitoring sites located within the seven cities. These were provided by the Korean National Institute of Environmental Research. As short-term confounder measures, we used the daily max concentration of ozone (O_3) and the daily mean concentration for the other air pollutants (PM_{10}, NO_2, SO_2, O_3 and CO) within same city.

2.3. Study design

We applied a bi-directional case-crossover design (Figure 1) to estimate the short-term association between sunlight and ESRD death. A case-crossover design, which is described by Maclure to evaluate the transient acute effect, is a variant of the case-control design and produces sufficient statistical power with small cases. It has been used as an alternative to time series recently and an extension of this approach has also been used for observational studies in areas such as clinical-epidemiology, impairment-epidemiology, pharmaco-epidemiology and environmental-epidemiology. The case period was defined as the day ESRD led to the death of the patient. We used bi-directional case-crossover study as a two-to-one matched case-control study which sampled control periods as the exposure, seven days before and seven days after the date of event (ESRD death); resulting in four control days per case (Figure 1). For example, if ESRD death occurred on April 13, four control days were selected as follows: March 30, April 6, April 20, and April 27.

Figure 1. Bi-directional sampling of control time in the case-crossover study



In the case−crossover design, the time−invariant individual characteristics such as sex and genetic predisposition and the slowly varying characteristics such as age, marital status, employment status, and seasonality can be controlled. In our study, the daily sunlight exposure hours during the case and control periods were compared. There are several designs such as bi−directional, time−stratified, uni−directional case−crossover studies which are determined by control selections and we compared the results.

2.4. Statistical analysis

The conditional logistic regression analytic method is an extension of the logistic regression method, which allows one to take into account the stratification and matching that is mainly utilized in observational studies. We investigated the association between sunlight and ESRD death risk by conditional logistic regression performed via the Cox proportional−hazard function. The comparisons within subject were made between the case and control periods. The odds ratios (ORs) and 95% confidence intervals (CIs) for the risk of ESRD death on sunlight exposure were calculated by the conditional logistic regression analysis. We used ambient temperature and humidity as a potential confounder and five other air-pollutants (PM_{10}, NO_2, SO_2, O_3 and CO) were also used in order to have five different models as a potential effect modification. The conditional logistic model can be simplified by the following formula after matching for the time-invariant individual risk factors;

$$\log\frac{p_{ij}}{1-p_{ij}} = \alpha_i + \beta_1 \times \text{sunlight}_{ij} + \beta_2 \times \text{temperature}_{ij} + \beta_3 \times \text{humidity}_{ij} + \beta_4 \times \text{air pollutants}_{ij}$$

where β_1, β_2, β_3 and β_4 represent the vectors whose components denote the log odds of mortality associated with sunlight, ambient temperature, humidity, and air pollutants separately as confounders. Using the formula above, represents $Y_{ij} \epsilon \{0,1\}$ case status (case = 1, control = 0) of the jth observation of ith strata where α_i is constant term of ith strata. The ambient temperature and humidity are stationary confounder factors and five air pollutants (PM_{10}, NO_2, SO_2, O_3 and CO) were applied in each models.

We examined higher risk patients in the ESRD cohort as having diabetes, being older adults (over 75 years), undergoing peritoneal dialysis or hemodialysis, for the subgroup analysis, compared to the lower−risk group. The statistical analysis was performed using a statistical programing language R 3.4.0.

Chapter 3. Results

3.1. Descriptive results

We identified 134,472 patients registered in the Korean Society of Nephrology for kidney dialysis registry. Among those, 31,291(23.30%) patients died between 2001 and 2014 in the seven Korea metropolitan cities. The following characteristics of patients with ESRD deaths are shown in Table 1: sex (male, 59.96% and female, 41.04%), age at death (< 75 years, 51.38%, and > 75 years, 48.6%), comorbidity (diabetes, 53.58% and hypertension, 40.50%), kidney dialysis types (peritoneal dialysis, 26.98% and hemodialysis, 73.02%), primary disease (diabetes, 53.6%; hypertension, 15.2%; glomerulonephritis (GN), 8.16%; others, 7.31%; and unknown, 14.1%), and cause of death (cardiovascular disease, 28.31%; peripheral vessel disease, 12.7%; infection, 19.33%; cancer, 4.7%; and others, 34.9%). The average BMI in our study population was 21.21 for male and 21.20 for female. ESRD deaths occurred more frequently in males and those having diabetes as a primary disease.

Table 1. Baseline characteristics of study population (2001-2014)

Variables		**ESRD death**
Overall		31,291
Sex		
	Male (%)	18,448 (58.96)
	Female (%)	12,843 (41.04)
Age (Death) (mean ± SD)		65.6 ± 12.26
	< 75 (%)	16,076 (51.38)
	≥76 (%)	15,208 (48.6)
Body mass index (BMI)		
	Male (mean ± SD)	21.21 ± 2.87
	Female (mean ± SD)	21.20 ± 3.48
Comorbidity		
	Diabetes (%)	53.58%
	Hypertension (%)	40.5%
Dialysis		
	Peritoneal dialysis (%)	8,442 (26.98)
	Hemodialysis (%)	22,849 (73.02)
Primary Disease		
	Diabetes	16,766 (53.6)
	Hypertension	4,753 (15.2)
	Glomerulonephritis	2,553 (8.16)
	Others	2,287 (7.31)
	Unknown	4,406 (14.1)
Cause of death		
	CAD (Cardiovascular ds.)	8,859 (28.31)
	PVD (Peripheral vessel ds.)	3,976 (12.7)
	Infection	6,049 (19.33)
	Cancer	1,469 (4.7)
	Others	10,928 (34.9)

Abbreviations: ESRD, end-stage renal disease; ds, disease

The mortality rate of this cohort was 23.3 % among 134,472 ESRD patients.

The number of ESRD deaths and the distributions by sunlight hours, temperature, humidity, and air−pollutants (the daily concentrations of particulate matter less than 10 μm in diameter [PM_{10}], carbon monoxide [CO], nitrogen dioxide [NO_2], sulfur dioxide [SO_2] and ozone [O_3]) concentrations by city in our study period are shown in Table 2.

Table 2. City-specific descriptive information on the study period, ESRD death, and the levels of environmental variables

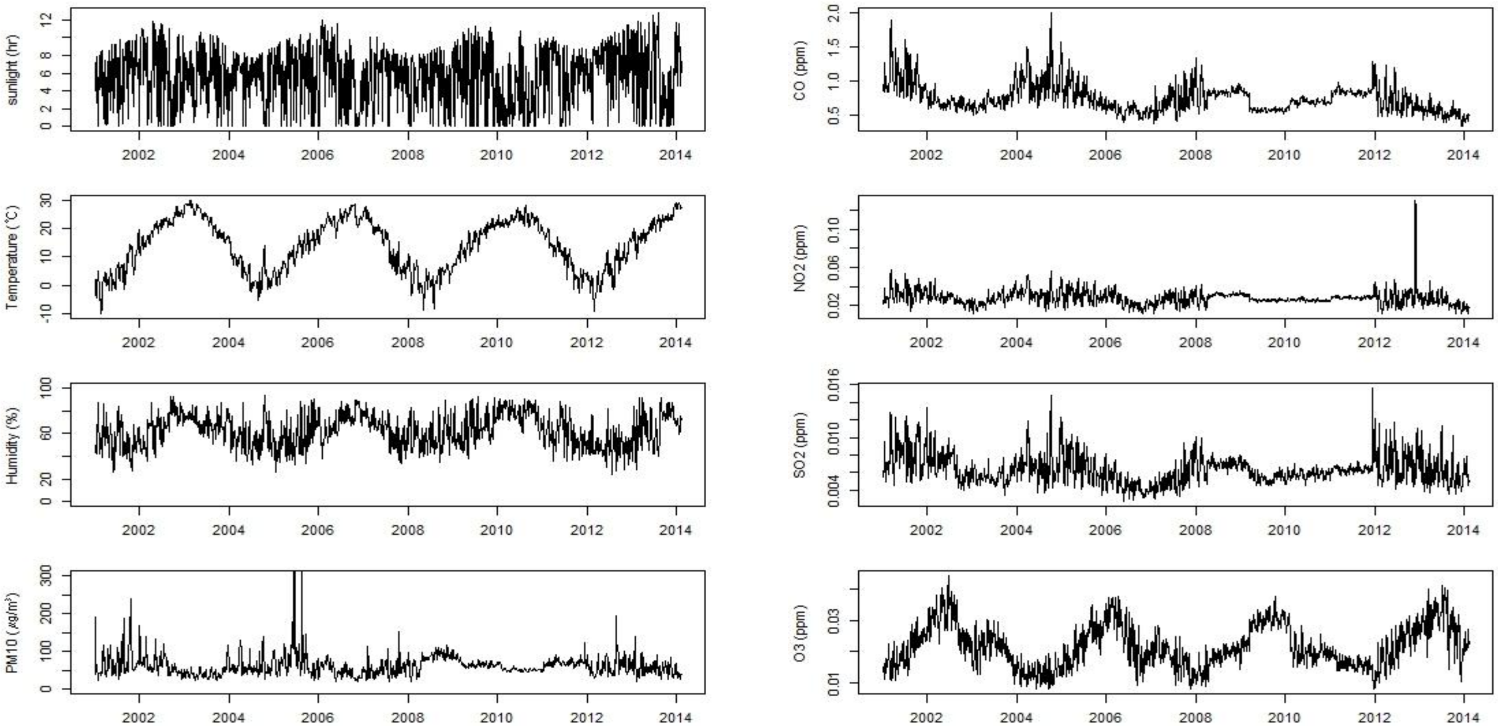
Cities	Study period	Number of ESRD death	Number of monitoring sites	Sunlight (hrs.) Percentiles		Temperature (℃) Percentiles		Humidity (%) Percentiles		PM_{10} ($\mu g/m^3$) Percentiles	
				50	90	50	90	50	90	50	90
Seoul	2001-2014	5,021	27	6.00	10.20	14.40	25.40	61.00	81.30	51.26	96.37
Busan	2001-2014	1,197	16	7.30	10.80	15.90	25.20	63.90	85.58	50.37	88.49
Daegu	2001-2014	856	11	7.20	10.80	15.65	26.80	57.90	79.28	50.18	88.49
Incheon	2001-2014	1,035	11	7.10	10.90	13.90	24.60	69.10	89.00	52.53	93.26
Gwangju	2001-2014	719	5	6.20	10.40	15.30	26.00	67.30	84.10	45.20	86.95
Daejeon	2001-2014	524	6	6.40	10.60	14.30	25.40	67.50	85.10	43.95	81.10
Ulsan	2001-2014	343	13	7.20	10.70	15.40	25.70	64.80	83.80	45.32	80.43
Cities	Study period	Number of ESRD death	Number of monitoring sites	CO (ppm) Percentiles		NO_2 (ppm) Percentiles		SO_2 (ppm) Percentiles		O_3 (ppm) Percentiles	
				50	90	50	90	50	90	50	90
Seoul	2001-2014	5,021	27	0.607	1.002	0.037	0.056	0.005	0.008	0.053	0.087
Busan	2001-2014	1,197	16	0.473	0.786	0.024	0.037	0.006	0.009	0.056	0.087
Daegu	2001-2014	856	11	0.604	1.025	0.026	0.041	0.005	0.010	0.051	0.086
Incheon	2001-2014	1,035	11	0.596	0.958	0.028	0.046	0.007	0.011	0.055	0.089
Gwangju	2001-2014	719	5	0.597	0.976	0.023	0.035	0.004	0.006	0.048	0.075
Daejeon	2001-2014	524	6	0.588	1.096	0.021	0.035	0.004	0.008	0.018	0.035
Ulsan	2001-2014	343	13	0.479	0.772	0.020	0.031	0.006	0.010	0.024	0.037

Abbreviations: ESRD, end-stage renal disease; PM_{10}, particulate matter less than 10μm in diameter; CO, carbon monoxide; NO_2, nitrogen dioxide; SO_2, sulfur dioxide; O_3, ozone

Table 3. Sunlight hour descriptive statistics by cities

	Spring			Summer			Fall			Winter		
Cities	Q1	median	Q3	Q1	median	Q3	Q1	median	Q3	Q1	median	Q3
Seoul	0.45	4.55	9.95	0.45	4.55	9.95	2.25	6.5	9	0.975	5.85	8.675
Busan	0.85	4.15	10.15	2.25	7.4	10.175	4.05	7.2	9.55	4.35	7.8	9.1
Daegu	0.3	4.75	10	1.525	4.7	8.075	3.3	6.8	9.05	4.25	7.2	9
Incheon	0.925	4.95	10.6	0.95	4.95	9.1	4.1	7.4	9.5	1.025	6.1	8.575
Gwangju	0.35	6.35	10.3	0.85	3.7	6.825	3	6.6	8.8	1.325	5.35	7.7
Daejeon	0.3	4.75	10	1.525	4.7	8.075	3.3	6.8	9.05	4.25	7.2	9
Ulsan	0.575	5.65	10.375	1.425	7	10.325	3.8	6.6	9.3	3.775	8.25	9.2

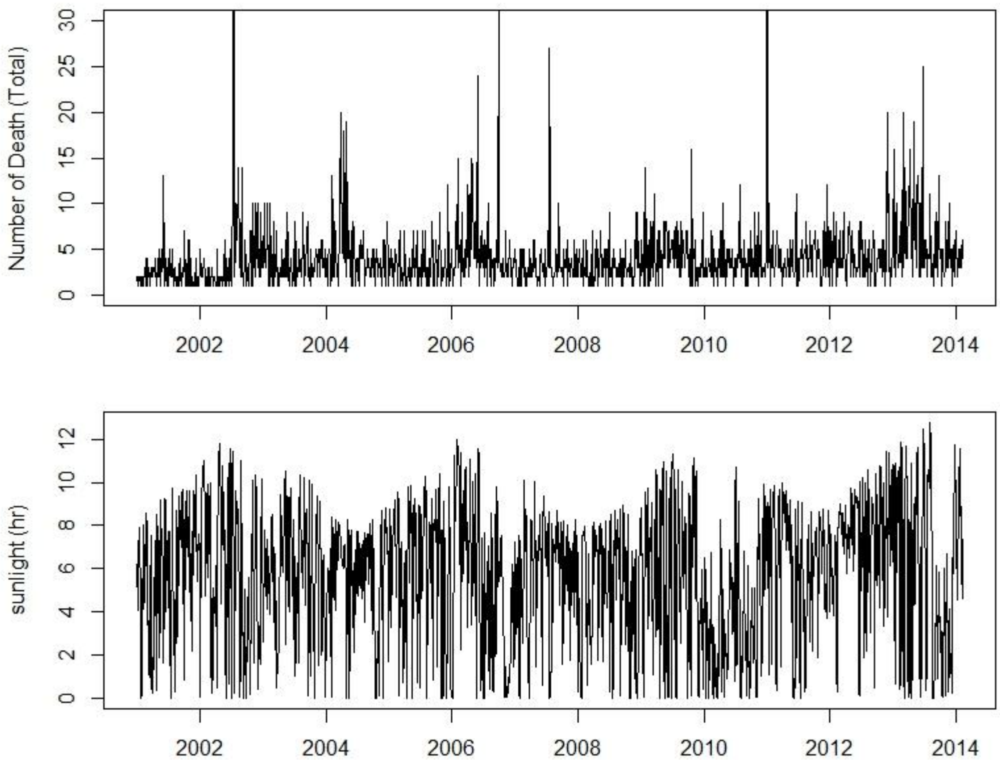
Figure 2. Daily weather and five major air pollutants from 2001 to 2014



3.2. Effect modification by metrological and air pollution factors

The distributions of the meteorological variables (daily sunlight hour, ambient temperature and humidity) and five major pollutants (the daily concentrations of particle matter [PM_{10}], carbon monoxide [CO], nitrogen dioxide [NO_2], sulfur dioxide [SO_2] and ozone [O_3]) differed by city and are shown in Table 2. Temperature, humidity and ozone (O_3) showed strong seasonal patterns in figure 2 shows the time-series plots of both the number of death and exposure (sunlight hours) over time for the entire study period.

Figure 3. The trend of ESRD mortality and sunlight



3.3. Difference in daily levels of environmental variables between case and control periods (2001–2014)

Table 4 shows the daily levels of weather variables and the major five pollutants in the case and control periods. The difference in the daily level and our main exposure variable, sunlight hours per day, was significantly less in the case period compared to the control period for t–test with probability value 0.004.

Table 4. Difference in daily levels of environmental variables between case and control periods (2001-2014)

	Case Period		Control Period		Mean difference	95% Confidence limit	*P for t-test*
	Mean	SD	Mean	SD			
Sun light (hrs.)	5.638	3.906	5.777	3.935	-0.139	(-0.233 -0.046)	0.004
Temperature (℃)	13.813	10.148	13.824	10.191	-0.010	(-0.253, 0.233)	0.934
Humidity (%)	62.849	15.988	62.533	15.992	0.315	(-0.067, 0.698)	0.106
PM_{10} ($\mu g/m^3$)	53.711	30.357	53.695	35.809	0.016	(-0.742, 0.774)	0.967
CO (ppm)	0.623	0.255	0.618	0.242	0.005	(-0.001, 0.011)	0.128
NO_2 (ppm)	0.032	0.017	0.032	0.014	0.000	(0.032, 0.032)	0.600
SO_2 (ppm)	0.006	0.002	0.006	0.002	0.000	(-0.00007, 0.00004)	0.652
O_3 (ppm)	0.991	0.093	0.991	0.095	0.000	(-0.002, 0.003)	0.674

Abbreviations: SD, standard deviation; PM_{10}, particulate matter less than 10μm in diameter; CO, carbon monoxide; NO_2, nitrogen dioxide; SO_2, sulfur dioxide; O_3, ozone.

3.4. Effect of sunlight exposure on ESRD death

There was a statistically significant negative association between daily sunlight hours and ESRD mortality overall (Table 5). Moreover, we identified that patients with comorbidities in diabetes and older adult (> 75 years) have higher mortality in the lower sunlight exposure. A decrease in daily sunlight hours was associated with a decrease in the ESRD related deaths (ORs [95%CI] for overall: 0.99 [0.98−0.99]). The figure 4 also shows that diabetes as a comorbidity and older adults (>75 years) showed strong association with sunlight hours (ORs [95%CI] for diabetes: 0.98 [0.97−0.99], ORs [95%CI] for older adults (>75 years): 0.97 [0.96 - 0.99]). However, there was no associations with the kidney dialysis types (ORs [95%CI] for peritoneal dialysis: 0.98 [0.95−1.01], ORs [95%CI] for hemodialysis: 0.99 [0.98−1.00]). However, hemodialysis had higher relative risk with a probability value of 0.053, as indicated in Table 5, which is close to the statistically significant value 0.05. These analyses were performed with PM_{10} as an air−pollutant potential confounder in Models 1 to 5 with similar pattern in all models (Table 5).

Table 5. Effect modification of association between ESRD death and sunlight exposure with environmental confounders in conditional logistic regression models

		Total		Diabetes		Non-DM		PD		HD		Over 75		Below 75	
		Beta	*P*	*Beta*	*P*	*Beta*	*P*	*Beta*	*P*	*Beta*	*P*	*Beta*	*P*	*Beta*	*P*
Model 1	Sunlight (hrs.)	-0.009	0.042	-0.015	0.016	-0.002	0.721	-0.013	0.419	-0.009	0.053	-0.021	0.02	-0.005	0.317
	Temperature(℃)	0.001	0.781	0.001	0.888	0.002	0.788	0.013	0.351	-0.001	0.765	0.012	0.117	-0.004	0.411
	Humidity (%)	-0.001	0.667	-0.002	0.251	0.001	0.666	-0.003	0.561	0.000	0.796	-0.003	0.244	0.001	0.541
	PM_{10} (㎍/㎥)	0.000	0.838	0.0004	0.459	0.000	0.624	-0.001	0.675	0.000	0.889	0.0004	0.653	0.000	0.791
Model 2	Sunlight (hrs.)	-0.009	0.044	-0.015	0.018	-0.003	0.672	-0.015	0.359	-0.009	0.060	-0.021	0.017	-0.005	0.341
	Temperature(℃)	0.002	0.647	0.000	0.999	0.004	0.560	0.022	0.152	-0.002	0.617	0.014	0.077	-0.004	0.321
	Humidity (%)	-0.001	0.654	-0.002	0.309	0.001	0.609	-0.002	0.619	0.000	0.818	-0.003	0.277	0.001	0.560
	NO2 (ppm)	0.427	0.707	1.383	0.266	-2.463	0.263	-8.970	0.099	0.958	0.388	-2.848	0.311	1.059	0.369
Model 3	Sunlight (hrs.)	-0.009	0.039	-0.015	0.014	-0.002	0.717	-0.013	0.439	-0.009	0.048	-0.021	0.020	-0.005	0.303
	Temperature(℃)	0.002	0.647	0.002	0.755	0.002	0.733	0.010	0.478	0.000	0.945	0.012	0.104	-0.003	0.488
	Humidity (%)	-0.001	0.661	-0.002	0.314	0.001	0.646	-0.003	0.561	0.000	0.805	-0.003	0.003	0.001	0.553
	SO_2 (ppm)	5.125	0.482	-2.914	0.769	-7.830	0.467	16.750	0.519	-7.269	0.326	-11.51	0.454	-2.924	0.717
Model 4	Sunlight (hrs.)	-0.009	0.041	-0.015	0.014	-0.002	0.748	-0.012	0.458	-0.009	0.504	-0.021	0.019	-0.006	0.237
	Temperature(℃)	0.001	0.719	0.001	0.875	0.002	0.726	0.017	0.243	-0.001	0.762	0.010	0.192	-0.003	0.434
	Humidity (%)	-0.001	0.641	-0.002	0.345	0.001	0.721	-0.004	0.459	0.001	0.707	-0.003	0.296	0.001	0.442
	O_3 (ppm)	-0.178	0.791	0.434	0.633	-0.888	0.380	-3.987	0.136	1.504	0.428	1.086	0.457	3.110	0.146
Model 5	Sunlight (hrs.)	-0.009	0.046	-0.015	0.017	-0.002	0.739	-0.014	0.402	-0.009	0.060	-0.021	0.020	-0.005	0.352
	Temperature(℃)	0.000	0.966	-0.001	0.884	0.001	0.912	0.016	0.266	-0.003	0.388	0.013	0.097	-0.006	0.156
	Humidity (%)	-0.001	0.569	-0.002	0.251	0.001	0.671	-0.002	0.637	0.000	0.987	-0.003	0.296	0.001	0.721
	CO (ppm)	0.093	0.221	0.146	0.154	0.027	0.812	-0.268	0.361	0.158	0.033	-0.117	0.445	0.192	0.020

Abbreviations: ESRD, end-stage renal disease; DM, diabetes mellitus; PD, peritoneal dialysis; HD, hemodialysis; PM_{10}, particulate matter less than 10μm in diameter.

3.5. Comparison of the results in Case-crossover designs

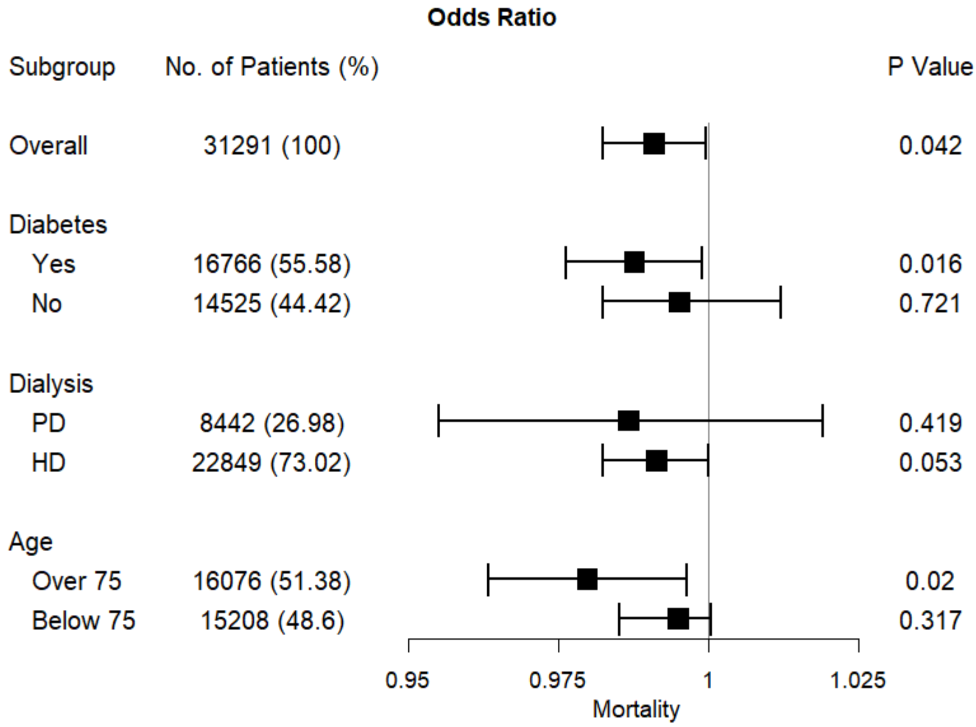
This study employed bi-directional, uni-directional and time-stratified case-crossover design that have different control selections (Table 6). Bi-directional sampling of control time has the significant results compare to other two (ORs [95%CI] for bi-directional: 0.9876 [0.9763- 0.9991], ORs [95%CI] for uni-directional (pre): 0.99 [0.9756-1.005], ORs [95%CI] for time-stratified (matched): 0.0199[0.9741-0.9977]) in diabetes patients. In the bi-directional method produced statistically significant in both for ESRD (end-stage renal disease) and high-risk patients (diabetes and old-adults) to investigate the relationship between sunlight hours and death. In the time-stratified method, high-risk patients (diabetes and older adults) have strong negative association between sunlight exposure and death but not in the overall group. In the uni-directional method produced quite similar results but not significant because the smaller number of controls makes lower power

Table 6. Comparison the results of control selection in the Case-crossover design

Case-crossover design	Criteria	ESRD	Diabetes	Older adult
Bi-directional	Beta	-0.0091	-0.0124	-0.0200
	Std.error	0.0044	0.0059	0.0086
	Odds ratio(95% CI)	0.9910 (0.9825, 0.9995)	0.9876 (0.9763, 0.9991)	0.9802 (0.9637, 0.9969)
	P	0.0379	0.0341	0.0203
Uni-directional (Pre)	Beta	-0.0068	-0.0101	-0.0134
	Std.error	0.0056	0.0075	0.9867
	Odds ratio (95% CI)	0.9932 (0.9823, 1.004)	0.99 (0.9756, 1.005)	0.9867 (0.9653, 1.009)
	P	0.2220	0.1780	0.2300
Time-stratified (matched)	Beta	-0.0080	-0.0142	-0.0207
	Std.error	0.0046	0.0061	0.0091
	Odds ratio(95% CI)	0.9921 (0.9832, 1.001)	0.0199 (0.9741, 0.9977)	0.9795 (0.9622, 0.9971)
	P	0.0797	0.0199	0.0227

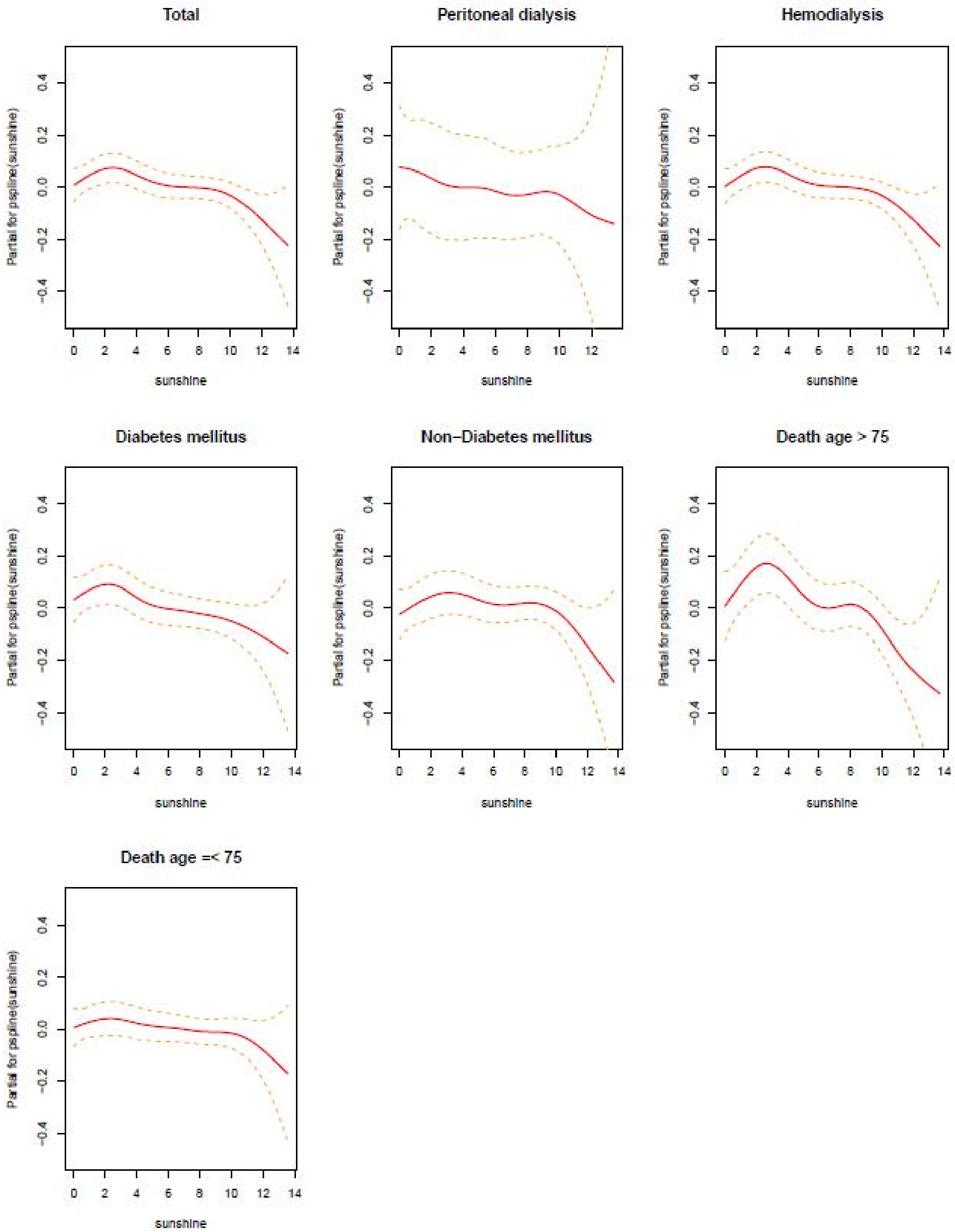
Abbreviations: ESRD, end-stage renal disease

Figure 4. Percent decrease in odds ratios of sunlight exposures for ESRD death



The penalized smoothing spline in Figure 5 also illustrated that lower sunlight exposure was associated with increased risk of mortality between sunlight exposure and ESRD death.

Figure 5. Penalized spline terms on exposure



Chapter 4. Discussion

This is the first study, to our knowledge, to examine the association between short-term sunlight exposure and mortality, in a nationwide ESRD cohort in Korea using a bi-directional case-crossover method. In the present study, the daily sunlight exposure hours were measured in the seven metropolitan cities along with ambient temperature and relative humidity from 2001 to 2014 (14 years). The daily concentrations of PM_{10}, NO_2, SO_2, O_3 and CO were adjusted for as confounders. We have demonstrated that low-level daily sunlight exposures significantly increased the risk of all-cause mortality in dialysis patients, especially in high-risk patients with diabetes and old age >75 years.

To date, there has been limited research on the relationship between sunlight exposure and mortality in ESRD patients. In 2014, Shapiro et al. reported that among 47,286 US dialysis patients, those residing in higher ultraviolet (UV) index regions had lower all-cause mortality compared to those living in moderate-high UV regions.[26] The average of the annual noon-time UV index value was calculated in each patient during the follow-up periods. In our study, we applied a case crossover method and compared the daily sunlight exposure on the day of the mortality event with the daily sunlight exposure for 1 or 2 weeks on the same day of the week. Findings from our study are similar to Shapiro's report that sunlight or UV exposure has a negative correlation with mortality in dialysis patients, but differed in that we also observed the effect of short-term sunlight exposure on mortality.

The principal response to sunlight exposure is elevation of vitamin D status. It is reported that the mean serum concentration of 25(OH)D was about 115 mmol/L in two traditionally living populations in East Africa with lifelong exposure to tropical sunlight.[27] In a cross-sectional study of patients with CKD inhabiting a subtropical region of Brazil where sunlight exposure is elevated throughout the year, the serum 25(OH)D was higher than that found in patients residing in higher-latitude regions. Also, narrow-band UVB exposure is known to increase serum 25(OH)D and 1,25$(OH)_2$D in dialysis patients.

It is well known that vitamin D deficiency, which is caused by limited sunlight exposure, is highly prevalent in patients with ESRD and is associated with various adverse outcomes including death.[14, 30, 31] Cardiovascular disease is one of the most common cause of death in ESRD which is in concordance with our data, while moderate to severe vitamin D deficiency is a risk factor for developing cardiovascular disease. Previous studies showed that lower serum 25(OH)D concentration is associated with an increased risk of cardiovascular events, in not only peritoneal dialysis, but also hemodialysis patients.

Infectious disease remains the leading cause of death in ESRD patients. Increasing evidence demonstrates that vitamin D has immune-modulatory effects on both the innate and adaptive immune systems. $1,25(OH)_2D$ is known to suppress adaptive immunity by inhibiting the proliferation and differentiation of CD4 cells into T helper cell type 1 (Th1) and Th17 cells and by promoting the production of Th2 and regulatory T cells. Activated macrophages by toll-like receptors (TLRs) promote the production of $1,25(OH)_2D$ and then $1,25(OH)_2D$ induces the expression of the antimicrobial peptides, cathelicidin. The association of vitamin D deficiency and infectious events, such as septic shock, respiratory infection, and influenza, is supported by a large number of epidemiologic studies.

As reported previously, several observational studies showed that vitamin D supplement may be associated with reduced risk for cardiovascular and all-cause death among ESRD patients. Contrary to this, a recent review article with 17 randomized controlled trials (RCTs) involving 1,819 patients demonstrated that vitamin D treatment did not affect the risk of cardiovascular or all-cause death.[20] These differences between observational studies and RCTs might be explained by selection bias, because patients with vitamin D supplement are generally healthier than untreated patients. Therefore, large-scale RCTs are needed to assess the efficacy of vitamin D treatment for ESRD patients.

The strengths of our study include the examination of a large, contemporary Korean dialysis population with long-term follow-up of 14 years; comprehensive availability of clinical data allowing for adjustment of multiple weather and air-pollution confounders. Moreover, this study employed a case-crossover design, which is particularly powerful for matching potential confounding factors individually and avoiding the selection bias, healthy-day bias, and healthy-volunteer bias which are the limitations of ecological epidemiologic studies. Although the sunlight exposure has seasonality such as shorter sunlight hours during the winter period (December, January, and February) compared to other seasons, we did not need to adjust the confounder for the season or holiday as we made the controls in the same day of the week within two weeks in the case-crossover design. However, several limitations of our study bear mention. First, we were unable to measure the serum vitamin D concentration in our study population. Second, given that the Korean National Institute of Environmental Research measures the sunlight exposure time in major cities only, our study cohort may not be representative of dialysis patients living in outlier or rural regions.

For the selection of control days in the case-crossover design, several selection schemes, have been used and compared, a recent research showed that three methods, bi-directional and time-stratified (day of the week) matched had yielded no difference in results in the assessment of the association between air pollution exposure and acute myocardial infarction.[44] This experimental comparison of the control selection schemes in the case-crossover study design could support the fact that our use of the bi-directional method in selecting control days would likely produce unbiased estimates.

In conclusion, in the Korean ESRD population from 2001 to 2014, sunlight exposure was inversely correlated with increased risk of all-cause mortality, especially in high-risk patients with diabetes and older adults. Further studies are needed to evaluate the effect of extended sunlight exposure and vitamin D supplement on survival.

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Abstract in Korean (국문초록)

연구 배경

햇빛비타민으로 불려지는 비타민 D 는 자외선 B 가 노출되는 동안 먼저 피부를 통하여 합성된다. 햇빛 또는 음식과 약으로 복용되어 비타민 D 가 활성화 되는 과정은 간에서 첫 번째 합성이 이루어지고 콩팥에서 두 번째 합성이 이루어진다. 말기 신부전증으로 진단된 사구체 여과 율 15% 미만으로 혈액투석 혹은 복막투석을 받고 있는 환자들은 일반인과 비교하여 수산화 되는 과정에서 호르몬 분비 활성도가 적음으로써 떨어진다. 투석 환자의 햇빛 노출과 사망률과의 연관성은 아직 연구된바 없다.

연구 방법

2001 년부터 2014 년까지 한국 말기 신부전 환자 134,478 명 중 7 개 도시에서 31,291 명의 환자를 대상으로 bi-directional case-crossover design 으로 자료를 디자인 하였다. Conditional logistic regression 을 이용하여 ESRD 환자에서 단기 햇빛 노출과 사망률 사이의 관련성을 분석했다. 우리는 일일 농도와 온도, 습도를 고정적인 보정변수로 적용하였고, 이산화질소 (NO2), 이산화황 (SO2), 오존 (O3), 일산화탄소 (CO) 및 미세먼지(PM10)를 대기오염 보정변수로 사용하였다.

연구 결과

연구 대상자의 성별은 연령 (65.6 ± 12.26 (mean ± SD)), 성별 (남성 59.96 %, 여성 41.04 %), 합병증 (당뇨병 53.58 %, 고혈압 40.5 %), 신장 투석 형 (혈액 투석 73.02 %, 복막 투석 26.98 %)이 있었다. 평균 ± SD 추적 기간은 4.68 ± 4.37 년이었다. 대조군에 비해 일일 햇빛 노출은 대조군에 비해 유의하게 감소 하였다 (P = 0.004). 햇빛 노출은 완전히 조절 된 모델에서 전체 원인 사망과 관련이 있었다 (OR [95 % CI] : 0.99 [0.98−0.99], P = 0.042). 당뇨병성신증 (OR [95 % CI] : 0.98 [0.97−0.99], P = 0.016) 또는 75 세 이상 (OR [95 % CI], 0.97 [0.96−0.99], P = 0.020) 으로 당뇨병성 신증이 아닌 환자 나 75 세 미만의 환자보다 사망률이 더 높다.

결론

투석 환자, 특히 당뇨병성신증 및 고령의 고위험 환자에서 햇빛 노출은 모든 원인 사망과 관계가 있음을 보여준다.

주요어: 비타민 D, 햇빛비타민, 햇빛 노출, 사망률, 말기 신부전증,