International Journal of
Environmental Research and Public Health

MDPI

Article

The Risk of the Aggravation of Diabetic Foot According to Air Quality Factors in the Republic of Korea: A Nationwide Population-Based Study

Saintpee Kim [1], Sungho Won [2,3] and Young Yi [4,*]

[1] Department of Orthopedic Surgery, Gangbuk Etteum Hospital, Seoul 01170, Republic of Korea; ksb8060@gmail.com
[2] RexSoft Corps, Seoul 08826, Republic of Korea; won1@snu.ac.kr
[3] Graduate School of Public Health, Seoul National University, Seoul 08826, Republic of Korea
[4] Department of Orthopedic Surgery Foot and Ankle Service, Inje University Paik Central Hospital, Seoul 04551, Republic of Korea
* Correspondence: 20vvin@naver.com

Abstract: This study aims to examine the association between the occurrence of diabetic foot and air quality (SO_2, CO, NO_2, O_3). Open data were collected to conduct a big data study. Patient information was gathered from the National Health Insurance Service, and the National Institute of Environmental Science's air quality data were used. A total study population of 347,543 cases were reviewed (case = 13,353, control = 334,190). The lag period from air quality changes to the actual amputation operation was calculated for each factor. The frequency of diabetic foot amputation in each region was identified and analyzed using a distributed lag non-linear model. Gangwon-do showed the highest relative risks (RRs) for SO_2 and CO, while Chungcheongnam-do exhibited the highest RR for NO_2. Jeju had the highest RR for O_3. Regions like Incheon, Busan, and the capital region also showed significant risk increases. These findings emphasize the importance of tailored air quality management to address diabetic foot complications effectively.

Keywords: diabetic foot; lower extremity amputation; air quality; diabetic vasculopathy; diabetic neuropathy

check for updates

Citation: Kim, S.; Won, S.; Yi, Y. The Risk of the Aggravation of Diabetic Foot According to Air Quality Factors in the Republic of Korea: A Nationwide Population-Based Study. *Int. J. Environ. Res. Public Health* **2024**, *21*, 775. https://doi.org/10.3390/ijerph21060775

Academic Editor: Paul B. Tchounwou

Received: 4 April 2024
Revised: 23 May 2024
Accepted: 7 June 2024
Published: 14 June 2024

Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

The burden of chronic disease has been increasing over the past several decades as life expectancy has increased, and the number of people with diabetes has increased exponentially [1]. Diabetic foot is a typical complication of patients with diabetes in the area of foot ankle orthopedic surgery. Diabetic foot refers to the comprehensive case of sensory changes and blood flow abnormalities in the foot associated with diabetic neuropathy and diabetic vasculopathy, from which ulcers and wounds occur [2]. In particular, it shows a characteristic of not healing easily if foot wounds occur as a result of decreased white blood cell function due to hyperglycemia or ischemia and malnutrition due to impaired circulation. For the above reasons, diabetic feet are not easily treatable, wound recovery is often delayed, and there is a high risk of infection and necrosis leading to atraumatic lower limb amputation.

It was reported that approximately 15 to 25% of people experience diabetic foot at least once in their lifetime [3]. Foot ulcers account for around 85% of the causes of amputations performed on patients with diabetes [3,4]. The prevalence of diabetic foot ulcers and diabetic foot wounds that require surgical treatment is reported to be 2–5% of the total population. Diabetic foot ulcers increase the five-year mortality risk by 2.5 times, and the five-year mortality rate of diabetes-related amputation is over 70%. A study that reported a five-year survival rate of 50–60% for diabetic foot ulcers also reported that diabetic foot ulcers showed worse outcomes than the survival rate for common cancers [5].

According to a previous study on diabetic foot amputation in Korea, the number of patients with diabetic foot and the number of procedures have been continuously increasing every year, and the related social and economic costs are steadily increasing. Preventing the aggravation of diabetic foot and accurately predicting how often it occurs is of the utmost importance in various areas, including public health, the socioeconomic field, and academia.

A dynamic analysis of diabetic foot and analysis of major aggravating factors are fundamental. The aggravating factors can be categorized into personal, socioeconomic, and environmental factors. In Korea, analytical studies on personal and socioeconomic factors are actively conducted to prevent diabetic foot [5], whereas a systematic analysis and big data studies on environmental factors are not conducted as actively.

It has also been reported that the condition of air quality contributes to the occurrence and exacerbation of diabetes as a major external factor [6–8]. The decline in air quality increases the impairment of glucose tolerance in patients with diabetes and degrades the function of the lining of blood vessels through oxidation. However, most studies so far have analyzed the correlation between the decline in air quality and the exacerbation or occurrence of diabetes [6–8]. There have been reports of the correlation between air quality and the worsening of complications [9], but there are no reports of the aggravation of diabetic foot due to changes in air quality. Accordingly, it is necessary to conduct studies related to wound deterioration and amputation due to changes in air quality in patients with diabetic feet through a nationwide big data investigation.

Recently, an epidemiological analysis was conducted in Korea using nationwide big data related to atraumatic lower extremity amputation caused by the aggravation of diabetic foot wounds [10–12]. Studies on diabetic foot- and diabetes-related amputations conducted overseas using big data can be analyzed for each country's regional characteristics and population structure and extended to establishing plans to provide health services, policy interventions to mediate regional inequity, and preventive measures.

Accordingly, using open data to predict and inform risk for the systematic prevention and education of the aggravation of diabetic foot is crucial [7]. The present authors hypothesized that changes in the air quality in Korea would affect the aggravation of diabetic foot, amputation, and vascular surgery through a systematic literature review of previous studies and articles.

This study aimed to analyze the association between the aggravation of diabetic foot and the air quality in all regions and the entire population of Korea by using big data on air quality.

This study examined the association between atmospheric particulates, such as SO_2, NO_2, CO, and O_3, and the frequency of diabetic foot amputation or vascular intervention.

The ultimate purpose of this study was to provide a basis for establishing large-scale diabetic foot management policies and implementing risk notices by tracing the association between air quality and diabetic foot deterioration and wounds and categorizing the identified associations into regions.

2. Materials and Methods

2.1. Study Population

Data were collected for a comprehensive analysis from open sources. Patient information, constituting big data, was extracted from the customized database of the National Health Insurance. The study cohort comprised 347,543 patients with diabetes diagnosed with diabetes or diabetic neuropathy between 2011 and 2019. Exclusion criteria were applied to ensure the integrity of the study cohort. Patients were excluded if they met any of the following criteria: 1503 individuals whose eligibility could not be determined according to the inclusion criteria, 206,688 who were diagnosed with diabetes in 2002, 4701 with less than two diabetes diagnoses, 145,936 with no history of a diabetes diagnosis (ICD 8, E104/114/124/134/144, or G590/632/990) or diabetes medication prescription, and

432 with missing addresses. After applying these exclusion criteria, 13,353 patients who underwent diabetic foot amputation and treatment were included (Figure 1).

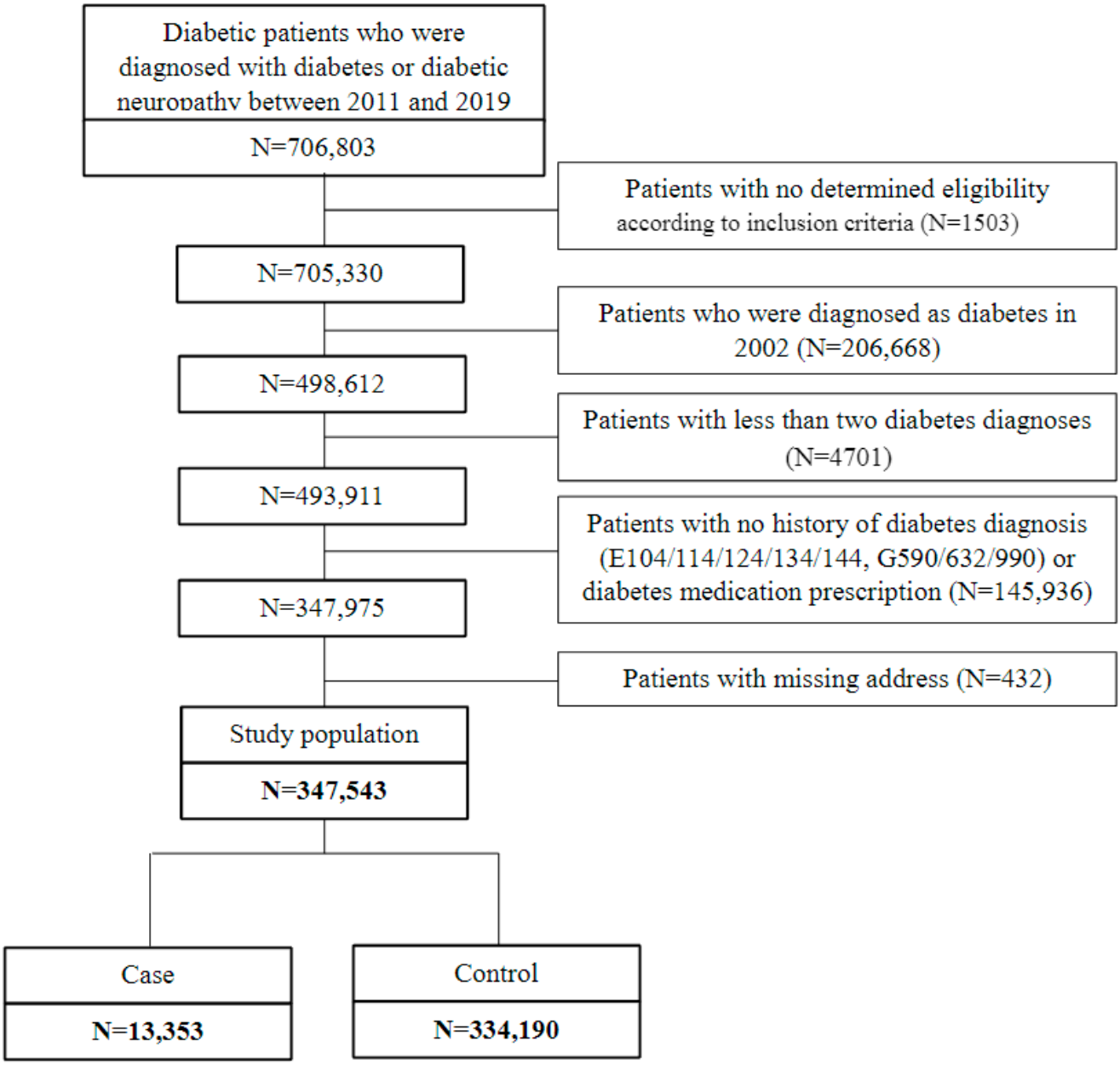


Figure 1. Schematics of subject selection. Note that "Case" means experimental group, and "Control" means control group.

2.2. Air Pollution Data

Big data on air quality were obtained from the Air Korea portal and the National Institute of Environmental Sciences. Each dataset was collected and preprocessed to analyze the impact of air quality factors on diabetic foot prognoses and amputation.

Air quality factors analyzed included sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), and ozone (O_3).

The air quality variables were standardized before the analysis to account for differences in units and scale. All independent variables were treated as quantitative data to ensure consistency in the analysis.

2.3. Health Data

Patient information, including diabetic foot exacerbation events, was extracted from the National Health Insurance database. The onset of diabetic foot aggravation was operationally defined as the first day of the operation or procedure, and relevant analyses were conducted using specified procedure codes. Atraumatic lower limb amputations due to diabetic foot complications were classified into major and minor categories based on procedure codes.

The analysis utilized the Korean Standard Classification of Diseases (KCD) 8 code entered at the time of surgical procedures. Procedure codes for lower limb vascular procedures included M6597, M6605, M6612, M6613, M6620, M6632, and M6633. Codes for vascular operations of the lower extremities included O0161-O0171 and O1643-6. Atraumatic lower limb amputations were categorized into major (N0571, N0572, and N0573) and minor (N0574 and N0575) types (Table 1).

Table 1. The operational definition of the event of diabetic foot deterioration. Surgery codes for lower limb artery procedures and operations and lower extremity amputations due to aggravation of diabetic foot.

Category		Surgery Codes
A.	Lower limb artery procedures	M6597, M6605, M6612, M6613, M6620, M6632, M6633
B.	Lower limb artery operations	O0161-O0171, O1643-6
C.	Lower limb amputation operation	N0571 to N0575 (major amputation: N0571, N0572, N0573; minor amputation: N0574, N0575)

2.4. Statistical Analysis

The lag period, representing the time interval between changes in air quality and subsequent amputation events, was calculated for each air quality factor. The frequency of diabetic foot amputations in each region was analyzed using a distributed lag non-linear model (DLNM).

All statistical analyses were conducted using SAS (version 9.4, SAS Institute, Cary, NC, USA) and R (version 3.6.3, R Foundation for Statistical Computing, Vienna, Austria). The monthly mean of daily climatic factors was calculated and normalized to the annual average and standard deviation to analyze the frequency of all procedures. A seasonal and trend decomposition analysis of time series was performed using X11, Seasonal Extraction in Arima Time Series (seat), and STL (Loess) methods to assess the time trend and seasonality of the monthly frequency of diabetic foot deterioration. The lag effect was determined using distributed lag non-linear models (DLNMs) combined with the Quasi-Poisson generalized linear model to estimate the time required for each climatic and air quality factor to impact the exacerbation of diabetic foot. Lag days ranging from approximately 1 to 14 days were computed based on the correlation estimation between the risk of diabetic foot amputation and DTR (per 1-degree Celsius increase), relative humidity (per 1% increase), and air pollutants (per 1 standard deviation increase) using the DLNM. Air quality variables were standardized before the analysis due to differences in units and scale. All independent variables were treated as quantitative data, and the DLNM was further analyzed using the Poisson generalized non-linear model. The regional risk of diabetic foot amputation was predicted and mapped for 16 cities and provinces using the DLNM, Kor-maps, and T-map packages (version 10.6.0).

3. Results

3.1. Study Population

Among individuals with diabetic foot ulcers, the mean age is 59.94 years, with a standard deviation of 11.81 years. The gender distribution shows a notable difference, with 60.79% being male and 32.21% female. Dyslipidemia is the most prevalent underlying condition among this group, followed by cardiovascular disease, anxiety, cerebrovascular disease, and depression. The distribution of subjects across different regions reveals that Gyeonggi-do has the largest proportion, while Jeju-do has the smallest (Table 2).

Table 2. Baseline characteristics of the study subjects.

Variable	Total (N = 347,543)	No Diabetic Foot Ulcer (N = 334,190)	Diabetic Foot Ulcer (N = 13,353)	*p*-Value
Age (years)	61.69 ± 11.53	61.76 ± 11.52	59.94 ± 11.81	<0.001
Sex, n (%)				<0.001
Male	164,524 (47.34%)	155,472 (46.52%)	9052 (67.79%)	
Female	183,019 (52.66%)	178,718 (53.48%)	4301 (32.21%)	
Baseline comorbidities, n (%) †				
Hypertension	160,871 (46.29%)	155,781 (46.61%)	5090 (38.12%)	<0.001
Coronary artery disease	22,383 (6.44%)	21,445 (6.42%)	938 (7.02%)	0.005
Cerebrovascular disease	30,768 (8.85%)	29,623 (8.86%)	1145 (8.57%)	0.249
Region				<0.001
Seoul	56,423 (16.23%)	54,210 (16.22%)	2213 (16.57%)	
Incheon	13,521 (3.89%)	12,876 (3.85%)	645 (4.83%)	
Gyeong-gi	61,001 (17.55%)	58,559 (17.52%)	2442 (18.29%)	
Busan	27,437 (7.89%)	26,229 (7.85%)	1208 (9.05%)	
Daegu	13,617 (3.92%)	13,032 (3.9%)	585 (4.38%)	
Daejeon	8641 (2.49%)	8232 (2.46%)	409 (3.06%)	
Gwangju	7162 (2.06%)	6903 (2.07%)	259 (1.94%)	
Ulsan	6553 (1.89%)	6272 (1.88%)	281 (2.1%)	
Kyeongsangnam-do	27,378 (7.88%)	26,250 (7.85%)	1128 (8.45%)	
Kyeongsangbuk-do	31,871 (9.17%)	30,797 (9.22%)	1074 (8.04%)	
Jeollanam-do	21,589 (6.21%)	20,847 (6.24%)	742 (5.56%)	
Jeollabuk-do	17,622 (5.07%)	17,016 (5.09%)	606 (4.54%)	
Chungcheongnam-do	23,986 (6.90%)	23,294 (6.93%)	692 (5.18%)	
Chungcheongbuk-do	12,180 (3.5%)	11,726 (3.51%)	454 (3.4%)	
Gangwon-do	15,615 (4.49%)	15,120 (4.52%)	495 (3.71%)	
Jeju-do	2936 (0.84%)	2816 (0.84%)	120 (0.9%)	

Abbreviation: Data was reported as mean ± SD for continuous variables and n (%) for categorical variables. *p*-Value was computed by t-test for continuous variables and chi-square test or Fisher's exact test for categorical variables as appropriate. † Number of samples with each comorbidity is given (ICD 10: Hypertension I10–16, Coronary artery disease I21–I25, Cerebrovascular disease I60, I61, I63, I64, I69).

3.2. Health Data

The study analyzed the annual frequency of lower limb vascular procedures, lower limb vascular operations, and atraumatic lower limb amputations in patients with diabetic foot up to 10 years before the study period. The frequency of all procedures demonstrated a steady increase from 2001 to 2019 (refer to Figure 2, Table A1). No statistically significant cycles were observed for the annual procedures.

The rate of increase in the frequency of lower limb vascular procedures was the highest, while the rate of increase in the frequency of lower limb vascular operations was the lowest. An annual periodicity of lower limb amputations was noted, with significant increases observed in March, July, and November. Additionally, the frequency of amputation operations was relatively low in February and September (Figure 3).

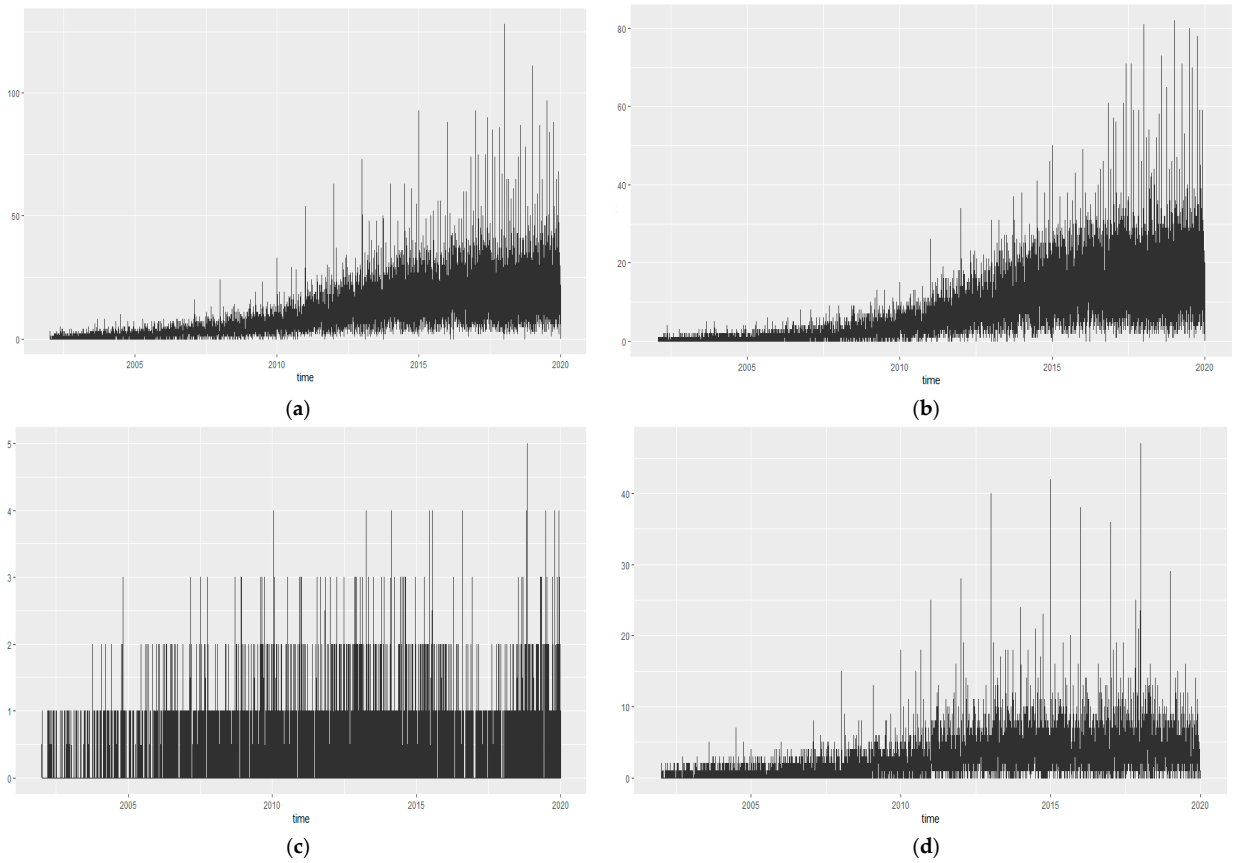


Figure 2. Frequencies of lower limb artery procedures, lower limb artery operations, and lower limb amputation in patients with diabetic foot. (**a**): Frequency of all procedures and operations; (**b**): Frequency of lower limb vascular procedures; (**c**): Frequency of lower limb vascular operations; (**d**): Frequency of lower limb amputations. Detailed values are presented in Appendix A. Y axis: number of cases performed.

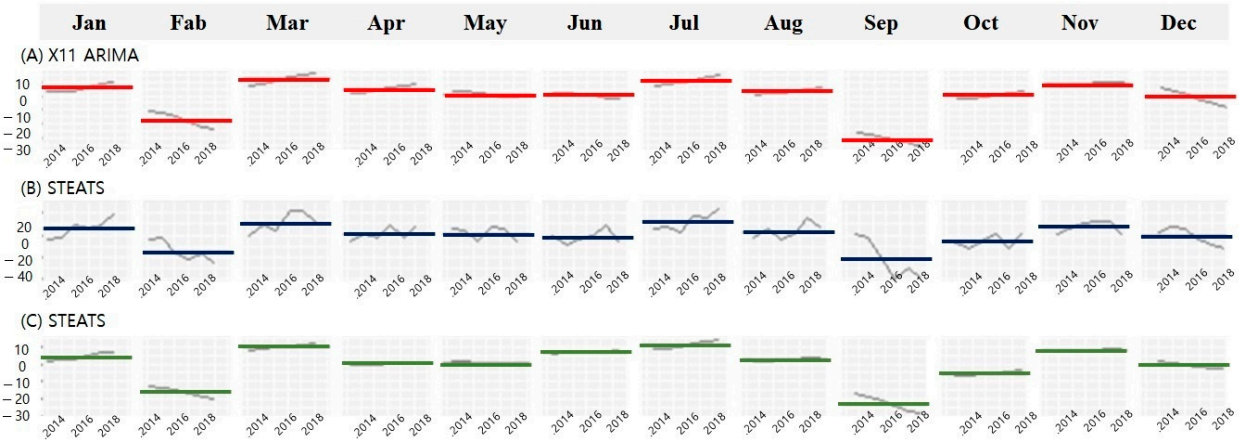


Figure 3. Trends in monthly lower limb amputation rates of patients with diabetic foot analyzed using three different time series decomposition methods. (**A**) X11-ARIMA: integrated autoregressive moving average processes. (**B**) SEATS: seasonal extraction in ARIMA time series. (**C**) STL: seasonal and trend decomposition using Loess methods. (Note) Black line: adjusted amputation rate by each method, blue line: mean of adjusted amputation rate by each method.

3.3. Statistical Analysis (Associations between Air Pollution and Diabetic Foot Ulcer)

3.3.1. Between Air Quality and SO_2

The DLNM analysis results of SO_2 concentration and diabetic foot amputation by region were expressed as RR according to the increase in 1 standard deviation of SO_2.

The highest RR was observed in the Gangwon region, and Incheon showed a significant increase in risk at lag effects of 5 days or more.

Contrarily, some lag days of Daejeon, Ulsan, and Jeollabuk-do reduce the risk (Figure 4). Detailed values are included in Table A2.

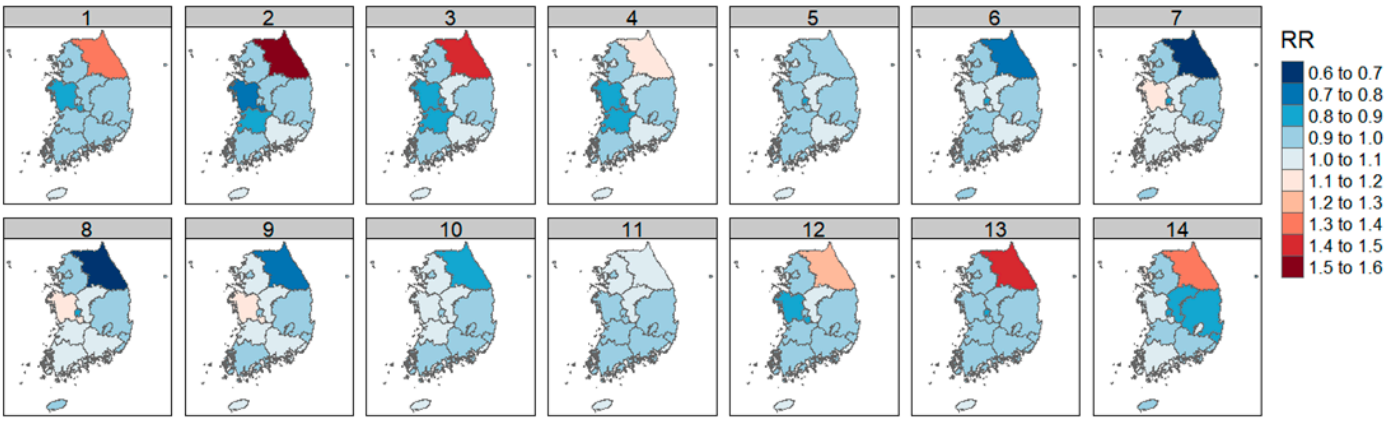


Figure 4. Correlation of diabetic foot amputation risk according to atmospheric sulfur dioxide concentration by region in Republic of Korea.

3.3.2. Between Air Quality and CO

The results of the DLNM analysis of CO concentration and diabetic foot amputation by region were expressed as RR with an increase in 1 standard deviation of CO.

As with SO_2, the highest significant RR was found in the Gangwon region (RR = 1.456, $p < 0.05$, lag = 12; Figure 5).

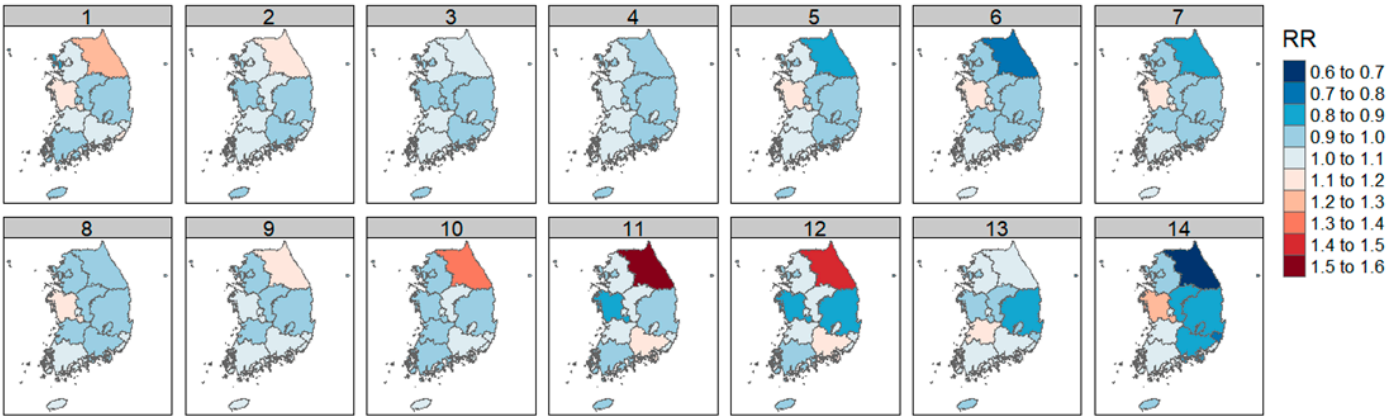


Figure 5. Correlation of diabetic foot amputation risk according to atmospheric carbon monoxide concentration by region in Republic of Korea.

Lag days of 1–4 days and 9 to 13 days in Busan significantly increased the risk (Figure 4). Detailed values are included in Table A3.

3.3.3. Between Air Quality and NO_2

The DLNM analysis results of NO_2 concentration and diabetic foot amputation by region were expressed as RR with an increase in 1 standard deviation of NO_2.

NO_2 concentration significantly increased risk in the capital region, including Seoul, Incheon, and Gyeonggi-do, and in Chungcheongnam-do, Daegu, Ulsan, Gyeongsangbuk-do, and Jeollabuk-do.

In particular, a high RR was observed in Chungcheongnam-do (RR = 1.569, lag = 12; RR = 1.550, lag = 13; Figure 6). Detailed values are included in Table A4.

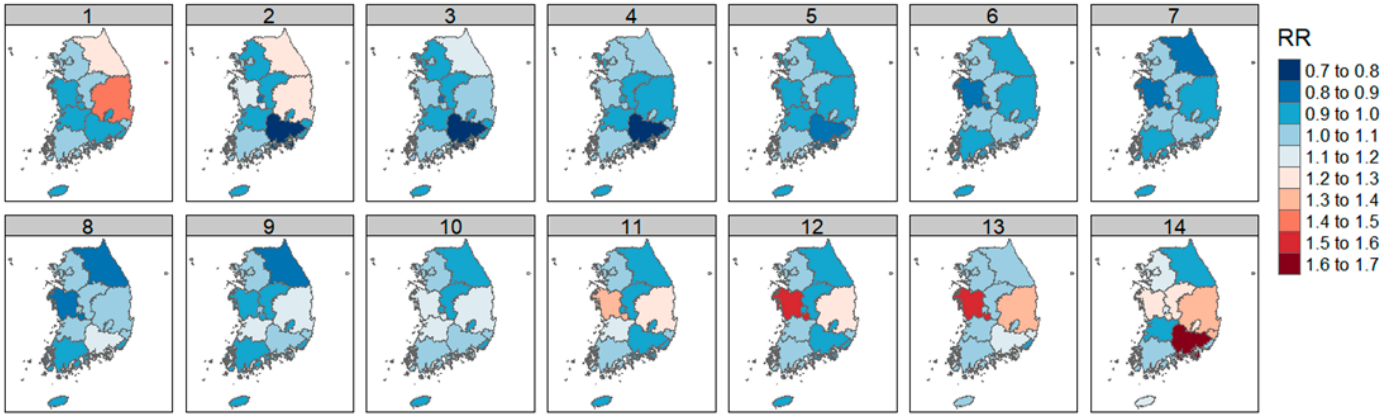


Figure 6. Correlation of diabetic foot amputation risk according to atmospheric nitrogen dioxide concentration by region in Republic of Korea.

3.3.4. Between Air Quality and O_3

The results of the DLNM analysis of O_3 concentration and diabetic foot amputation by region were expressed as RR according to an increase in 1 standard deviation of O_3.

The highest RR was observed in Jeju (RR = 1.148, $p > 0.5$, lag = 14). Seoul, Gyeonggi-do, and Chungcheongbuk-do showed an increase in RR on shorter lag days, while Gwangju, Gyeongsangbuk-do, and Jeollabuk-do showed an increase in RR on longer lag days.

In Busan and Ulsan, a trend of increasing RR over most lag days was observed (Figure 7). Detailed values are included in Table A5.

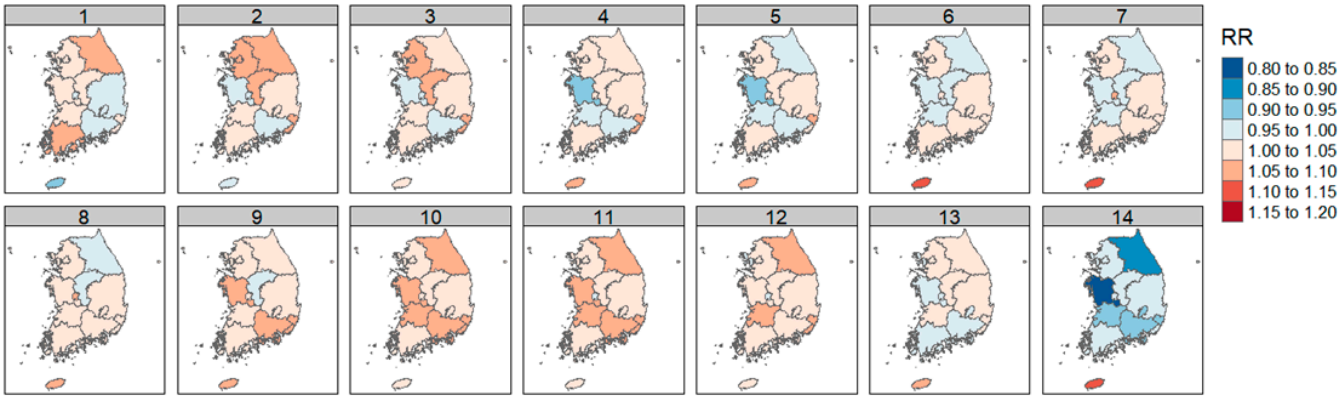


Figure 7. Correlation of diabetic foot amputation risk according to atmospheric ozone concentration by region in Republic of Korea.

4. Discussion

Diabetic foot is aggravated by diabetic vasculopathy, diabetic neuropathy, worsening of wounds and ulcers related to diabetic vasculopathy and neuropathy, and foot infections [3,4]. Prevention and management are particularly essential because of the risk of amputation of the lower limbs in the case of the aggravation of diabetic foot [5]. Patients who undergo the amputation of lower extremities have low survival rates, require a long time to adapt to daily life, and incur high socioeconomic costs due to medical expenditure and disability. The number of diabetic foot amputations in Korea increased every year

from 2011 to 2016, resulting in a 47% increase in socioeconomic costs over five years [13,14]. These results implicate a higher rate of increase in socioeconomic costs for patients with diabetic feet in Korea compared to other developed countries. Therefore, it is necessary to analyze the aggravating factors of patients with diabetic feet, conduct a systematic analysis to prevent the amputation of the lower extremities, and manage and prevent diabetic feet at the national level.

Health education on diabetic foot is always important regardless of when, but an analysis of contributing factors of amputations and prevention are crucial to deter the exacerbation of the disease from progressing to amputation. As part of such an effort, it is necessary to consider changes in air quality factors, such as SO_2, NO_2, CO, and O_3, to manage patients at home, medical institutions, and hospitals.

Although the precise underlying pathways between air pollution and diabetes have not yet been analyzed, various hypotheses have been proposed. It has been reported that exposure to relatively small particles increases the systemic inflammatory response and is associated with the oxidative reaction, endoplasmic reticulum stress, impaired endothelial function, cardiac autonomic nervous system dysfunction, and mitochondrial dysfunction [15–17]. It has also been shown that exposure to air pollutants can cause epigenetic changes, which can lead to changes in indicators of clotting, inflammation, and endothelial function [18,19].

NOx refers to nitrogen oxides, a byproduct of the high-temperature combustion process, and is an indicator of traffic-related air pollution. CO, or black carbon, is a component of particulate matter formed during diesel fuel combustion and is an indicator of air pollution produced by internal combustion engines. Notably, it is an indicator of air pollution caused by diesel engines. Ground-level O_3 is formed when NO_2 and volatile organic compounds react with sunlight and heat. SO_2 is a byproduct of fossil fuel combustion, primarily in industrial resources. These factors may be measured more accurately in models describing the source of air pollutants than in models analyzing a single source of pollutants for individual exposures resulting from potential interactions [20–23]. Therefore, even if the exact mechanism of air pollution inducement and exacerbation of diseases has not been completely proven, this correlation study between the aggravation of diabetic foot and air pollution through a big data analysis is very significant as a model for epidemiological evidence.

In this study, SO_2, CO, NO_2, and O_3 were identified to have significant RR for the aggravation of diabetic foot.

The examination of each air quality factor and weight by region showed a significant increase in RR in Gangwon-do and Incheon for SO_2, in Gangwon-do and Busan for CO, and in the capital area, including Seoul, Incheon, and Gyeonggi-do, and Chungcheongnam-do, Daegu, Ulsan, Gyeongsangbuk-do, and Jeollabuk-do for NO_2. O_3 was shown to increase RR in cases of shorter lag effects in Seoul, Gyeonggi-do, and Chungcheongbuk-do, and in the cases of more prolonged lag effects in Gwangju, Gyeongsangbuk-do, and Jeollabuk-do.

This study also found that various air quality factors appeared to be related to the aggravation of diabetic foot. However, the effects of various air quality factors on the aggravation of diabetic foot differed slightly depending on the characteristics of each region. It is determined that various factors, such as demographic characteristics, socioeconomic differences, number of vehicles per unit area, distribution of internal combustion engines, cumulative exposure to air pollutants, hospital bed distribution by region, traffic conditions, and level of education, affected the regional RRs for each air quality factor.

This study has several limitations. This study used a self-controlled model in conjunction with the self-controlled case series design to control individual-level confounding factors, such as education level, basic medications, and disease history. However, individual-level confounders cannot be directly adjusted in the model, and confounder bias may remain. Further investigation is required to control more environmental information and individual-level variables. In addition, the land area of Korea is around 100,210 km^2, which is very small compared to other countries that study the correlation between atmo-

spheric factors and diabetes, such as the United States and China. Consequently, it was difficult to identify any noticeable changes in air quality factors for each region in this study. Furthermore, although there is open-source data on various information, such as dew point, wind speed, and air pressure, in addition to air quality, no studies have analyzed the association between these factors and diabetes.

Lastly, there is a limitation in that the present study did not include clinically detailed factors, such as the underlying disease of each patient, or personalized data, such as lifelog data among open personal health records.

Nevertheless, this study analyzed the factors affecting the actual living environment through a residence-based analysis rather than one based on the location of medical institutions and attempted to analyze big data more effectively by applying various models of the aggravation of diabetic foot, including vascular intervention, instead of analyzing only the lower extremity amputations as in previous studies.

5. Conclusions

Based on the results of this study, significance was observed between the aggravation of diabetic foot and various air quality factors. However, the air quality factors with high RRs differed by region.

Considering different variables and regional characteristics of air quality factors, it is believed that the cornerstone for regionally customized diabetic foot management should be refined.

Author Contributions: Conceptualization, S.W. and Y.Y.; methodology, S.K.; software, Y.Y.; validation, S.K., S.W., and Y.Y.; formal analysis, S.K.; investigation, S.K. and S.W.; resources, S.K. and S.W.; data curation, S.K. and S.W.; writing—original draft preparation, S.K. and S.W.; writing—review and editing, Y.Y.; visualization, Y.Y.; supervision, Y.Y.; project administration, Y.Y.; funding acquisition, Y.Y. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by a National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (No. 2021R1C1C1013218). This work was supported by a grant from Research year of Inje University in 2022 (20220007).

Institutional Review Board Statement: The Institutional Review Board of Seoul Paik Hospital approved the present retrospective cohort study (IRB approval no. PAIK 2018-08-007, PAIK 2020-04-013, PAIK 2021-04-008).

Informed Consent Statement: Patient consent was waived since anonymous open-source data were used.

Data Availability Statement: Due to the extensive volume of original data, it was not feasible to include it within this manuscript. Nevertheless, the data is available upon request via email. Further inquiries can be directed to the corresponding author.

Acknowledgments: We would like to express our sincere gratitude to National Health Insurance, Air Korea portal, and National Institute of Environmental Sciences for providing access to all the data used in this research. Their contribution has been invaluable in facilitating the data collection process and enabling the analysis conducted in this study.

Conflicts of Interest: Author Sungho Won was employed by the RexSoft Corps. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Abbreviations

DLNM	Distributed lag non-linear model
ICD	International Classification of Diseases
KCD	Korean Standard Classification of Diseases

RR	Relative risk
SO_2	Sulfur dioxide
CO	Carbon monoxide
NO_2	Nitrogen dioxide
O_3	Ozone

Appendix A

Table A1. Annual frequency of outcome. Type 1: lower limb artery procedures, type 2: lower limb artery operations, type 3: lower limb amputation operations.

Year	Type			Total
	1	2	3	
2002	111	30	125	266
2003	197	37	156	390
2004	230	61	214	505
2005	330	68	235	633
2006	492	104	358	954
2007	637	123	445	1205
2008	890	105	556	1551
2009	1149	122	675	1946
2010	1691	141	876	2708
2011	2634	148	1257	4039
2012	3409	196	1400	5005
2013	4315	164	1536	6015
2014	5165	183	1603	6951
2015	5594	159	1559	7312
2016	6359	128	1586	8073
2017	6812	75	1636	8523
2018	6875	156	1697	8728
2019	7618	234	1485	9337
Total	54,508	2234	17,399	74,141

Table A2. Association between SO_2 and risk of diabetic foot ulcer in each region.

Region	Risk Ratio (95% CI) along Lag Day (Range: 1–14) [1]													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Seoul	0.962 (0.924–1.002)	1.010 (0.967–1.056)	1.026 (0.982–1.072)	1.021 (0.984–1.059)	1.005 (0.973–1.039)	0.988 (0.954–1.024)	0.975 (0.939–1.012)	0.969 (0.935–1.004)	0.969 (0.938–1.002)	0.975 (0.940–1.011)	0.983 (0.941–1.026)	0.985 (0.942–1.029)	0.973 (0.934–1.013)	0.936 (0.856–1.023)
Incheon	**1.079 (1.024–1.136)**	1.037 (0.979–1.099)	1.026 (0.969–1.086)	1.031 (0.984–1.081)	**1.045 (1.002–1.089)**	**1.061 (1.014–1.109)**	**1.073 (1.024–1.124)**	**1.079 (1.033–1.127)**	**1.078 (1.036–1.123)**	**1.072 (1.025–1.122)**	**1.065 (1.007–1.125)**	**1.061 (1.003–1.123)**	**1.070 (1.016–1.126)**	1.101 (0.983–1.233)
Gyeong-gi	**0.939 (0.904–0.975)**	0.965 (0.926–1.005)	0.977 (0.938–1.017)	0.980 (0.947–1.014)	0.981 (0.951–1.012)	0.982 (0.950–1.016)	0.986 (0.953–1.022)	0.993 (0.961–1.027)	1.002 (0.971–1.033)	1.008 (0.974–1.044)	1.009 (0.968–1.051)	0.996 (0.955–1.038)	0.963 (0.927–1.000)	0.903 (0.831–0.980)
Busan	1.008 (0.985–1.031)	1.017 (0.992–1.043)	1.011 (0.987–1.036)	1.000 (0.979–1.020)	0.988 (0.970–1.007)	0.982 (0.963–1.002)	0.983 (0.962–1.004)	0.991 (0.971–1.011)	1.004 (0.985–1.023)	1.018 (0.997–1.039)	**1.026 (1.002–1.051)**	1.020 (0.995–1.045)	0.988 (0.965–1.011)	**0.921 (0.876–0.968)**
Daegu	0.977 (0.924–1.034)	0.967 (0.907–1.031)	0.972 (0.913–1.036)	0.984 (0.934–1.037)	0.996 (0.951–1.042)	1.001 (0.953–1.052)	0.998 (0.947–1.052)	0.987 (0.940–1.037)	0.970 (0.927–1.015)	0.951 (0.904–1.002)	**0.937 (0.880–0.998)**	**0.937 (0.879–0.998)**	0.961 (0.909–1.015)	1.024 (0.903–1.162)
Daejeon	0.943 (0.845–1.052)	0.918 (0.814–1.035)	0.895 (0.795–1.007)	**0.878 (0.795–0.970)**	**0.870 (0.795–0.952)**	**0.871 (0.791–0.959)**	**0.881 (0.796–0.975)**	**0.898 (0.816–0.988)**	0.918 (0.840–1.002)	0.934 (0.849–1.028)	0.940 (0.839–1.054)	0.926 (0.825–1.040)	**0.882 (0.791–0.982)**	0.800 (0.636–1.008)
Gwangju	1.012 (0.901–1.136)	0.959 (0.837–1.099)	0.942 (0.822–1.078)	0.943 (0.844–1.054)	0.951 (0.862–1.050)	0.959 (0.861–1.067)	0.960 (0.857–1.076)	0.955 (0.858–1.063)	0.944 (0.857–1.041)	0.936 (0.841–1.041)	0.938 (0.823–1.068)	0.964 (0.845–1.098)	1.033 (0.928–1.150)	1.180 (0.918–1.517)
Ulsan	**0.942 (0.898–0.989)**	**0.949 (0.902–0.999)**	0.954 (0.907–1.002)	**0.958 (0.919–0.998)**	0.963 (0.927–1.000)	0.969 (0.931–1.009)	0.978 (0.937–1.020)	0.986 (0.948–1.026)	0.993 (0.957–1.029)	0.994 (0.955–1.035)	0.987 (0.940–1.036)	0.966 (0.919–1.016)	**0.926 (0.883–0.972)**	**0.865 (0.782–0.957)**
Kyeongsangnam-do	0.982 (0.833–1.158)	1.054 (0.863–1.286)	1.088 (0.891–1.329)	1.095 (0.937–1.280)	1.083 (0.949–1.236)	1.062 (0.916–1.232)	1.039 (0.887–1.218)	1.019 (0.883–1.176)	1.004 (0.886–1.137)	0.994 (0.853–1.159)	0.990 (0.809–1.213)	0.989 (0.805–1.215)	0.986 (0.834–1.165)	0.975 (0.632–1.506)
Kyeongsangbuk-do	0.950 (0.890–1.014)	0.972 (0.903–1.047)	0.975 (0.907–1.049)	0.969 (0.913–1.029)	0.961 (0.912–1.014)	0.958 (0.904–1.014)	0.960 (0.903–1.021)	0.969 (0.915–1.026)	0.982 (0.932–1.035)	0.995 (0.938–1.056)	1.000 (0.930–1.076)	0.987 (0.916–1.063)	0.944 (0.883–1.009)	0.863 (0.740–1.005)
Jeollanam-do	0.971 (0.925–1.019)	0.944 (0.891–1.001)	0.946 (0.893–1.003)	0.962 (0.918–1.009)	0.983 (0.943–1.024)	0.999 (0.955–1.045)	1.006 (0.959–1.056)	1.002 (0.957–1.049)	0.989 (0.949–1.032)	0.972 (0.928–1.018)	0.958 (0.906–1.013)	0.958 (0.906–1.014)	0.987 (0.942–1.034)	1.065 (0.960–1.183)
Jeollabuk-do	**0.921 (0.851–0.996)**	**0.866 (0.787–0.953)**	**0.865 (0.787–0.952)**	**0.896 (0.829–0.968)**	0.941 (0.880–1.007)	0.987 (0.917–1.061)	1.021 (0.944–1.103)	1.035 (0.963–1.113)	1.029 (0.963–1.099)	1.004 (0.932–1.081)	0.971 (0.886–1.064)	0.942 (0.859–1.032)	0.934 (0.865–1.008)	0.968 (0.806–1.163)
Chungcheongnam-do	0.870 (0.594–1.275)	0.798 (0.525–1.215)	0.822 (0.546–1.238)	0.899 (0.638–1.265)	0.998 (0.734–1.359)	1.091 (0.784–1.519)	1.149 (0.809–1.631)	1.153 (0.826–1.610)	1.106 (0.816–1.499)	1.025 (0.741–1.418)	0.942 (0.638–1.390)	0.888 (0.588–1.343)	0.901 (0.607–1.337)	1.042 (0.494–2.198)
Chungcheongbuk-do	0.977 (0.921–1.038)	0.994 (0.926–1.066)	1.006 (0.938–1.078)	1.015 (0.961–1.073)	1.024 (0.976–1.075)	1.032 (0.979–1.089)	1.040 (0.982–1.101)	1.046 (0.992–1.103)	1.048 (0.998–1.100)	1.044 (0.986–1.105)	1.029 (0.958–1.106)	1.001 (0.931–1.075)	0.955 (0.898–1.015)	0.888 (0.762–1.034)
Gangwon-do	1.348 (0.688–2.643)	1.576 (0.778–3.196)	1.462 (0.740–2.892)	1.200 (0.681–2.113)	0.950 (0.564–1.599)	0.775 (0.434–1.385)	0.683 (0.363–1.287)	0.666 (0.357–1.245)	0.721 (0.397–1.310)	0.852 (0.452–1.606)	1.057 (0.515–2.171)	1.298 (0.629–2.677)	1.456 (0.735–2.883)	1.348 (0.334–5.439)
Jeju-do	1.017 (0.894–1.158)	1.045 (0.902–1.210)	1.044 (0.905–1.205)	1.029 (0.916–1.155)	1.009 (0.909–1.121)	0.994 (0.884–1.117)	0.987 (0.870–1.118)	0.990 (0.880–1.113)	1.003 (0.900–1.117)	1.022 (0.904–1.154)	1.041 (0.896–1.208)	1.050 (0.903–1.220)	1.037 (0.909–1.182)	0.987 (0.729–1.338)

[1] Risk ratio: per 1 SD increase, estimated from a quasi-Poisson generalized linear model, combined with a distributed lag non-linear model. Adjusted for CO, O_3, NO_2, PM_{10}. **Bold content**: p value < 0.05.

Table A3. Association between CO and risk of diabetic foot ulcer in each region.

Region	Risk Ratio (95% CI) along Lag Day (Range: 1–14) [1]													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Seoul	1.010 (0.973–1.048)	1.000 (0.957–1.045)	0.995 (0.953–1.040)	0.993 (0.959–1.029)	0.993 (0.962–1.025)	0.994 (0.961–1.029)	0.995 (0.960–1.032)	0.996 (0.962–1.031)	0.996 (0.965–1.027)	0.994 (0.959–1.030)	0.990 (0.948–1.034)	0.984 (0.943–1.028)	0.976 (0.941–1.013)	0.966 (0.883–1.057)
Incheon	**0.900 (0.838–0.965)**	0.958 (0.884–1.038)	0.988 (0.913–1.071)	0.998 (0.934–1.065)	0.992 (0.936–1.051)	0.977 (0.917–1.040)	0.959 (0.896–1.025)	0.941 (0.883–1.003)	**0.927 (0.874–0.984)**	**0.919 (0.860–0.982)**	**0.917 (0.846–0.993)**	0.922 (0.850–1.000)	0.933 (0.869–1.003)	0.950 (0.808–1.117)
Gyeong-gi	1.005 (0.971–1.041)	1.031 (0.990–1.073)	1.032 (0.991–1.075)	1.020 (0.987–1.055)	1.004 (0.974–1.034)	0.988 (0.957–1.021)	0.979 (0.946–1.013)	0.977 (0.946–1.009)	0.983 (0.954–1.012)	0.994 (0.961–1.028)	1.006 (0.966–1.048)	1.014 (0.973–1.056)	1.008 (0.973–1.044)	0.979 (0.900–1.064)
Busan	**1.107 (1.052–1.166)**	**1.091 (1.032–1.155)**	**1.073 (1.015–1.134)**	**1.056 (1.008–1.106)**	1.043 (0.999–1.088)	1.036 (0.989–1.085)	1.035 (0.985–1.087)	1.040 (0.993–1.090)	**1.049 (1.005–1.096)**	**1.060 (1.010–1.113)**	**1.068 (1.008–1.133)**	**1.069 (1.008–1.133)**	**1.055 (1.000–1.114)**	1.021 (0.904–1.153)
Daegu	0.987 (0.941–1.035)	1.025 (0.972–1.080)	1.026 (0.974–1.082)	1.010 (0.966–1.055)	0.988 (0.950–1.028)	0.972 (0.931–1.014)	0.965 (0.923–1.009)	0.970 (0.930–1.012)	0.985 (0.947–1.024)	1.003 (0.960–1.048)	1.016 (0.964–1.071)	1.008 (0.956–1.063)	0.962 (0.916–1.011)	**0.865 (0.775–0.966)**
Daejeon	0.975 (0.920–1.033)	0.979 (0.917–1.045)	0.985 (0.923–1.051)	0.992 (0.941–1.046)	0.999 (0.953–1.046)	1.003 (0.955–1.055)	1.007 (0.955–1.061)	1.009 (0.960–1.060)	1.010 (0.965–1.057)	1.012 (0.962–1.066)	1.017 (0.956–1.083)	1.027 (0.964–1.094)	1.046 (0.989–1.105)	1.076 (0.946–1.224)
Gwangju	**0.936 (0.880–0.995)**	0.987 (0.918–1.061)	0.999 (0.929–1.075)	0.989 (0.932–1.049)	0.968 (0.920–1.020)	0.949 (0.897–1.003)	**0.936 (0.882–0.994)**	**0.935 (0.883–0.989)**	**0.943 (0.896–0.993)**	0.960 (0.907–1.018)	0.980 (0.913–1.053)	0.994 (0.925–1.067)	0.988 (0.931–1.048)	0.947 (0.820–1.094)
Ulsan	1.037 (0.942–1.142)	1.071 (0.962–1.193)	1.058 (0.950–1.178)	1.025 (0.937–1.121)	0.994 (0.915–1.078)	0.976 (0.893–1.068)	0.979 (0.891–1.076)	1.002 (0.917–1.095)	1.039 (0.957–1.128)	1.078 (0.983–1.182)	1.096 (0.980–1.226)	1.065 (0.952–1.191)	0.956 (0.866–1.055)	**0.762 (0.605–0.959)**

Table A3. *Cont.*

Region	Risk Ratio (95% CI) along Lag Day (Range: 1–14) [1]													
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Kyeongsangnam-do	1.034 (0.836–1.279)	0.995 (0.775–1.278)	0.955 (0.744–1.226)	0.925 (0.753–1.135)	0.911 (0.758–1.094)	0.916 (0.749–1.121)	0.942 (0.759–1.169)	0.986 (0.802–1.211)	1.041 (0.859–1.261)	1.095 (0.884–1.357)	1.130 (0.873–1.463)	1.121 (0.863–1.455)	1.042 (0.821–1.322)	0.882 (0.520–1.497)
Kyeongsangbuk-do	**0.925 (0.859–0.996)**	0.962 (0.880–1.052)	0.982 (0.898–1.073)	0.988 (0.919–1.061)	0.984 (0.924–1.048)	0.976 (0.911–1.046)	0.965 (0.897–1.039)	0.954 (0.890–1.022)	0.942 (0.884–1.004)	0.930 (0.864–1.001)	0.916 (0.837–1.003)	**0.899 (0.822–0.984)**	**0.876 (0.813–0.943)**	0.842 (0.701–1.012)
Jeollanam-do	0.999 (0.958–1.042)	1.004 (0.953–1.058)	1.015 (0.963–1.070)	1.028 (0.985–1.072)	1.036 (0.999–1.074)	1.038 (0.997–1.080)	1.032 (0.988–1.077)	1.019 (0.979–1.061)	1.002 (0.966–1.040)	0.987 (0.945–1.030)	0.977 (0.927–1.031)	0.982 (0.931–1.035)	1.010 (0.968–1.054)	1.077 (0.967–1.199)
Jeollabuk-do	1.021 (0.948–1.100)	1.075 (0.980–1.178)	1.077 (0.982–1.181)	1.050 (0.976–1.130)	1.013 (0.951–1.078)	0.979 (0.913–1.049)	0.957 (0.888–1.031)	0.951 (0.886–1.020)	0.963 (0.903–1.026)	0.990 (0.921–1.065)	1.030 (0.940–1.128)	1.071 (0.979–1.172)	**1.100 (1.023–1.183)**	1.096 (0.910–1.321)
Chungcheongnam-do	1.101 (0.883–1.372)	0.960 (0.763–1.208)	0.957 (0.764–1.199)	1.019 (0.848–1.225)	1.103 (0.940–1.294)	1.169 (0.984–1.389)	1.186 (0.986–1.425)	1.142 (0.961–1.358)	1.052 (0.899–1.231)	0.946 (0.793–1.128)	0.860 (0.692–1.070)	0.832 (0.664–1.042)	0.912 (0.745–1.117)	1.227 (0.786–1.913)
Chungcheongbuk-do	0.991 (0.932–1.053)	1.008 (0.938–1.083)	0.999 (0.929–1.073)	0.979 (0.923–1.038)	0.959 (0.911–1.010)	0.948 (0.896–1.003)	0.948 (0.893–1.007)	0.961 (0.908–1.017)	0.983 (0.934–1.036)	1.009 (0.951–1.070)	1.028 (0.956–1.104)	1.024 (0.954–1.101)	0.982 (0.923–1.045)	0.886 (0.762–1.031)
Gangwon-do	1.244 (0.867–1.784)	1.199 (0.826–1.742)	1.056 (0.739–1.507)	0.915 (0.678–1.234)	0.824 (0.628–1.082)	0.799 (0.600–1.063)	0.843 (0.628–1.132)	0.962 (0.730–1.268)	1.153 (0.886–1.501)	1.381 (1.019–1.871)	1.539 (1.070–2.213)	**1.456 (1.014–2.091)**	1.046 (0.750–1.458)	0.499 (0.236–1.053)
Jeju-do	0.952 (0.836–1.084)	0.923 (0.783–1.090)	0.933 (0.790–1.101)	0.962 (0.842–1.099)	0.998 (0.889–1.121)	1.030 (0.906–1.170)	1.049 (0.915–1.202)	1.049 (0.925–1.190)	1.032 (0.921–1.157)	1.002 (0.876–1.146)	0.966 (0.815–1.144)	0.935 (0.791–1.106)	0.924 (0.809–1.055)	0.948 (0.671–1.339)

[1] Risk ratio: per 1 SD increase, estimated from a quasi-Poisson generalized linear model, combined with a distributed lag non-linear model. Adjusted for SO_2, O_3, NO_2, PM_{10}. **Bold content**: p value < 0.05.

Table A4. Association between NO_2 and risk of diabetic foot ulcer in each region.

Region	Risk Ratio (95% CI) along Lag Day (Range: 1–14) [1]													
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Seoul	1.001 (0.968–1.035)	1.001 (0.965–1.039)	1.011 (0.975–1.048)	1.024 (0.994–1.056)	**1.036 (1.008–1.064)**	**1.043 (1.013–1.073)**	**1.044 (1.012–1.076)**	**1.039 (1.009–1.070)**	**1.031 (1.003–1.059)**	1.022 (0.992–1.053)	1.019 (0.983–1.056)	1.027 (0.990–1.065)	**1.056 (1.021–1.092)**	**1.118 (1.041–1.200)**
Incheon	1.038 (0.955–1.128)	1.002 (0.917–1.095)	0.989 (0.907–1.079)	0.989 (0.919–1.066)	0.998 (0.933–1.069)	1.012 (0.941–1.087)	1.026 (0.952–1.106)	1.039 (0.967–1.117)	1.050 (0.982–1.124)	1.058 (0.984–1.139)	1.065 (0.978–1.161)	1.073 (0.983–1.171)	1.085 (0.998–1.179)	1.106 (0.936–1.308)
Gyeong-gi	1.023 (0.992–1.055)	0.997 (0.964–1.030)	0.997 (0.965–1.030)	1.012 (0.985–1.040)	**1.031 (1.006–1.057)**	**1.047 (1.019–1.075)**	**1.055 (1.025–1.085)**	**1.053 (1.025–1.081)**	**1.043 (1.017–1.069)**	**1.029 (1.001–1.058)**	1.020 (0.986–1.054)	1.025 (0.990–1.060)	**1.058 (1.026–1.091)**	**1.141 (1.069–1.216)**
Busan	**0.942 (0.907–0.980)**	0.960 (0.921–1.000)	0.971 (0.933–1.011)	0.978 (0.945–1.012)	0.980 (0.950–1.011)	0.979 (0.947–1.012)	0.975 (0.942–1.010)	0.971 (0.939–1.003)	**0.966 (0.937–0.997)**	**0.964 (0.931–0.998)**	0.965 (0.927–1.005)	0.972 (0.933–1.013)	0.987 (0.950–1.025)	1.012 (0.934–1.096)
Daegu	0.969 (0.919–1.021)	0.968 (0.914–1.026)	0.983 (0.929–1.041)	1.003 (0.956–1.052)	1.019 (0.976–1.064)	1.025 (0.979–1.073)	1.020 (0.972–1.071)	1.005 (0.960–1.053)	0.986 (0.944–1.029)	0.970 (0.925–1.017)	0.967 (0.914–1.023)	0.993 (0.937–1.051)	**1.067 (1.011–1.125)**	**1.226 (1.096–1.372)**
Daejeon	0.920 (0.845–1.001)	**0.883 (0.806–0.966)**	**0.890 (0.814–0.974)**	**0.922 (0.855–0.995)**	0.961 (0.898–1.029)	0.996 (0.928–1.069)	1.016 (0.944–1.094)	1.018 (0.949–1.093)	1.004 (0.940–1.073)	0.982 (0.913–1.056)	0.964 (0.885–1.050)	0.967 (0.886–1.054)	1.014 (0.936–1.100)	1.146 (0.968–1.355)
Gwangju	**1.086 (1.013–1.165)**	1.030 (0.953–1.114)	0.996 (0.921–1.077)	0.979 (0.917–1.045)	0.973 (0.919–1.031)	0.976 (0.918–1.037)	0.984 (0.922–1.049)	0.994 (0.936–1.057)	1.005 (0.950–1.063)	1.014 (0.952–1.080)	1.020 (0.945–1.100)	1.020 (0.944–1.101)	1.013 (0.947–1.084)	1.000 (0.858–1.164)
Ulsan	1.040 (0.966–1.121)	0.985 (0.908–1.068)	0.981 (0.906–1.062)	1.004 (0.940–1.073)	1.035 (0.975–1.098)	1.060 (0.993–1.130)	1.070 (0.999–1.145)	1.063 (0.996–1.133)	1.043 (0.983–1.107)	1.021 (0.956–1.089)	1.012 (0.936–1.094)	1.038 (0.958–1.124)	**1.131 (1.054–1.215)**	**1.355 (1.162–1.580)**
Kyeongsangnam-do	0.913 (0.666–1.251)	0.743 (0.534–1.032)	0.727 (0.526–1.006)	0.791 (0.595–1.051)	0.893 (0.682–1.170)	1.001 (0.752–1.332)	1.078 (0.802–1.447)	1.100 (0.832–1.455)	1.069 (0.823–1.389)	1.009 (0.760–1.341)	0.961 (0.690–1.340)	0.976 (0.694–1.372)	1.135 (0.833–1.547)	1.653 (0.921–2.969)
Kyeongsangbuk-do	**1.456 (1.242–1.707)**	**1.209 (1.010–1.446)**	1.067 (0.892–1.276)	0.992 (0.853–1.154)	0.963 (0.841–1.103)	0.967 (0.837–1.117)	0.996 (0.856–1.160)	1.045 (0.904–1.207)	1.105 (0.966–1.265)	**1.172 (1.011–1.360)**	**1.236 (1.037–1.474)**	**1.288 (1.079–1.537)**	**1.317 (1.124–1.543)**	1.313 (0.924–1.864)
Jeollanam-do	1.028 (0.970–1.089)	1.048 (0.983–1.117)	1.042 (0.978–1.110)	1.022 (0.969–1.078)	1.000 (0.953–1.050)	0.983 (0.933–1.036)	0.976 (0.923–1.032)	0.979 (0.929–1.032)	0.993 (0.947–1.042)	1.015 (0.962–1.070)	1.037 (0.973–1.106)	1.051 (0.985–1.122)	1.045 (0.986–1.107)	1.003 (0.883–1.138)
Jeollabuk-do	0.941 (0.848–1.044)	0.906 (0.808–1.016)	0.905 (0.808–1.015)	0.927 (0.843–1.020)	0.963 (0.885–1.048)	1.007 (0.921–1.101)	1.051 (0.956–1.154)	1.088 (0.996–1.189)	**1.113 (1.026–1.207)**	**1.120 (1.023–1.226)**	1.106 (0.992–1.234)	1.072 (0.958–1.198)	1.018 (0.919–1.128)	0.950 (0.757–1.192)
Chungcheongnam-do	0.954 (0.687–1.324)	1.107 (0.791–1.549)	1.095 (0.790–1.517)	1.001 (0.757–1.323)	0.901 (0.691–1.175)	0.837 (0.624–1.122)	0.826 (0.604–1.131)	0.876 (0.647–1.187)	0.993 (0.749–1.317)	1.176 (0.873–1.583)	1.396 (0.988–1.972)	**1.569 (1.093–2.254)**	**1.550 (1.101–2.182)**	1.226 (0.661–2.274)
Chungcheongbuk-do	1.020 (0.967–1.076)	0.973 (0.917–1.033)	0.975 (0.919–1.034)	0.999 (0.951–1.050)	1.028 (0.983–1.075)	1.047 (0.998–1.099)	1.049 (0.997–1.103)	1.031 (0.983–1.081)	0.999 (0.956–1.044)	0.965 (0.919–1.014)	0.946 (0.892–1.003)	0.961 (0.906–1.020)	1.043 (0.990–1.100)	**1.253 (1.116–1.406)**
Gangwon-do	1.292 (0.704–2.372)	1.218 (0.645–2.300)	1.127 (0.606–2.097)	1.041 (0.609–1.780)	0.969 (0.588–1.598)	0.918 (0.540–1.563)	0.890 (0.511–1.550)	0.882 (0.518–1.502)	0.894 (0.540–1.482)	0.922 (0.531–1.601)	0.959 (0.502–1.832)	0.993 (0.507–1.947)	1.010 (0.543–1.880)	0.990 (0.323–3.033)
Jeju-do	0.941 (0.802–1.103)	0.936 (0.785–1.116)	0.939 (0.790–1.117)	0.944 (0.817–1.092)	0.948 (0.831–1.082)	0.948 (0.821–1.093)	0.943 (0.811–1.097)	0.936 (0.811–1.080)	0.930 (0.814–1.063)	0.930 (0.802–1.079)	0.944 (0.791–1.128)	0.981 (0.820–1.174)	1.057 (0.902–1.239)	1.197 (0.847–1.691)

[1] Risk ratio: per 1 SD increase, estimated from a quasi-Poisson generalized linear model, combined with a distributed lag non-linear model. Adjusted for SO_2, CO, O_3, PM_{10}. **Bold content**: p value < 0.05.

Table A5. Association between O3 and risk of diabetic foot ulcer in each region.

Region	Risk Ratio (95% CI) along Lag Day (Range: 1–14) [1]													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Seoul	**1.047 (1.015–1.079)**	**1.058 (1.022–1.094)**	**1.054 (1.020–1.090)**	**1.044 (1.016–1.073)**	**1.031 (1.006–1.057)**	1.020 (0.993–1.048)	1.013 (0.984–1.042)	1.009 (0.983–1.037)	1.010 (0.985–1.036)	1.014 (0.986–1.042)	1.016 (0.983–1.051)	1.014 (0.980–1.049)	1.001 (0.970–1.033)	0.972 (0.907–1.042)
Incheon	1.002 (0.960–1.045)	1.003 (0.955–1.053)	1.002 (0.955–1.053)	1.002 (0.962–1.043)	1.002 (0.966–1.038)	1.003 (0.964–1.042)	1.004 (0.964–1.046)	1.006 (0.968–1.046)	1.008 (0.973–1.045)	1.008 (0.969–1.050)	1.005 (0.957–1.056)	0.997 (0.949–1.047)	0.981 (0.940–1.025)	0.956 (0.864–1.057)
Gyeong-gi	**1.037 (1.009–1.066)**	**1.055 (1.024–1.087)**	**1.054 (1.024–1.086)**	**1.044 (1.019–1.070)**	**1.032 (1.009–1.055)**	1.023 (0.999–1.048)	1.020 (0.994–1.046)	1.023 (0.999–1.048)	**1.032 (1.009–1.055)**	**1.042 (1.016–1.068)**	**1.048 (1.017–1.080)**	**1.043 (1.011–1.075)**	1.016 (0.988–1.045)	0.958 (0.900–1.020)
Busan	**1.032 (1.000–1.064)**	**1.064 (1.028–1.102)**	**1.068 (1.032–1.105)**	**1.057 (1.028–1.087)**	**1.042 (1.016–1.069)**	**1.032 (1.004–1.060)**	**1.029 (1.000–1.060)**	**1.037 (1.009–1.066)**	**1.052 (1.026–1.079)**	**1.071 (1.041–1.101)**	**1.084 (1.047–1.121)**	**1.079 (1.043–1.117)**	**1.042 (1.010–1.075)**	0.960 (0.894–1.031)
Daegu	0.985 (0.944–1.029)	1.022 (0.975–1.071)	1.030 (0.984–1.079)	1.024 (0.986–1.064)	1.013 (0.979–1.049)	1.005 (0.968–1.043)	1.003 (0.964–1.043)	1.009 (0.972–1.047)	1.020 (0.986–1.056)	1.034 (0.995–1.074)	1.041 (0.994–1.090)	1.031 (0.984–1.080)	0.991 (0.949–1.036)	0.911 (0.827–1.002)
Daejeon	0.984 (0.939–1.031)	0.972 (0.923–1.024)	0.983 (0.934–1.035)	1.005 (0.963–1.049)	1.029 (0.991–1.069)	**1.048 (1.006–1.091)**	**1.056 (1.011–1.102)**	**1.051 (1.009–1.095)**	1.035 (0.997–1.075)	1.011 (0.969–1.054)	0.985 (0.936–1.036)	0.966 (0.917–1.017)	0.964 (0.919–1.010)	0.991 (0.891–1.102)
Gwangju	**1.110 (1.030–1.197)**	1.073 (0.986–1.168)	1.015 (0.933–1.103)	0.958 (0.894–1.026)	**0.916 (0.862–0.974)**	**0.897 (0.839–0.959)**	**0.902 (0.841–0.968)**	**0.932 (0.872–0.995)**	0.981 (0.924–1.042)	1.042 (0.974–1.115)	**1.097 (1.011–1.190)**	**1.119 (1.031–1.216)**	**1.077 (1.000–1.159)**	0.945 (0.797–1.122)
Ulsan	1.049 (0.986–1.117)	**1.095 (1.022–1.173)**	**1.099 (1.027–1.177)**	**1.082 (1.023–1.144)**	**1.058 (1.007–1.112)**	1.039 (0.984–1.097)	1.031 (0.973–1.093)	1.036 (0.981–1.094)	**1.052 (1.001–1.106)**	**1.074 (1.015–1.135)**	**1.090 (1.019–1.166)**	**1.086 (1.015–1.163)**	1.043 (0.981–1.110)	0.946 (0.820–1.090)
Kyeongsangnam-do	0.978 (0.889–1.076)	0.967 (0.874–1.070)	0.967 (0.876–1.068)	0.977 (0.899–1.062)	0.993 (0.920–1.072)	1.013 (0.932–1.100)	1.032 (0.945–1.127)	1.049 (0.965–1.141)	1.060 (0.981–1.146)	1.063 (0.978–1.155)	1.053 (0.954–1.161)	1.029 (0.931–1.137)	0.989 (0.900–1.086)	0.933 (0.765–1.138)
Kyeongsangbuk-do	1.000 (0.969–1.031)	1.011 (0.976–1.048)	1.017 (0.982–1.053)	1.020 (0.992–1.049)	1.022 (0.997–1.048)	1.025 (0.997–1.053)	1.029 (0.999–1.059)	**1.034 (1.006–1.062)**	**1.039 (1.013–1.065)**	**1.043 (1.013–1.073)**	**1.043 (1.007–1.081)**	**1.038 (1.001–1.076)**	1.023 (0.992–1.056)	0.996 (0.926–1.071)
Jeollanam-do	**1.055 (1.014–1.098)**	1.038 (0.991–1.088)	1.025 (0.979–1.074)	1.015 (0.978–1.054)	1.009 (0.977–1.042)	1.006 (0.971–1.042)	1.006 (0.969–1.044)	1.007 (0.973–1.043)	1.010 (0.977–1.043)	1.011 (0.974–1.049)	1.010 (0.964–1.057)	1.004 (0.958–1.052)	0.991 (0.952–1.032)	0.969 (0.880–1.067)
Jeollabuk-do	1.019 (0.968–1.072)	1.022 (0.964–1.083)	1.011 (0.954–1.071)	0.997 (0.951–1.046)	0.988 (0.947–1.030)	0.988 (0.944–1.034)	1.000 (0.953–1.049)	1.022 (0.976–1.069)	**1.050 (1.007–1.095)**	**1.077 (1.028–1.129)**	**1.092 (1.031–1.156)**	**1.079 (1.018–1.143)**	1.022 (0.971–1.076)	0.910 (0.808–1.026)
Chungcheongnam-do	1.024 (0.905–1.157)	0.982 (0.849–1.135)	0.955 (0.828–1.101)	0.943 (0.839–1.060)	0.946 (0.851–1.052)	0.962 (0.856–1.081)	0.988 (0.873–1.119)	1.021 (0.908–1.147)	1.052 (0.946–1.171)	1.074 (0.953–1.211)	1.074 (0.928–1.242)	1.040 (0.898–1.204)	0.962 (0.842–1.098)	0.837 (0.616–1.137)
Chungcheongbuk-do	1.042 (0.992–1.095)	**1.073 (1.016–1.133)**	**1.069 (1.013–1.127)**	**1.046 (1.001–1.093)**	1.019 (0.979–1.059)	0.996 (0.954–1.039)	0.983 (0.939–1.028)	0.982 (0.941–1.025)	0.994 (0.955–1.034)	1.013 (0.969–1.060)	1.035 (0.980–1.092)	1.047 (0.991–1.106)	1.036 (0.985–1.089)	0.986 (0.882–1.102)
Gangwon-do	1.092 (0.928–1.284)	1.073 (0.902–1.276)	1.041 (0.877–1.235)	1.009 (0.873–1.166)	0.986 (0.865–1.125)	0.977 (0.849–1.124)	0.982 (0.847–1.137)	1.000 (0.871–1.147)	1.027 (0.906–1.165)	1.055 (0.918–1.213)	1.072 (0.905–1.270)	1.062 (0.890–1.268)	1.006 (0.847–1.195)	0.893 (0.624–1.276)
Jeju-do	0.943 (0.873–1.019)	0.979 (0.897–1.068)	1.021 (0.937–1.113)	1.061 (0.988–1.140)	**1.091 (1.023–1.164)**	**1.107 (1.033–1.186)**	**1.106 (1.028–1.189)**	**1.090 (1.017–1.167)**	1.064 (0.997–1.135)	1.036 (0.961–1.117)	1.016 (0.928–1.113)	1.017 (0.929–1.113)	1.053 (0.973–1.139)	1.148 (0.956–1.379)

[1] Risk ratio: per 1 SD increase, estimated from a quasi-Poisson generalized linear model, combined with a distributed lag non-linear model. Adjusted for SO_2, CO, NO_2, PM_{10}. **Bold content**: p value < 0.05.

References

1. Won, J.C.; Lee, J.H.; Kim, J.H.; Kang, E.S.; Won, K.C.; Kim, D.J.; Lee, M.-K. Diabetes Fact Sheet in Korea, 2016: An Appraisal of Current Status. *Diabetes Metab. J.* **2018**, *42*, 415–424. [CrossRef] [PubMed]
2. Stratton, I.M.; Adler, A.I.; Neil, H.A.; Matthews, D.R.; Manley, S.E.; Cull, C.A.; Hadden, D.; Turner, R.C.; Holman, R.R. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. *BMJ* **2000**, *321*, 405–412. [CrossRef] [PubMed]
3. Guariguata, L.; Whiting, D.R.; Hambleton, I.; Beagley, J.; Linnenkamp, U.; Shaw, J.E. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res. Clin. Pract.* **2014**, *103*, 137–149. [CrossRef]
4. Jeffcoate, W.J.; Harding, K.G. Diabetic foot ulcers. *Lancet* **2003**, *361*, 1545–1551. [CrossRef]
5. Chun, D.I.; Kim, S.; Kim, J.; Yang, H.J.; Kim, J.H.; Cho, J.H.; Yi, Y.; Kim, W.J.; Won, S.H. Epidemiology and Burden of Diabetic Foot Ulcer and Peripheral Arterial Disease in Korea. *J. Clin. Med.* **2019**, *8*, 748. [CrossRef]
6. Bailey, M.J.; Naik, N.N.; Wild, L.E.; Patterson, W.B.; Alderete, T.L. Exposure to air pollutants and the gut microbiota: A potential link between exposure, obesity, and type 2 diabetes. *Gut Microbes* **2020**, *11*, 1188–1202. [CrossRef] [PubMed]
7. Honda, T.; Pun, V.C.; Manjourides, J.; Suh, H. Associations between long-term exposure to air pollution, glycosylated hemoglobin and diabetes. *Int. J. Hyg. Environ. Health* **2017**, *220*, 1124–1132. [CrossRef] [PubMed]
8. Sørensen, M.; Poulsen, A.H.; Hvidtfeldt, U.A.; Christensen, J.H.; Brandt, J.; Frohn, L.M.; Ketzel, M.; Andersen, C.; Valencia, V.H.; Lassen, C.F.; et al. Effects of Sociodemographic Characteristics, Comorbidity, and Coexposures on the Association between Air Pollution and Type 2 Diabetes: A Nationwide Cohort Study. *Environ. Health Perspec.* **2023**, *131*, 027008. [CrossRef]
9. Dales, R.E.; Cakmak, S.; Vidal, C.B.; Rubio, M.A. Air pollution and hospitalization for acute complications of diabetes in Chile. *Environ. Int.* **2012**, *46*, 1–5. [CrossRef] [PubMed]
10. Kim, J.K.; Jung, Y.R.; Kim, K.T.; Shin, C.S.; Lee, K.B. A report on diabetic foot and amputation from the Korean health insurance review & assessment service data. *J. Korean Foot Ankle Soc.* **2017**, *21*, 66–69.
11. Park, S.-A.; Ko, S.-H.; Lee, S.-H.; Cho, J.-H.; Moon, S.-D.; Jang, S.-A.; Son, H.-S.; Song, K.-H.; Cha, B.-Y.; Son, H.-Y.; et al. Incidence of diabetic foot and associated risk factors in Type 2 diabetic patients: A five-year observational study. *Korean Diabetes J.* **2009**, *33*, 315–323. [CrossRef]
12. Chung, C.H.; Kim, D.J.; Kim, J.; Kim, H.; Kim, H.; Min, K.W.; Park, S.W.; Park, J.H.; Baik, S.H.; Son, H.S.; et al. Current status of diabetic foot in Korean patients using national health insurance database. *J. Korean Diabetes Assoc.* **2006**, *30*, 372–376. [CrossRef]
13. Won, S.H.; Chung, H.-J.; Lee, J.; Jeon, Y.J.; Chun, D.-I.; Min, T.-H.; Cho, J.; Won, S.; Yi, Y. Diurnal Temperature Ranges in Relation to Lower Limb Amputation Rate of Diabetic Foot in South Korea: A Population Based Nationwide Study. *Int. J. Environ. Res. Public Health* **2021**, *18*, 9191. [CrossRef]
14. Kim, J.; Chun, D.-I.; Kim, S.; Yang, H.-J.; Kim, J.H.; Cho, J.-H.; Yi, Y.; Kim, W.J.; Won, S.H. Trends in lower limb amputation in patients with diabetic foot based on vascular intervention of peripheral arterial disease in Korea: A population-based nationwide study. *J. Korean Med. Sci.* **2019**, *34*, e178. [CrossRef]
15. Brook, R.D.; Jerrett, M.; Brook, J.R.; Bard, R.L.; Finkelstein, M.M. The relationship between diabetes mellitus and traffic-related air pollution. *J. Occup. Environ. Med.* **2008**, *50*, 32–38. [CrossRef]
16. Rajagopalan, S.; Brook, R.D. Air pollution and type 2 diabetes: Mechanistic insights. *Diabetes* **2012**, *61*, 3037–3045. [CrossRef]
17. Thiering, E.; Heinrich, J. Epidemiology of air pollution and diabetes. *Trends Endocrinol. Metab.* **2015**, *26*, 384–394. [CrossRef]
18. Bind, M.A.; Baccarelli, A.; Zanobetti, A.; Tarantini, L.; Suh, H.; Vokonas, P.; Schwartz, J. Air pollution and markers of coagulation, inflammation and endothelial function: Associations and epigene-environment interactions in an elderly cohort. *Epidemiology* **2012**, *23*, 332–340. [CrossRef]
19. Carmona, J.J.; Barfield, R.T.; Just, A.C.; Colicino, E.; Testa, P.; Pafundi, P.; Mehta, A.J.; Peng, C.; Chen, J.; Schwartz, J.; et al. DNA methylation signatures in the Normative Aging Study: Epigenome-wide association analyses of air pollution exposure, biological aging, metabolism, and lung function decline. In Proceedings of the PQG Conference 2013, Harvard School of Public Health, Boston, MA, USA, 14–15 November 2013.
20. Balti, E.V.; Echouffo-Tcheugui, J.B.; Yako, Y.Y.; Kengne, A.P. Air pollution and risk of type 2 diabetes mellitus: A systematic review and meta-analysis. *Diabetes Res. Clin. Pract.* **2014**, *106*, 161–172. [CrossRef]
21. Eze, I.C.; Hemkens, L.G.; Bucher, H.C.; Hoffmann, B.; Schindler, C.; Kuenzli, N.; Schikowski, T.; Probst-Hensch, N.M. Association between ambient air pollution and diabetes mellitus in Europe and North America: Systematic review and meta-analysis. *Environ. Health Perspect.* **2015**, *123*, 381–389. [CrossRef]
22. Andersen, Z.J.; Raaschou-Nielsen, O.; Carstensen, B.; Hvidberg, M.; Jensen, S.S.; Ketzel, M.; Loft, S.; Tjønneland, A.; Overvad, K.; Sørensen, M. Diabetes incidence and long-term exposure to air pollution: A cohort study. *Diabetes Care* **2012**, *35*, 92–98. [CrossRef] [PubMed]
23. Janghorbani, M.; Momeni, F.; Mansourian, M. Systematic review and metaanalysis of air pollution exposure and risk of diabetes. *Eur. J. Epidemiol.* **2014**, *29*, 231–242. [CrossRef] [PubMed]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.