

Article

Health Effects of Air-Quality Regulations in Seoul Metropolitan Area: Applying Synthetic Control Method to Controlled-Interrupted Time-Series Analysis

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Abstract: Despite enormous investment in air-quality regulations, there are only a few studies about the health effects of the air-quality regulations. By applying synthetic control methods to controlled-interrupted time-series analysis, this study aimed to test whether air-quality regulations implemented in Seoul metropolitan area since 2005 had reduced cardiovascular mortality rate in Seoul and Incheon. Each synthetic control for Seoul and Incheon was constructed to predict the counterfactual cardiovascular mortality rate through synthetic control methods. By using a synthetic control as a control group in controlled-interrupted time-series analysis, we tested whether the air-quality regulations had changed the trend of cardiovascular mortality rate in Seoul and Incheon after the intervention. The results showed a significant slope change in cardiovascular mortality rate in Seoul (coefficient: -0.001 , 95% confidence interval (CI): -0.0015 , -0.0004) and Incheon (coefficient: -0.0006 , 95% CI: -0.0012 , 0). This study suggests additional evidence that air-quality regulations implemented in the Seoul metropolitan areas since 2005 had beneficial effects on cardiovascular mortality rate in Seoul and Incheon.

Keywords: air pollution; cardiovascular mortality rate; accountability research; quasi-experimental study; controlled-interrupted time-series analysis; synthetic control method

1. Introduction

As exposure to air pollution became a major public health concern [1–4], diverse air-quality regulations had been introduced worldwide. However, relatively small numbers of studies have been conducted to investigate whether an air-quality regulation had beneficial effects on public health and if it had, how much the air-quality regulation contributed to the improvement of public health (also called the accountability research). Even though there is a growing interest in the health effect of air-quality regulations in recent years, there remains a need for further studies to help decision-makers design more effective policies [5,6].

In South Korea, exposure to particulate matter (PM) especially became the most serious health problem. The budget allocated to reduce PM air pollution has continued to grow from 800 million US dollars in 2016 to 27 billion US dollars in 2019 [7]. Especially in the Seoul metropolitan area, there were massive air-quality regulations since 2005, which had followed a special law enacted to improve the air quality of the Seoul metropolitan area. Although an enormous amount of funds has been invested in air-quality regulations in South Korea, only a few studies were conducted about the health effects of the air-quality regulations. For example, Han et al. (2018) found that the air-quality regulations

implemented in the Seoul metropolitan area after 2005 had beneficial effects on cardiovascular and cerebrovascular deaths [8]. Kim et al. (2019) also found that the same regulations had beneficial effects on reducing hospital visits for asthma [9].

On the other hand, many previous studies—including the studies in South Korea—have used quasi-experimental study designs to evaluate health effects of regulations. These study designs estimate health effects of an intervention by comparing the longitudinal trend of a health outcome between an intervention group and its control group. Therefore, the validity of the results from quasi-experimental study designs is susceptible to the selection of a control group [10,11]. Nevertheless, there is no standard criterion to select a control group in quasi-experimental study designs. Therefore, it is crucial to provide evidence from different control selections and check the robustness of the results.

Previous studies in South Korea have used a single region as a control group with similar characteristics as an intervention group [8,9]. However, results from studies using a single region as a control group can be easily confounded when the single region has any difference in longitudinal trend of potential confounders with the intervention group. To overcome this problem, this study constructed a virtual control group, the ‘synthetic control’, which could prevent these problems. The synthetic control method (SCM) constructs an optimal synthetic control that can predict a counterfactual outcome that would occur if the intervention would not have been implemented in the intervention group [12,13].

Because the air quality in the Seoul metropolitan area has improved after air-quality regulations, this study hypothesizes that the air-quality regulations in the Seoul metropolitan area after 2005 would have led to decreases in cardiovascular mortality rate in Seoul and Incheon. This study tested the hypothesis by applying SCM to controlled-interrupted time-series analysis (C-ITSA), which is one of the most common types of quasi-experimental study designs. Finally, this study aimed to suggest additional evidence about the health effects of air-quality regulations in South Korea.

2. Materials and Methods

2.1. Intervention and Study Population

This study defined an intervention as a series of air-quality regulations implemented in Seoul metropolitan area after 2005. The regulations had been implemented based on a region-specific law, ‘The Special Act on The Improvement of Air Quality in Seoul Metropolitan Area (2003)’, which was set to improve air quality in the Seoul metropolitan area. Even though diverse air-quality regulations were conducted, much of the effort was focused on reducing the emission of air pollutants from on-road mobile sources (Supplementary Table S1) [14].

The Seoul metropolitan area consists of two metropolitan cities, Seoul and Incheon and one province, Gyeonggi. The intervention groups were defined as Seoul and Incheon (Figure 1). Gyeonggi was not included as an intervention group because the regulations were not implemented in some districts in Gyeonggi. To construct the synthetic control, this study also defined potential control groups as each region in South Korea other than the Seoul metropolitan area. The potential control groups should have similar characteristics with the intervention groups, but should not be affected by the intervention of interest. For this reason, the potential control groups include five metropolitan cities (Busan, Daegu, Gwangju, Daejeon and Ulsan) and eight provinces (Gangwon, Chungbuk, Chungnam, Jeonbuk, Jeonnam, Gyeongbuk, Gyeongnam and Jeju) (Figure 1).

The study period was from January 1998 to December 2017. Pre- and post-intervention periods were defined by a descriptive analysis of air quality, not by the time point of the first regulation. The health effects would not have occurred as soon as the implementation of regulations, but it would have followed the improvement of air quality. Moreover, a significant part of the regulations was conducted simultaneously and through several phases. Although the local governments carried out some regulations from 2005, most of the major regulations were implemented after 2007. Therefore,

this study defined the time point from when the health effects would have appeared by a descriptive analysis of air quality.

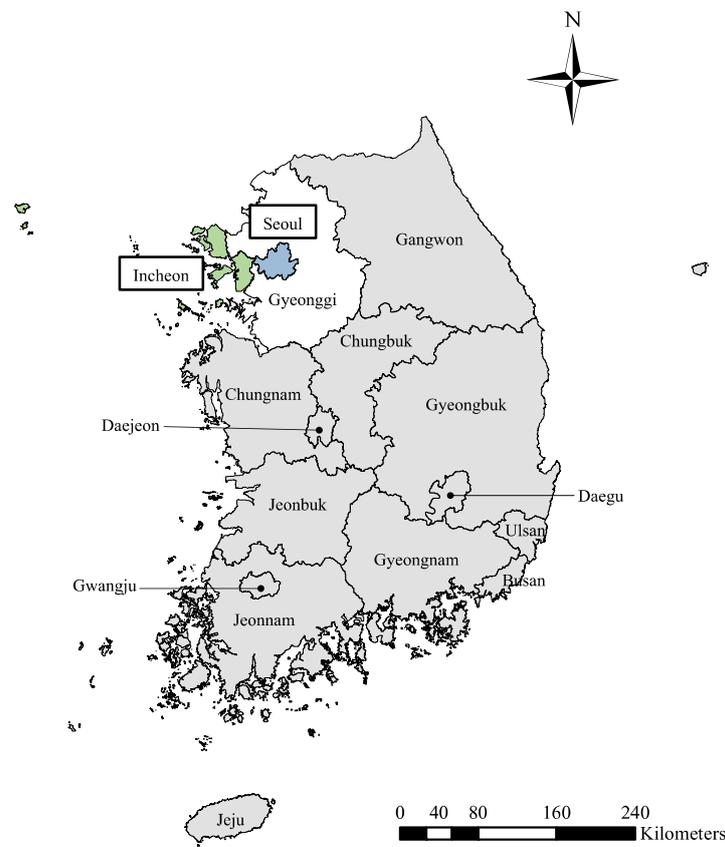


Figure 1. Map of cities and provinces in South Korea (colored regions—the intervention groups; gray regions—the potential control groups; Seoul metropolitan area—Seoul, Incheon and Gyeonggi).

2.2. Data

For the descriptive analysis of air quality, data for hourly measured concentration of particulate matters less than $10\ \mu\text{m}$ (PM_{10}), nitrogen dioxides (NO_2) and sulfur dioxide (SO_2) of each monitoring station in South Korea for 1998–2017 were obtained from the National Institute of Environmental Research. There were 25 and 15 monitoring stations in Seoul and Incheon, respectively, which located in residential areas. The representative value for hourly concentration in each city was computed by averaging hourly measured concentration in the stations. Then, the annual mean concentration was calculated from the 24-h mean for each city.

Daily mortality data were obtained from National Statistics Korea for 1998–2017. The monthly age-standardized mortality rate due to cardiovascular deaths [ICD-10, I00–I99] was calculated for January 1998–December 2017. The age-standardized mortality rate was computed using the direct method with a standard population of South Korea in 2005. For constructing synthetic controls, we used some indicators that predict cardiovascular mortality rate. The predictors included smoking rate [15,16], ambient concentration of PM_{10} [17–19], temperature [20–22], influenza epidemic measured by age-standardized mortality rate for pneumonia [ICD-10, J12–17] [23–25], gross regional domestic product (GRDP) which means the gross domestic product for each region [26], proportion of urban population [27] and the quality of healthcare services measured by age-standardized mortality rate for the avoidable deaths [28,29].

The annual smoking rate in each region during 1998, 2001 and 2005–2017 was calculated using the data from the Korean National Health and Nutrition Examination Survey (K-NHANES). Because K-NHANES was not conducted in 1999–2000 and 2002–2004, missing values during this period were

imputed by predicting values with simple linear regression. The annual smoking rate was assumed to remain the same during months in the same year. The data for the monthly temperature in each region from January 1998 to December 2017 were obtained from the Korea Meteorological Administration. The monthly age-standardized mortality rate due to pneumonia and the avoidable deaths in each region from January 1998 to December 2017 were computed using daily mortality data from the National Statistics Korea. Pneumonia mortality rate and the avoidable mortality rate were used as a proxy of the influenza epidemic and the quality of healthcare services, respectively [23,28]. Annual GRDP and proportion of urban population in each region during 1998–2017 were obtained from the National Statistics Korea. The annual GRDP and annual proportion of urban population were also assumed that the annual value would remain the same during months in the same year.

2.3. Statistical Analysis

2.3.1. Descriptive Analysis of Air Quality

In the descriptive analysis of air quality, the annual ambient concentrations of PM₁₀, NO₂ and SO₂ in Seoul and Incheon were compared with that in the potential control groups. The representative value of the potential control groups was calculated by averaging annual ambient concentration of PM₁₀, NO₂ and SO₂ among the potential control groups. Based on the descriptive results of air quality, we defined the time point from when the health effect would have appeared. In addition—at the stage of C-ITSA—whether the health effect would have appeared abruptly (a step change) or gradually (a slope change) was determined by the descriptive analysis of air quality.

2.3.2. Synthetic Control Method

Using the data of cardiovascular mortality rate and its predictors for the pre-intervention period, optimal synthetic controls were constructed to predict the counterfactual mortality rate for the post-intervention period. Two kinds of weights were determined for each potential control group and each predictor, respectively. Both weights were restricted to have nonnegative values and to sum to one.

At first, the weights for each predictor (v_m in Equation (1)) were selected depending on their relative importance in predicting the mortality rate. Then, the weights for each potential control group (W in Equation (1)) were chosen so that a synthetic control had similar values with the intervention group in cardiovascular mortality rate and the other predictors. The optimal weights for each potential control group are chosen to minimize the Equation (1). Both weights for the potential control groups and the predictors were determined by the *Synth* package in R (version 3.6.0) (For more details, see Abadie et al. 2011) [30].

$$\sum_{m=1}^8 v_m (X_{im} - X_{0m}W)^2 \quad (1)$$

(X_{im} : the value of m -th predictor for the intervention group ($i = 1, 2$), X_{0m} : a 1*13 vector of m -th variable for the potential control groups ($j = 1, \dots, 13$), v_m : a weight for m -th predictor, W : a 13*1 vector of weights for the potential control groups).

After determining the optimal weights for each potential control group W^* , the counterfactual mortality rate at a specific time point in each synthetic control of Seoul and Incheon was estimated as a weighted average of mortality rate in the potential control groups (Equation (2)).

$$Y_{it} = \sum_{j=1}^{13} w_j^* Y_{jt} \quad (2)$$

(t : month, Y_{it} : estimated mortality rate in i -th intervention group at time t ($i = 1, 2$), w_j^* : a weight assigned for j -th potential control group, Y_{jt} : mortality rate in j -th potential control group at time t).

In order to predict the counterfactual mortality rate in Seoul and Incheon accurately, good prediction in the pre-intervention period should be premised. Therefore, the prediction fit of the synthetic controls in the pre-intervention period was checked through prediction errors [12,13,31]. The normalized root mean squared error (NRMSE) was calculated to measure the extent of prediction errors. The NRMSE was calculated by dividing root mean squared error (RMSE) of each variable to the average value of the variable in the intervention group, as shown in Equation (3). The NRMSE of synthetic controls was compared with Daejeon, which was used as a control group in the previous studies in South Korea [8,9]:

$$NRMSE_{ij} = RMSE_{ij} / \bar{X}_{ij} = \frac{1}{\bar{X}_{ij}} \sqrt{\frac{\sum_{t=1}^{T_0} (X_{ijt} - X_{0jt})^2}{T_0}} \tag{3}$$

(*i*: *i*-th intervention group (*i* = 1, 2), *j*: *j*-th predictor, *T*₀: the last months before the intervention, *X*_{*ijk*}: a value of *j*-th variable in *i*-th intervention group at time *k*, *X*_{*0jk*}: a value of *j*-th variable in a synthetic control at time *k*, \bar{X}_{ij} : mean value of *j*-th variable in *i*-th intervention group during pre-intervention period).

2.3.3. Controlled-Interrupted Time-Series Analysis

This study conducted C-ITSA using the generalized Poisson regression model to estimate the health effects of the intervention. In order to adjust the effects of time-varying confounders, the counterfactual mortality rate predicted by synthetic controls was controlled through the weighting method suggested by Yorifuji & Kashima (2016) [32]. As shown in Equation (4), the mortality rate observed in Seoul or Incheon was weighted with the ratio of the mortality rate in a synthetic control at time *t* to the mortality rate in the synthetic control at time *t*₀:

$$E(y) = mor_{i,t} \times (mor_{0,t_0} / mor_{0,t}) \tag{4}$$

(*t*: month, *i*: *i*-th intervention group (*i* = 1, 2) *mor*_{*i,t*}: mortality rate in *i*-th intervention group at time *t*, *mor*_{*0,t*}: mortality rate in a synthetic control at time *t*, *mor*_{*0,t*₀}: mortality rate in a synthetic control at the first month *t*₀ which is January 1998 in this study).

Equation (5) shows the final regression model. Since there was a gradual decrease in the ambient concentration of air pollution, this study modeled that there might be a gradual change (a slope change) in the mortality rate, not an abrupt change (a step change). In Equation (5), β₁ means the trend of the weighted mortality rate in the pre-intervention period and β₂ means the change in the trend after the intervention. If the intervention had effects on reducing cardiovascular mortality rate, an estimated β₂ would have a negative value. The seasonality and autoregression were additionally adjusted for in the model as a covariate. The seasonality was adjusted with a seasonal dummy variable. The autoregression was tested by autocorrelation function (ACF) and partial autocorrelation function (PACF) and was adjusted with the first-order autoregressive error term (AR (1)). SAS version 9.4 was used for the analysis:

$$\log E(y) = \beta_0 + \beta_1 \times t + \beta_2 \times t_{after} + season + AR(1) \tag{5}$$

(*t*: month that ranged from January 1998 to December 2017, *t*_{*after*}: time after the intervention that has zero values during pre-intervention periods and increase by one from a time point of the intervention, *season*: seasonal dummy variable, AR(1): first-order autoregressive error term (only adjusted when there is autoregression)).

2.3.4. Sensitivity Analysis

Several sensitivity analyses were conducted to confirm the robustness of the results. First, because there is no gold standard method to control the counterfactual mortality rate in C-ITSA, the direct adjustment of the counterfactual mortality rate in the synthetic control was used alternatively. We directly adjusted the mortality rate in synthetic controls as a covariate using smoothing spline function.

Secondly, synthetic controls were reconstructed by restricting the inclusion criteria for the potential control group. Although the air-quality regulations in the Seoul metropolitan area were implemented much intensely than any other air-quality regulations in other regions in South Korea, there were similar air-quality regulations in some regions [33]. In particular, Busan, Daegu and Jeonnam (Gwangyang bay) were designated as ‘air quality control region’ in 1999 [34]. These three regions also had planned and implemented comprehensive air-quality regulations during the 2000s. The inclusion of these regions in the potential control group may underestimate the health effects of the intervention. Thus, these regions were excluded from the potential control groups in a sensitivity analysis. For the same reason, synthetic controls were reconstructed excluding neighboring regions (Gangwon, Chungbuk, Chungnam and Daejeon) on the intervention groups to rule out spillover effects of the air-quality regulations in the Seoul metropolitan area.

Third, we tested whether the results were sensitive to the time point of the health effects. Although the reduction of air pollution started in 2007, early regulations were implemented from 2005. In addition, it is possible that the health effects of the improved air quality may have appeared with a lag [35]. Therefore, synthetic controls were reconstructed using 2005 and 2008 as a time point of the health effects.

3. Results

3.1. Descriptive Results of Air Quality

Figure 2 shows the annual ambient concentration of PM₁₀, NO₂ and SO₂ in South Korea during 1998–2017. PM₁₀ concentration in the intervention groups had a rapid decrease compared to the potential control groups. PM₁₀ concentration in Seoul showed a decline since the early 2000s. The early decline of PM₁₀ concentration in Seoul may be due to other air-quality regulations implemented before 2005, for example, the replacement of a diesel bus by a compressed natural gas (CNG) bus [36,37]. PM₁₀ concentration in Incheon showed a remarkable change in longitudinal trend after 2007. PM₁₀ concentration in Incheon had increased until 2006, however, it turned into a decreasing trend in 2007. For the case of NO₂, Seoul and Incheon showed a relatively rapid decrease than the potential control groups since 2007. There was no noticeable difference in the trend of SO₂ concentration between the intervention groups and the potential control groups. To summarize, the effects of the air-quality regulations on air quality in Seoul and Incheon appeared from 2007. The time point of 2007 was also consistent with the time point when most major regulations were started to be implemented.

Based on the descriptive results, the pre-intervention period was defined as from January 1998 to December 2006. The health effects of the air-quality regulations were assumed to appear from January 2007 (the post-intervention period: January 2007–December 2017). In addition, because the air quality had changed gradually, this study modeled in C-ITSA that there would have been gradual health effects on cardiovascular mortality rate as well.

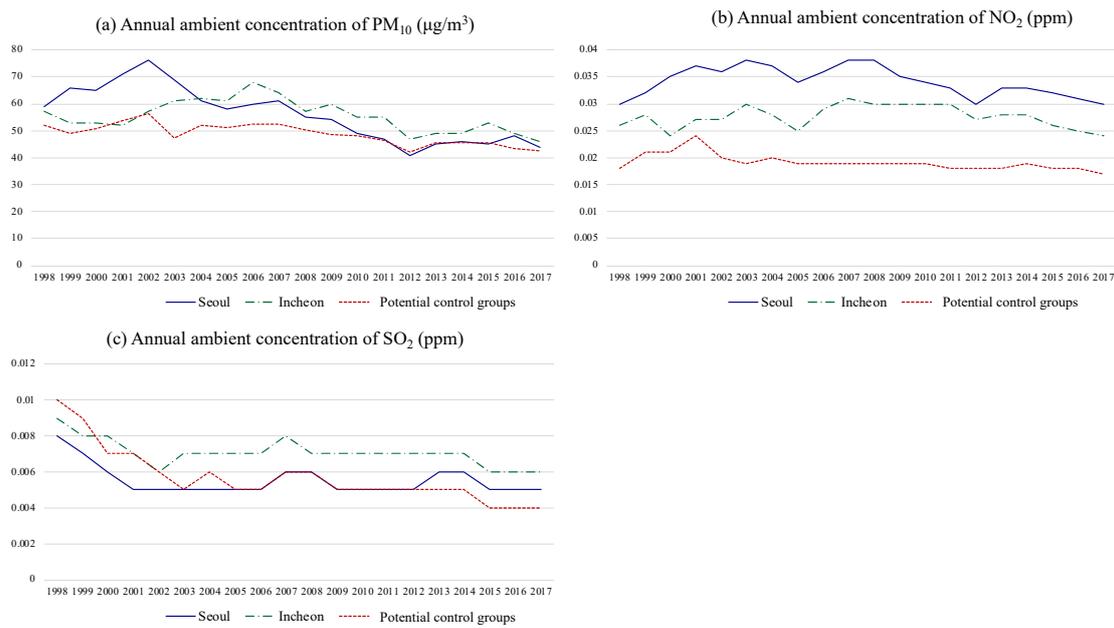


Figure 2. Annual ambient concentration of particulate matters less than 10 µm (PM₁₀), NO₂ and SO₂ in Seoul, Incheon and the potential control groups.

3.2. Synthetic Controls

Synthetic controls for Seoul and Incheon were made as a weighted average of the potential control groups (the weights of the potential control groups are suggested in Supplementary Table S2). Table 1 shows the monthly age-standardized cardiovascular mortality rate in Seoul, Incheon and its synthetic controls for the pre- and post-intervention period. In the pre-intervention period, synthetic controls had a similar level in the mortality rate with its intervention group. In the post-intervention period, synthetic controls showed a higher level in the mortality rate than its intervention group. Figure 3 shows the time-series trend in cardiovascular mortality rate in Seoul, Incheon and its synthetic controls. Similar to the results from Table 1, synthetic controls showed a similar time-series trend in the mortality rate with each intervention group in the pre-intervention period. In the post-intervention period, the intervention groups showed a steeper decreasing trend than in synthetic controls. The discrepancy of the mortality rate in the post-intervention period was more evident in Seoul than in Incheon.

Table 1. Monthly age-standardized cardiovascular mortality rate (per 100,000) in Seoul, Incheon and synthetic controls.

Area	Pre-Intervention Period		Post-Intervention Period	
	Mean	Total	Mean	Total
Seoul	10.19	1101.01	5.63	743.65
Synthetic control of Seoul	10.36	1118.38	6.79	896.64
Incheon	12.48	1347.55	7.46	985.31
Synthetic control of Incheon	12.48	1347.55	7.84	1034.35

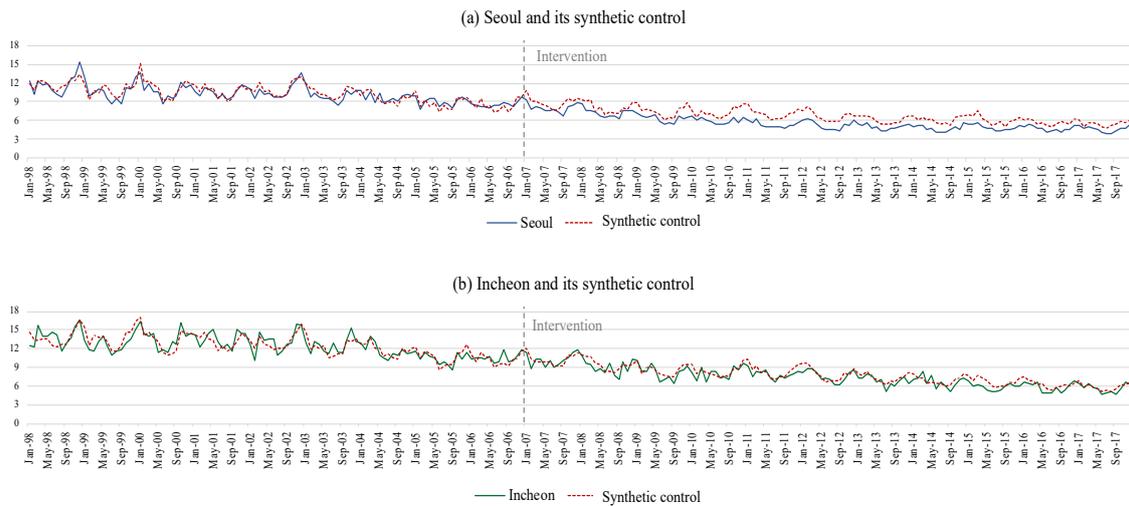


Figure 3. Monthly age-standardized cardiovascular mortality rate (per 100,000) in Seoul, Incheon and synthetic controls.

Table 2 shows the NRMSEs of the predictors in the synthetic controls and Daejeon for the pre-intervention period. Even though NRMSEs for some predictors were larger in the synthetic controls than Daejeon, NRMSE for the main outcome variable (cardiovascular mortality rate), was much smaller in synthetic controls than Daejeon (Seoul vs. synthetic control: 0.07; Seoul vs. Daejeon: 0.14; Incheon vs. synthetic control: 0.08; Incheon vs. Daejeon: 0.18). The mean value of NRSMEs was also smaller in the synthetic controls than Daejeon (Seoul vs. synthetic control: 0.25; Seoul vs. Daejeon: 0.28; Incheon vs. synthetic control: 0.12; Incheon vs. Daejeon: 0.22). Thus, the synthetic controls were more comparable with each intervention group than Daejeon.

Table 2. Normalized root mean squared errors (NRMSEs) in synthetic controls and Daejeon.

	Seoul		Incheon	
	Synthetic Control	Daejeon	Synthetic Control	Daejeon
Cardiovascular Mortality Rate	0.07	0.14	0.08	0.18
Smoking rate	0.07	0.06	0.05	0.10
PM ₁₀ concentration	0.25	0.29	0.17	0.23
Temperature	0.08	0.05	0.13	0.08
Pneumonia mortality rate	0.38	0.60	0.34	0.49
Gross regional domestic product (GRDP)	0.88	0.91	0.06	0.51
% of urban population	0.11	0.00	0.04	0.03
Avoidable mortality rate	0.16	0.15	0.06	0.14
Mean	0.25	0.28	0.12	0.22

3.3. Controlled-Interrupted Time-Series Analysis

Results from C-ITSA are described in Table 3. The slope change of cardiovascular mortality rate toward negative directions was statistically significant in both Seoul and Incheon. β_2 was estimated as -0.001 (95% confidence interval [CI]: $-0.0015, -0.0004$) for Seoul and -0.0006 (95% CI: $-0.0012, 0$) for Incheon. The estimates indicated that the decreasing trend in cardiovascular mortality rate got strengthened after the intervention.

In the sensitivity analyses, this study alternatively used the direct adjustment approach to control the counterfactual mortality rate. The results did not change significantly in both Seoul and Incheon (Supplementary Table S3). When reconstructing synthetic control with restricted potential control groups, we observed consistent results with the main results (Supplementary Table S4). When

redefining the time point of the health effects, the results were also consistent with the main results (Supplementary Table S5). With sensitivity analyses, this study identified the robustness of the results.

Table 3. Main results from controlled-interrupted time-series analysis.

	Seoul	Incheon
	Coefficient (95% CI)	Coefficient (95% CI)
β_0 (Intercept)	−9.0387 (−9.0691, −9.0083) ^b	−8.8282 (−8.8618, −8.7946) ^a
β_1 (Time trend)	−0.0006 (−0.001, −0.0003) ^b	0 (−0.0004, 0.0003) ^a
β_2 (Slope change)	−0.001 (−0.0015, −0.0004) ^b	−0.0006 (−0.0012, 0) ^a

^a adjusted for seasonal dummy variable. ^b adjusted for seasonal dummy variable and autoregressive term.

4. Discussion

This study evaluated the effects of air-quality regulations implemented in Seoul metropolitan area after 2005 on cardiovascular mortality rates by applying SCM to C-ITSA. This study identified synthetic controls would have had a good prediction of the counterfactual mortality rate in Seoul and Incheon. Using the synthetic control as a control group, this study found beneficial effects of the air-quality regulations on cardiovascular mortality rate in both Seoul and Incheon. This study confirmed the robustness of the results through several sensitivity analyses.

Several studies reported the beneficial effects of air-quality regulations on cardiovascular mortality rate [8,32,38–44]. One of the studies evaluated the association between the same air-quality regulations as this study and cause-specific mortality rate, using Daejeon as a control group [8]. Although estimates from this study and Han et al. (2018) cannot be directly compared due to differences in modeling strategy, our results were partially consistent with the results from the study of Han et al. (2018) [8]. They found that cardiovascular mortality rate in Seoul changed −7.3% (95% CI: −11.1, −3.5) in 2008–2009, −10.2% (95% CI: −13.9, −6.5) in 2010–2011 and −8.3% (95% CI: −12, −4.4) in 2012–2013 compared to the referent period, 2004–2006. In contrast, results for Incheon were statistically significant only in 2008–2009 as −4.5% (95% CI: −8.1, −0.7). Results from quasi-experimental study designs can differ by the selection of the control group. Nonetheless, since there is no standard norm to select a control group, it is important to accumulate evidence with different control selections. Our findings consistent with Han et al. (2018) imply possible beneficial effects of the air-quality regulations on cardiovascular mortality rate.

The beneficial effects on cardiovascular mortality rate may be primarily attributed to the reduction in the ambient concentration of PM₁₀ and NO₂. The exposure to ambient PM₁₀ and NO₂ is a well-known risk factor for cardiovascular deaths in South Korea [18,19,45]. However, it is possible for other explanations of how the regulations affected the mortality rate, such as changes in PM composition or behavioral changes related to air pollution [46–48]. When diverse regulations were implemented simultaneously, it is challenging to demonstrate what specific regulations had affected the mortality rate and how each regulation had affected the mortality rate. Therefore, further studies are needed to clarify what and how air-quality regulations affect the mortality rate and quantify how much each regulation contributes to the total health benefit.

There were some limitations to this study. First, we could not include some critical indicators as a predictor due to the unavailability of data, such as alcohol drinking, physical activity or greenness. Nevertheless, this study used diverse predictors that were closely correlated with these unobserved confounders. Since both the main outcome variable and the other predictors of synthetic control are made to have values similar to an intervention group, unobserved confounders correlated with the predictors can be partially controlled in SCM [12,49,50]. Therefore, possible residual confounding effects by the unobserved confounders could be adequately controlled. However, even if SCM has the advantage in reducing the confounding effects from unobserved confounders, it cannot guarantee

the complete elimination of the confounding effects. Therefore, our results should still be interpreted with caution.

Second, other concurrent events may affect cardiovascular mortality rate differentially between each intervention group and the potential control groups. If it had, the beneficial health effects might be due to the concurrent events. However, because most of the health policies in South Korea had been conducted on a national basis, the effects of other health policies may not differ between the intervention groups and the potential control groups. Even though national targets of the Health Plan 2010 and Health Plan 2020 included interregional health equity between the Seoul metropolitan area and the other regions [51], it did not lead to practical policies [52,53]. For this reason, a great part of health policies, for example, expansion of health insurance coverage, awareness campaigns for cardiovascular diseases or anti-smoking policies, was conducted on a national basis [54–56].

Finally, there were some challenges that may violate the assumptions of SCM. An essential assumption of SCM is that potential control groups must not have been affected by the intervention of interest or similar interventions [12]. However, in some potential control groups such as Busan, Daegu and Jeonnam, there had been comprehensive air-quality regulations similar to the intervention of interest in this study. Because the intensity of the regulations was much weaker than in the intervention groups, these regions were included in the main analysis [33]. If the regulations in these regions had been effective, including these regions in the potential control groups could lead to underestimating the health effects in Seoul and Incheon. Nevertheless, we found significant beneficial effects on the mortality rate from the main results. In addition, a sensitivity analysis was conducted excluding these regions from the potential control groups and showed consistent results with the main results.

In addition, neighboring regions of the intervention groups, which were Gangwon, Chungnam, Chungbuk and Daejeon, could be affected by the spillover effects of the air-quality regulations. Air pollutants may be transported to neighboring regions depending upon weather conditions [57–59]. Because the prevailing wind in South Korea is northwesterly in spring and winter, air quality in the intervention groups could affect Gangwon, Chungnam, Chungbuk and Daejeon [60,61]. The spillover effect could underestimate the health effects in Seoul and Incheon if it effectively reduced the mortality rate in the neighboring regions. Nevertheless, we found significant beneficial effects on the mortality rate from the main results. In addition, in the sensitivity analysis excluding the neighboring regions from potential control groups, the results did not differ significantly.

Our study also has several strengths. Although SCM had been continuously suggested as a complementary method to C-ITSA in recent years, there has been no empirical study applying SCM to C-ITSA [62,63]. To the best of our knowledge, this is the first empirical research to suggest the health effects of air-quality regulations by applying SCM to C-ITSA. By using SCM, this study has the following advantages: (1) This study obtained a more comparable control group with the intervention group than previous studies. It would have improved the internal validity of the results by preventing possible residual confounding effects [64,65]; (2) It would have improved the generalizability of the results because the synthetic control was made as a weighted average of several non-intervention groups [64,66]. In addition, a broad range of sensitivity analyses was conducted, and this study confirmed the robustness of the results. Studies evaluating health effects of intervention have large uncertainties that stem from the complex mechanisms from intervention to health endpoints and the situation where randomized experiments are infeasible. Therefore, to identify whether the results are robust to various assumptions is very important [5]. Consequently, this study suggested additional evidence that the air-quality regulations in the Seoul metropolitan areas after 2005 had beneficial effects on cardiovascular mortality rate.

5. Conclusions

This study evaluated the effects of the air-quality regulations in the Seoul metropolitan area on cardiovascular mortality rate by applying SCM to C-ITSA. This study found beneficial effects of the regulations on cardiovascular mortality rate. The findings from this study can provide evidence

that can be used to assess previous policies' effectiveness and present the direction of future policies. However, because there is no gold-standard method to select a control group in C-ITSA so far, the accumulation of evidence through further studies with various methods is needed to provide more compelling evidence.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2073-4433/11/8/868/s1>, Table S1: Air-quality regulations in Seoul metropolitan area (SMA) after 2005, Table S2: Weights of the potential control groups, Table S3: Results from sensitivity analyses using direct adjustment of the counterfactual mortality rate, Table S4: Results from sensitivity analyses reconstructing synthetic controls (SC), Table S5: Results from sensitivity analyses with different time point of the health effects.

Author Contributions: Conceptualization, S.-Y.K. and H.K.; methodology, S.-Y.K. and H.K.; data processing and handling, S.-Y.K.; formal analysis, S.-Y.K.; manuscript writing, S.-Y.K.; reviewing and editing the manuscript, H.K. and J.-T.L.; supervision, J.-T.L. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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