



Adverse health effects of ferronickel manufacturing factory on local residents: An interrupted time series analysis

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ABSTRACT

The first ferronickel manufacturing factory of the Republic of Korea was opened in Gwangyang City on October, 23rd, 2008. There has been public concern regarding heavy metal dust blown from the factory and slag disposal site. Therefore, we evaluated the health impact of the ferronickel factory on Gwangyang City residents by using interrupted time series analysis. We analyzed the monthly incidence patterns of asthma, allergic rhinitis, and dermatitis in Gwangyang City residents from 2004 to 2014. Data were gathered from the National Health Insurance Service database which covers all the hospital use data of entire city residents. Seasonality adjusted quasi-Poisson regression model was used to evaluate whether the operation of the ferronickel factory was associated with the immediate changes in the monthly disease incidence patterns. We set a control region, Yeosu City, near Gwangyang City to ensure that the changes in the disease incidence were specific to Gwangyang City. We conducted sub-regional level analysis to evaluate whether the disease incidence patterns were affected by the distance from the ferronickel factory. The risk estimates after operation of the ferronickel factory showed an abrupt increase in the monthly incidence of unspecified dermatitis [RR (95% CI), 1.75 (1.17–2.60)] and vasomotor and allergic rhinitis [RR (95% CI), 1.23 (1.08–1.39)] in men, and pruritus [RR (95% CI), 1.95 (1.51–2.52)], unspecified dermatitis [RR (95% CI), 1.65 (1.04–2.60)], and vasomotor and allergic rhinitis [RR (95% CI), 1.17 (1.04–1.31)] in women. These findings were significant even after accounting for the changes of the corresponding disease incidence of the comparison city, Yeosu. The effects were greater in young children (aged 0–9) and sub-regions near the ferronickel factory. Our study suggests possible association between the operation of the ferronickel factory and an abrupt increase of pruritus, unspecific dermatitis, and vasomotor and allergic rhinitis in Gwangyang City residents.

1. Introduction

The first ferronickel manufacturing factory of the Republic of Korea was opened in Gwangyang City on October 23rd, 2008. The factory produces 30,000 tons of ferronickel products annually, which is used as the raw material for manufacturing stainless steel. As a by-product of ferronickel, slag is produced when nickel ore and bituminous coal are heated to a high temperature in an electric arc furnace (Demotica et al., 2012). Since its operation, the factory has produced a total of 8 million tons of slag, 4.2 million of which has been used as engineering aggregates. However, the remaining 3.8 million tons of slag is dumped at a waste disposal site near the factory without proper treatment.

The public has raised concerns regarding the adverse health effects of dust blown from the ferronickel factory and slag disposal site. Ferronickel slag contains diverse toxic substances such as silica and

chromium in addition to iron and nickel (Demotica et al., 2012). The literature shows that high levels of nickel have been detected in the air, dust, soil, and water sediments near the ferronickel mines in Columbia (Marrugo-Negrete et al., 2017; Marrugo-Negrete et al., 2014). High levels of chromium, cobalt and other heavy metals, as well as nickel, were also detected in the atmosphere, soil, and dust near a ferronickel smelter plant in the Republic of Macedonia (Bačeva et al., 2012; Boev et al., 2013). Micrometer-sized serpentine mineral dust can also be generated during the nickel ore crushing process at the ferronickel smelting factory (Boev et al., 2013).

In the occupational setting, exposure to airborne nickel, chromium, and cobalt are reported to be associated with dermatitis and asthma (Fernandez-Nieto et al., 2006; Huygens and Goossens, 2001). Among children, exposure to nickel in ambient air has been associated with nickel sensitization (Mann et al., 2010). Micrometer-sized serpentine

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mineral dust can be retained in the air for a long period and transported easily by the wind, thereby affecting the mineralogical composition of airborne particles near ferronickel factories (Boev et al., 2013). According to previous reports, exposure to dust containing diverse heavy metals was associated with an abrupt increase in the number of hospital visits due to asthma, allergic rhinitis, and conjunctivitis (Otani et al., 2012). Exposure to ferronickel slag dust may also cause skin irritation due to its alkaline pH and crystalline, glassy, and rough nature (Demotica et al., 2012).

A chemical composition analysis using X-ray fluorescence revealed that the ferronickel slag from the Gwangyang ferronickel factory's waste disposal site contained diverse metals including nickel, chromium, cobalt, iron, copper, and lead, in addition to silica and magnesium (Supplemental Table S1). After monitoring the heavy metal contents of particulate matter in the year 2016, the levels of nickel, chromium, and cobalt were found to be higher in Gwangyang City than the nearest industrial city, Yeosu (Supplemental Table S2 and Fig. S1) (National Institute of Environmental Research (NIER), 2017). In addition, ferrous and nickel contents of particulate matter in sub-regions of Gwangyang City were higher than any other sub-regions which are located near other industrial complexes of Korea. Although cautious interpretation is needed for the results of air monitoring due to limited monitoring sites and period of monitoring (7 consecutive days per season), it is reasonable to speculate that the operation of the ferronickel factory and dumping of ferronickel slag may affect the heavy metal content of airborne particles near the ferronickel factory. In addition, cross-sectional surveys of Gwangyang City residents showed a higher prevalence of allergic diseases such as allergic rhinitis and conjunctivitis when compared to the residents of other industrial cities near Gwangyang (National Institute of Environmental Research (NIER), 2010, 2015). However, the association between the operation of a ferronickel manufacturing factory and adverse health outcomes of residents has never been evaluated.

Therefore, by using a quasi-experimental method, an interrupted time series analysis, we tried to evaluate whether the monthly incidence patterns of asthma, allergic rhinitis, and dermatitis in Gwangyang City residents had changed after the operation of the ferronickel factory. Our main hypothesis was abrupt increase of irritant or allergic disease incidence of Gwangyang City residents after the operation of the ferronickel factory, due to dust originating from the factory and slag disposal site. To strengthen causal inferences, we additionally assessed the same association in a comparison city (Yeosu) near Gwangyang City. The sub-regional level analysis in Gwangyang City was also conducted to evaluate whether the disease incidence patterns were affected by the distance from the ferronickel factory.

2. Material and methods

2.1. Study design

We performed an interrupted time series analysis to evaluate whether the operation of the ferronickel manufacturing factory and ferronickel slag dumping affected the incidence of adverse health outcomes. Interrupted time series analysis is a useful quasi-experimental method of evaluating the effectiveness of an intervention or event at the population level.

A time series refers to a series of observations made on the same variable recorded at equal intervals. The patterns of time series outcomes show changes in slope or level (interrupted) when the event or intervention has impacts on the outcome. By comparing the post-intervention time series outcome with counterfactual outcome under the hypothetical scenario with no intervention or events, we would be able to assess the impacts of intervention or event (Bernal et al., 2017).

One of the major threats to the internal validity of an interrupted time series analysis is the existence of other factors affecting the time series outcome at the same time at which the intervention or event

occurred. Therefore, to strengthen causal inference in our analysis, we added several design features to the basic structure of an interrupted times series analysis. First, we added a dependent health outcome (fracture of the forearm) which is hypothesized to be irrelevant to opening the ferronickel factory or exposure to ferronickel slag dust. Second, we set a socioeconomically and geographically similar control region (Yeosu City) and evaluated the same association to prove that the disease incidence patterns in the control region had not been affected by the ferronickel factory operation. Last, we conducted additional sub-regional level analysis in Gwangyang City to prove the hypothesis that people residing near the ferronickel factory may be more affected than those residing in far sub-regional administrative districts.

2.2. Study areas

Gwangyang City (with an area of 458.89 km²) is an industrial city located in the southernmost part of the Republic of Korea (Supplemental Fig. S2). The comparison city Yeosu (with an area of 510.09 km²) is a neighboring industrial city located on the southern side of Gwangyang City. According to the National Statistical Office of the Republic of Korea, 144,414 and 273,761 residents lived in Gwangyang and Yeosu City in 2015, respectively. The ferronickel factory and waste disposal site are located at Geumho-dong, at the southeastern part of Gwangyang City (Fig. 1). Gwangyang Bay passes between Gwangyang and Yeosu City, and the main residential area of Yeosu City is located in the southern part of Yeosu City. Therefore, we hypothesized that the effects of ferronickel factory operation and ferronickel slag dumping was limited to Gwangyang City residents, and we set Yeosu City as a control region for our analysis.

If the effects of the ferronickel factory operation and ferronickel slag dumping were mediated by the airborne dust, the effects would be greater in the sub-regional administrative districts near the ferronickel factory compared to the sub-regional districts located far from the factory. Therefore, we selected 3 sub-regional administrative districts of Gwangyang City to perform the sub-regional level analysis. To secure enough incident cases for each disease outcome, we selected the three highest populated sub-regions where the mean yearly populations were over 15,000. We divided the selected sub-regional districts into the near



Fig. 1. Map of the study area, including Gwangyang City and the comparison city, Yeosu. Sub-regional administrative districts of Gwangyang (Jungma-dong, Geumho-dong, and Gwangyang-eup) are also included.

(within 10 km, Jungma-dong, Geumho-dong) and far (over 15 km, Gwangyang-eup) regions from the ferronickel factory site. Demographics and basic characteristics of Gwangyang and Yeosu cities, as well as sub-regions of Gwangyang City are summarized in Supplemental Table S3.

2.3. Basic characteristics of the ferronickel manufacturing factory

The ferronickel manufacturing factory at Gwangyang City released the first ferronickel products on October 23rd, 2008. Annually, the factory produces 30,000 tons of ferronickel products and 1 million tons of ferronickel slag. The general features of the ferronickel manufacturing process are as follows: nickel ore transported from New Caledonia is mixed and put in a dryer to remove the moisture. After drying, the ore goes through the preliminary reduction process to eliminate oxygen in nickel and iron. With additional smelting and reduction processes in an electric furnace, ferronickel molten iron and slag are produced. After the final casting, ferronickel molten iron is manufactured as ferronickel products in the form of Luppe. As a by-product of ferronickel production, ferronickel slag is produced when nickel ores are treated with a high temperature in an electric arc furnace. With natural air cooling or spraying of water, smelting slag becomes air-cooled slag and granulated slag. Granulated slag can easily be broken into small particles and used as concrete sand. Air-cooled slag is crushed and used as engineering aggregates.

2.4. Outcomes measure

We used the customized health information data provided by the National Health Insurance Service, which covers almost all the hospital use data of the Republic of Korea. The National Health Insurance Service created the National Health Insurance Database (NHID) for academic or administrative use of health insurance information. From the NHID, we obtained hospital use data of the Gwangyang and Yeosu City residents from 2002 to 2014, whose primary diagnosis codes were as follows: disease (*International Classification of Disease, 10th revision code*), (a) acute bronchitis (J20.X), (b) asthma (J45.X), (c) vasomotor and allergic rhinitis (J30.X), (d) atopic dermatitis (L20.X), (e) seborrheic dermatitis (L21.X), (f) allergic contact dermatitis (L23.X), (g) irritant contact dermatitis (L24.X), (h) unspecified contact dermatitis (L25.X), (i) pruritus (L29.X), (j) other dermatitis (L30.X), and (k) fracture of forearm (S52.X). Diseases (a)–(j) were selected based on prior literature reviews (Fernandez-Nieto et al., 2006; Huygens and Goossens, 2001; Otani et al., 2012), suggesting their possible association with heavy metal dust exposure, particularly nickel. Disease (k) was selected as a control outcome because it was hypothesized to be irrelevant to the ferronickel factory operation or exposure to ferronickel slag dust.

We first extracted the data of the initial hospital visit (incidence data) for each disease outcome for persons who resided in Gwangyang or Yeosu City. To capture actual incidence cases, we deleted the incidence data when the initial hospital visits occurred from 2002 to 2003, thereby leaving the incidence cases of Gwangyang and Yeosu City residents for each disease outcome from 2004 to 2014. Therefore, a person who was diagnosed with a certain disease outcome in November 2008 in our incidence data is a person who was never diagnosed with that disease from January 2002 to October 2008.

To calculate the monthly incidence rate (per 100,000 persons), we divided the number of monthly disease incidence cases by the number of yearly eligible persons who retained eligibility criteria for the health insurance service of the corresponding city or sub-region. We age-standardized the incidence rate by using the World Health Organization standard population and direct age standardization method (Boyle and Parkin, 1991). For the intuitive understanding of readers, we multiplied each monthly incidence rate in our figures and tables by 100,000. Number of yearly eligible person who retained eligibility criteria for the

health insurance service for Gwangyang City and sub-regions of Gwangyang City are presented at Supplemental Table S4.

The institutional review board of the Seoul National University Hospital, Republic of Korea, exempted this study from review because we used customized de-identified health information data provided by the National Health Insurance Service (IRB no. E-1609-010-789). To protect personal information, our analysis was conducted at the population level with minimal personal data such as sex, age, and sub-regional level addresses.

2.5. Statistical analysis

We performed an interrupted time series analysis to test whether the operation of the ferronickel factory changed the incidence levels of asthma, allergic rhinitis, and dermatitis among Gwangyang City residents (Bernal et al., 2017). We set November 2008, just after the opening of the factory, as the advent of the effect of the ferronickel manufacturing factory operation and ferronickel slag on the residents. We hypothesized an abrupt increase in the incidence of irritant or allergic disease after the opening of the ferronickel factory based on the results of previous studies suggesting that the exposure to heavy metal dust induces irritant or allergic symptoms within a short time (Otani et al., 2012). Therefore, the abrupt level change of each disease incidence after the opening of the ferronickel factory was assessed with a segmented quasi-Poisson regression model. To account for over-dispersion and seasonality issues, we used the quasi-Poisson model with harmonic terms for months in our model (Bernal et al., 2017). We used following equation model in our main analysis.

$$\log[\mu_t] = \beta_0 + \beta_1 I_t + \beta_2 T_t + \beta_3 M$$

The age-standardized disease specific monthly incidence rate was assumed to follow a quasi-Poisson distribution with the mean μ_t with t indexing the month, I_t as an indicator variable for operation of the factory ($I_t = 1$: after the factory operation, $I_t = 0$: before the factory operation), T_t as the time elapsed since the start of the study (from Jan 2004, in month unit), and M as the harmonic terms with 2 pairs of sin and cosine for 12 months to adjust seasonality. We exponentiated β_1 to get step change relative risk for our main analysis.

In a time series analysis, the basic regression assumption can be violated by residual autocorrelation of time series outcomes. Therefore, we evaluated the residual autocorrelation with the Breusch-Godfrey test for each time series, and if the residual autocorrelation was present ($p < 0.05$), we used robust standard errors by using a sandwich estimator to report more conservative estimates as suggested in previous studies (Andrews, 1991; Humphreys et al., 2017).

To compare differences between relative risk estimates of step change after the operation of the ferronickel factory between Gwangyang and Yeosu City, we used following equation (Altman and Bland, 2003).

$$(\beta_1 - \beta_2) / \sqrt{SE_1^2 + SE_2^2}$$

where β_1 and β_2 are step change estimates for Gwangyang and Yeosu cities at November 2008, and SE_1 and SE_2 are their respective standard errors. An absolute value larger than 1.96 indicates a statistically significant difference at the $\alpha = 0.05$ level. We conducted stratified analysis on different age groups (0–9, 10–29, 30–59, 60–) and different sub-regions of Gwangyang City residents (Jungma-dong, Geumho-dong, and Gwangyang-eup).

To confirm our findings from interrupted time series analysis, we conducted additional difference-in-difference analysis. The difference-in-difference analysis compares the changes in outcome over time between intervention and reference population (Gertler et al., 2016; Hanchate et al., 2015). We estimated the relative change in disease incidence rate associated with ferronickel factory operation of Gwangyang city residents as the difference of following two differences: First

difference, the difference in the before-and-after disease incidence rate for the Gwangyang city residents; Second difference, the difference in the before-and-after disease incidence rate for the Yeosu city residents. The first difference controls for the factors which are constant over time by comparing disease incidence in same Gwangyang city population. In addition, by subtracting first difference with second difference, we controlled time varying factors by assuming Yeosu city residents show the changes in disease incidence rate that would be experienced by the Gwangyang city residents in the absence of ferronickel factory operation. We divided study period into 2 years before (2006.11–2008.10, reference period) and 6 years after (2008.11–2010.10, 2010.11–2012.10, 2012.12–2014.10) the ferronickel factory operation and estimated how monthly disease incidence rate of Gwangyang city residents changed relative to Yeosu city residents. Detailed difference-in-difference analysis equation is presented at Supplemental Table S5. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R statistical software (version 3.1.3; R Foundation for Statistical Computing, Vienna, Austria) were used in our analysis.

3. Results

We estimated the abrupt changes in the monthly incidence patterns of asthma, allergic rhinitis, and dermatitis of residents before (January 2004–October 2008) and after (November 2008–December 2014) the operation of the ferronickel factory (Table 1, Fig. 2). In Gwangyang City men, we found an abrupt increase in the monthly incidence rates of pruritus [relative risk (RR), (95% confidence interval (CI)): 1.49 (1.12–1.99)], atopic dermatitis [RR (95% CI): 1.17 (1.04–1.31)], unspecified dermatitis [RR (95% CI): 1.75 (1.17–2.60)], asthma [RR (95% CI): 1.21 (1.00–1.46)], and vasomotor and allergic rhinitis [RR (95% CI): 1.23 (1.08–1.39)] after the operation of the ferronickel factory. In Gwangyang City women, an increase in the monthly incidence rates of pruritus [RR (95% CI): 1.95 (1.51–2.52)], atopic dermatitis [RR (95% CI): 1.17 (1.06–1.30)], unspecified dermatitis [RR (95% CI): 1.65 (1.04–2.60)], asthma [RR (95% CI): 1.25 (1.03–1.51)], and vasomotor and allergic rhinitis [RR (95% CI): 1.17 (1.04–1.31)] was observed after the operation of the ferronickel factory. In particular, there was an abrupt short-term increase in the monthly incidence of unspecified dermatitis in the summer period of 2009 in both men and women (Fig. 2). Detailed age-standardized monthly disease incidence patterns are summarized at Supplemental Figs. S3 and S4.

We compared the analysis results of Gwangyang City residents with the results of the comparison city, Yeosu. All the disease outcomes except pruritus showed a null association between the ferronickel factory operation and the changes in disease incidence of Yeosu City. By comparing step change RR estimates between Gwangyang and Yeosu city, a significant difference in ferronickel factory operation effects on unspecified dermatitis and vasomotor and allergic rhinitis in men, and pruritus, unspecified dermatitis, and vasomotor and allergic rhinitis in women were noticed (Table 1). Additional difference-in-difference analysis showed similar results to our main analysis (Supplemental Tables S5 and S6). By comparing 2008.11–2010.10 period to the reference period before the ferronickel factory operation (2006.11–2008.10), significant increase in monthly incidence rates of atopic dermatitis and unspecified dermatitis of Gwangyang City were observed even after accounting for the changes of Yeosu City [RR (95% CI), atopic dermatitis, men: 1.13 (0.99–1.29), women: 1.72 (1.29–2.31); unspecified dermatitis, men: 1.17 (1.06–1.30), women: 1.63 (1.19–2.24)]. By comparing 2010.11–2012.10 period to reference period, significant increase in monthly incidence rates of pruritus, other dermatitis, and vasomotor and allergic rhinitis in Gwangyang City were observed even after accounting for the changes of Yeosu City [RR (95% CI), pruritus, men: 1.69 (1.34–2.13), women: 1.55 (1.24–1.94); other dermatitis, men: 1.18 (1.03–1.36), women: 1.25 (1.06–1.47); vasomotor and allergic rhinitis, men: 1.24 (1.00–1.53), women: 1.22 (0.98–1.52)].

Stratified analysis of the different age groups of Gwangyang City residents showed that the impact of ferronickel factory operation on the monthly incidence patterns of irritant or allergic disease was greater among children aged between 0 and 9 (Table 2). However, the abrupt short-term increase in the incidence of unspecified dermatitis in the summer of 2009 was only observed in residents aged 10 years or older.

The analysis for the sub-regions of Gwangyang City showed that the magnitude of increase in monthly asthma, allergic rhinitis, and dermatitis incidence were greater in sub-regions near the factory site (< 10 km, Jungma-dong, Geumho-dong) compared to the farther located sub-region (> 15 km, Gwangyang-eup) (Fig. 3, Supplemental Table S7). Jungma-dong, the highest populated sub-region near the factory site, showed greater increase in the disease incidence compared to the other sub-regions. In particular, the abrupt short-term increase of unspecified dermatitis incidence in the summer of 2009 was only observed in sub-regions near the ferronickel factory (Fig. 3).

4. Discussion

Public concern regarding the adverse health effects of the ferronickel manufacturing factory on residents has been raised since the factory started its operation. Our study results showed abrupt increases in the monthly incidence of pruritus, atopic dermatitis, asthma, and vasomotor and allergic rhinitis among Gwangyang City residents after the opening of the factory. These findings were shown in both men and women, and the magnitude of the increase was greater in children (aged 0–9). In addition, an abrupt short-term increase in the monthly incidence of unspecified dermatitis was observed among Gwangyang City residents in the summer of 2009, several months after the factory opening.

By comparing the disease incidence patterns of Gwangyang City with the comparison city, Yeosu, we found a significant difference in the effects of ferronickel factory operation on unspecified dermatitis and vasomotor and allergic rhinitis in men, and pruritus, unspecified dermatitis, and vasomotor and allergic rhinitis in women. Yeosu City residents showed a null association between the operation of the ferronickel factory and changes in irritant or allergic disease incidence patterns except for pruritus. These findings support the consistency and specificity of the association between the ferronickel factory operation and the increase in irritant or allergic disease incidence among Gwangyang City residents.

In the stratified analysis of the sub-regions of Gwangyang City, the increase of irritant or allergic disease incidence was greater among residents living near the ferronickel factory compared to those living far from the factory. The abrupt short-term increase in the incidence of unspecified dermatitis in the summer of 2009 was observed among Gwangyang City residents living near the ferronickel factory, but not among Yeosu City residents or Gwangyang City residents living far from the factory. These findings suggest a biological gradient for the association between the changes in the disease incidence patterns and the distance from the ferronickel factory.

Nickel, cobalt, and chromium were detected from the air, soil, and water sediments near ferronickel manufacturing factories and ferronickel mines in previous studies (Bačeva et al., 2012; Boev et al., 2013; Marrugo-Negrete et al., 2017; Marrugo-Negrete et al., 2014). By analyzing attic dust samples collected from houses located near a ferronickel smelter plant, over 90% of the mineral constituents present in the ferronickel ore (serpentine and amphibole group of minerals), which are uncommon constituents of urban dust, were present in the attic dust samples (Boev et al., 2013). In addition, higher contents of nickel, cobalt, and chromium were detected in the attic dust sample when compared to the natural contents of soil and rocks from the surrounding region (Bačeva et al., 2011; Boev et al., 2013). By using a moss bio-monitoring method, moss samples near the ferronickel smelter plant were found to have a higher content of nickel, cobalt, and chromium (Bačeva et al., 2012). Particularly, the content of nickel was 31 times

Table 1

The association between the operation of the ferronickel factory (2008.11–) and the incidence of allergic disease in Gwangyang and Yeosu City.

Disease	Mean number of monthly incidence cases		Mean monthly incidence rate ^a × 100,000		Relative risk (95% CI)	Test of interaction
	Before (2004.01–2008.10)	After (2008.11–2014.12)	Before (2004.01–2008.10)	After (2008.11–2014.12)	Step change	(Gwangyang vs Yeosu)
Men						
Pruritus						
Gwangyang	26.53	39.58	35.70	63.77	1.49 (1.12, 1.99) ^b	0.17
Yeosu	48.45	68.95	32.94	46.88	1.19 (1.03, 1.39) ^b	
Acute bronchitis						
Gwangyang	483.97	369.35	719.83	563.19	1.05 (0.89, 1.22) ^b	0.96
Yeosu	1007.93	589.22	714.87	479.04	1.04 (0.86, 1.25) ^b	
Allergic dermatitis						
Gwangyang	329.57	267.31	474.54	380.84	1.04 (0.95, 1.13)	0.70
Yeosu	621.95	421.16	426.85	321.20	1.06 (0.98, 1.16) ^b	
Atopic dermatitis						
Gwangyang	86.57	62.34	156.85	122.51	1.17 (1.04, 1.31)	0.16
Yeosu	154.33	93.65	158.77	117.96	1.05 (0.95, 1.15) ^b	
Seborrheic dermatitis						
Gwangyang	55.43	59.93	74.74	77.62	1.04 (0.94, 1.15) ^b	0.38
Yeosu	141.90	142.59	88.79	94.31	0.97 (0.86, 1.09) ^b	
Irritant dermatitis						
Gwangyang	59.66	54.53	89.56	84.50	0.91 (0.79, 1.05) ^b	0.19
Yeosu	212.86	163.16	143.09	127.89	0.80 (0.72, 0.90) ^b	
Other dermatitis						
Gwangyang	78.66	93.28	123.08	162.01	0.90 (0.82, 1.00) ^b	0.85
Yeosu	164.12	174.01	113.90	134.96	0.91 (0.83, 1.00) ^b	
Unspecified dermatitis						
Gwangyang	35.22	36.89	48.74	47.85	1.75 (1.17, 2.60) ^b	< 0.01
Yeosu	66.79	58.85	45.57	40.97	0.85 (0.70, 1.03) ^b	
Asthma						
Gwangyang	125.22	105.80	215.33	183.91	1.21 (1.00, 1.46) ^b	0.40
Yeosu	363.67	230.39	299.56	226.09	1.08 (0.91, 1.28) ^b	
Vasomotor and allergic rhinitis						
Gwangyang	342.66	308.80	507.54	490.56	1.23 (1.08, 1.39) ^b	0.02
Yeosu	594.83	446.51	435.12	374.06	0.95 (0.80, 1.12) ^b	
Fracture of forearm						
Gwangyang	27.88	24.00	43.94	35.17	0.86 (0.73, 1.00)	0.69
Yeosu	46.38	39.01	36.90	32.55	0.89 (0.78, 1.01)	
Women						
Pruritus						
Gwangyang	23.81	44.72	31.33	68.54	1.95 (1.51, 2.52) ^b	< 0.01
Yeosu	50.41	86.19	31.68	56.16	1.28 (1.13, 1.45) ^b	
Acute bronchitis						
Gwangyang	545.00	369.09	838.21	602.20	1.01 (0.86, 1.18) ^b	0.56
Yeosu	1098.86	561.47	794.00	485.48	1.08 (0.91, 1.28) ^b	
Allergic dermatitis						
Gwangyang	390.43	286.61	578.04	425.77	1.03 (0.95, 1.12)	0.58
Yeosu	766.48	482.72	521.28	371.56	1.07 (0.98, 1.16) ^b	
Atopic dermatitis						
Gwangyang	91.47	66.34	172.87	131.21	1.17 (1.06, 1.30)	0.37
Yeosu	164.29	100.18	175.16	126.42	1.09 (0.99, 1.21) ^b	
Seborrheic dermatitis						
Gwangyang	49.97	55.12	71.00	79.29	1.07 (0.95, 1.21)	0.72
Yeosu	119.34	131.09	80.54	96.20	1.11 (0.97, 1.26) ^b	
Irritant dermatitis						
Gwangyang	86.84	79.91	129.16	121.37	0.91 (0.78, 1.05) ^b	0.87
Yeosu	253.28	201.12	167.01	155.98	0.89 (0.81, 0.98) ^b	
Other dermatitis						
Gwangyang	83.90	106.74	133.67	181.69	0.97 (0.87, 1.07) ^b	0.50
Yeosu	176.79	195.69	124.59	152.52	0.92 (0.84, 1.01) ^b	
Unspecified dermatitis						
Gwangyang	43.28	50.85	59.92	64.17	1.65 (1.04, 2.60) ^b	0.01
Yeosu	83.64	83.88	56.27	56.86	0.85 (0.71, 1.01) ^b	
Asthma						
Gwangyang	143.03	130.76	235.44	212.16	1.25 (1.03, 1.51) ^b	0.37
Yeosu	441.83	276.93	341.76	248.37	1.11 (0.92, 1.32) ^b	
Vasomotor and allergic rhinitis						
Gwangyang	383.34	319.84	590.57	535.58	1.17 (1.04, 1.31)	0.05
Yeosu	702.07	487.26	509.21	409.74	0.96 (0.82, 1.12) ^b	
Fracture of forearm						
Gwangyang	19.78	20.32	29.29	25.48	1.02 (0.82, 1.28)	0.53
Yeosu	43.50	43.36	27.25	24.42	0.95 (0.82, 1.10)	

^a Age standardized according to WHO standard population.^b Breusch-Godfrey test revealed serial autocorrelation. Therefore, robust standard errors are used to calculate 95% confidence intervals.

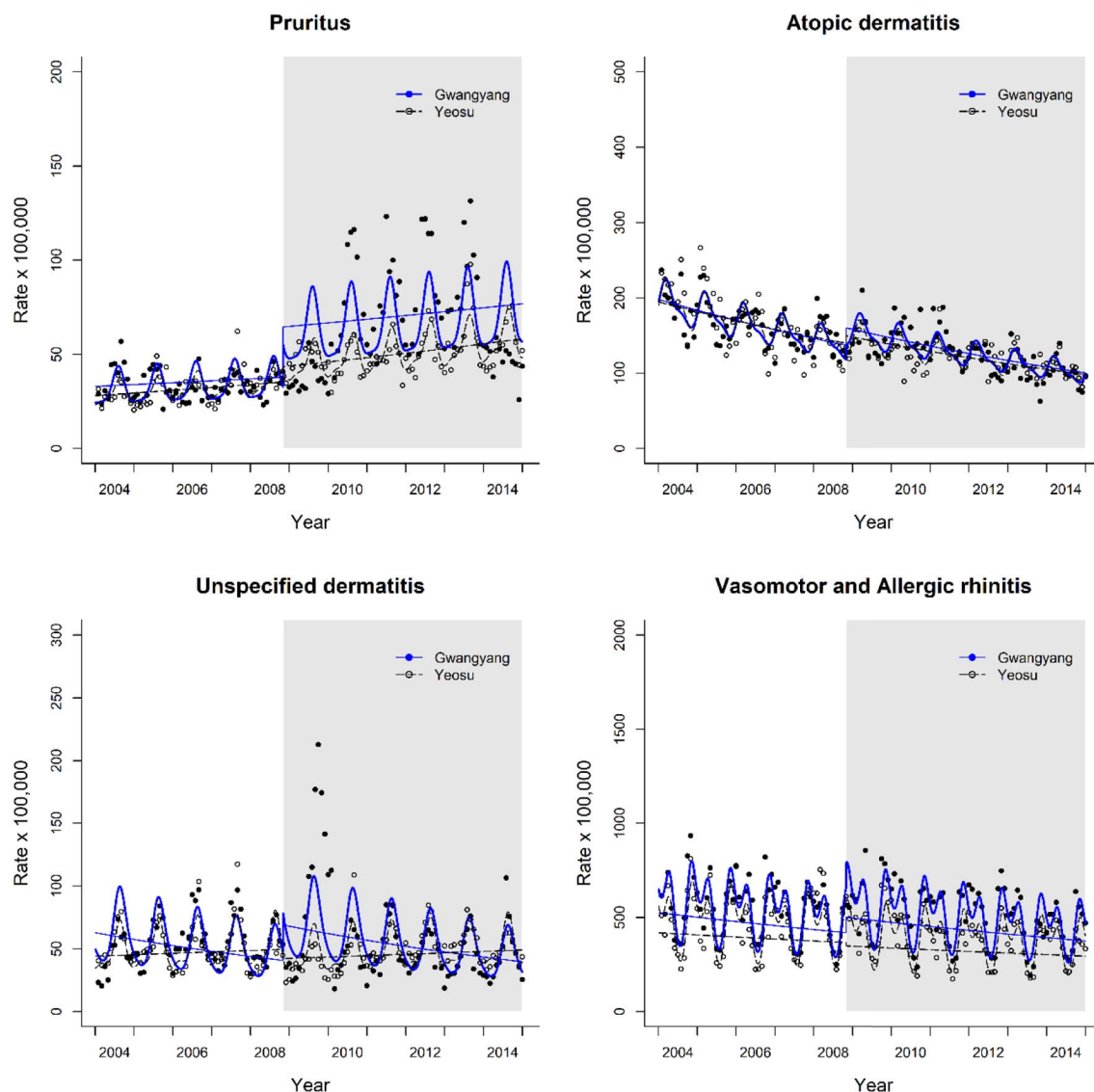


Fig. 2. The association between the operation of the ferronickel factory (2008.11–) and the monthly incidence of allergic and irritant disease in Gwangyang and Yeosu City. Data points represent the monthly incidence rates of each disease in Gwangyang and the comparison city, Yeosu. Straight lines represent fitted estimates using a linear step change model, and the curved lines represent the seasonality adjusted model. The white and gray backgrounds represent the periods before (2004.01–2008.10) and after (2008.11–2014.12) the operation of the ferronickel factory.

higher in the moss samples collected from the vicinity of the ferronickel plants compared to the moss samples collected from the entire territory of the Republic of Macedonia.

These previous studies suggest the ferronickel manufacturing factory as an important source of airborne heavy metal particles near the ferronickel factory. In a report from the National Institute of Environmental Research, the Republic of Korea, the levels of nickel and chromium were higher in the atmosphere of Gwangyang's sub-regions near the ferronickel factory compared to sub-regions of Yeosu (Supplementary Table S2). Therefore, it is reasonable to speculate that the nickel and other heavy metal contents of Gwangyang City's airborne particles are affected by the ferronickel manufacturing factory.

Nickel, cobalt, and chromium are heavy metals which are causal agents for airborne contact dermatitis (Huygens and Goossens, 2001). Lime (CaO) and magnesia (MgO) in ferronickel slag may increase the pH when ferronickel slag is dissolved in water (Demotica et al., 2012). In addition, crystalline, glassy, and rough regions are observed in the microstructure of ferronickel slag (Demotica et al., 2012). Probably, the alkalinity and abrasive surface of ferronickel slag may have contributed to the skin irritation after exposure to ferronickel slag dust.

Several occupational studies have reported a possible association between heavy metal dust exposure and allergic skin symptoms and asthma. Nickel contact dermatitis is a common disease among industrial workers who handle raw nickel materials (Blanco-Dalmau et al., 1984; Lidén, 1994). A worker from a metallurgical laboratory suffered highly pruritic rosacea-like symptoms after the airborne nickel exposure (Kanerva et al., 1999) and cement dust containing chromate caused allergic skin symptoms (Sayed and Bazex, 1994). Nickel sulfate and chromium in workplace dust are common sensitizing agents, which might induce asthma by inhalation (Block and Yeung, 1982). In addition, serum immunoglobulins were elevated in workers occupationally exposed to nickel and cobalt when compared to aged-matched control groups (Bencko et al., 1982). Therefore, occupational exposure to heavy metals and occurrence of the allergic and irritant symptoms are anticipated for field workers of the ferronickel factory. In addition, an abrupt increase in unspecified dermatitis just after the ferronickel factory operation was not shown among 0–9-year-old children group, who are less likely to be occupationally exposed to the heavy metals. Because field worker tends to reside near the factory, greater increase of allergic or irritant disease among residents living near the ferronickel

Table 2

The association between the operation of the ferronickel factory (2008.11–) and the incidence of allergic disease in Gwangyang City (by age group).

Disease	Mean number of monthly incidence cases		Mean monthly incidence rate ^a × 100,000		Relative risk (95% CI)
	Before (2004.01–2008.10)	After (2008.11–2014.12)	Before (2004.01–2008.10)	After (2008.11–2014.12)	Step change
Pruritus					
0–9	5.53	24.53	28.33	150.54	4.30 (2.66, 6.95) ^b
10–29	7.22	11.96	17.59	28.10	1.40 (1.09, 1.80)
30–59	25.76	31.14	41.00	43.84	1.01 (0.85, 1.20) ^b
60–	11.83	16.68	68.14	82.65	0.97 (0.78, 1.21)
Acute bronchitis					
0–9	245.91	198.82	1237.84	1214.91	1.19 (1.01, 1.41) ^b
10–29	243.26	150.34	597.66	350.61	1.04 (0.80, 1.36) ^b
30–59	431.88	322.00	689.83	455.54	0.84 (0.69, 1.03) ^b
60–	107.91	67.28	645.67	333.67	0.90 (0.74, 1.10) ^b
Allergic dermatitis					
0–9	132.60	104.72	675.03	639.45	1.06 (0.96, 1.16)
10–29	172.10	134.59	420.38	314.84	1.04 (0.94, 1.16)
30–59	323.78	252.66	516.47	357.81	1.02 (0.93, 1.11)
60–	91.52	61.95	541.43	308.37	1.02 (0.89, 1.16) ^b
Atopic dermatitis					
0–9	97.81	64.97	497.43	396.14	1.24 (1.12, 1.38)
10–29	39.74	26.93	97.31	63.01	0.99 (0.84, 1.15) ^b
30–59	33.03	28.49	52.68	40.36	1.06 (0.89, 1.27) ^b
60–	7.45	8.28	43.52	41.01	1.18 (0.88, 1.56)
Seborrheic dermatitis					
0–9	9.41	11.54	48.92	70.43	1.43 (1.08, 1.88) ^b
10–29	30.00	38.01	73.00	89.37	0.94 (0.81, 1.09)
30–59	53.12	52.30	84.54	73.96	1.01 (0.91, 1.13)
60–	12.86	13.20	76.66	65.72	1.09 (0.85, 1.39) ^b
Irritant dermatitis					
0–9	26.34	28.26	135.15	172.66	1.14 (0.94, 1.37) ^b
10–29	36.93	36.42	89.99	85.58	0.84 (0.70, 0.99) ^b
30–59	59.31	49.64	94.45	69.98	0.77 (0.66, 0.91) ^b
60–	23.91	20.12	141.20	100.07	0.83 (0.66, 1.05) ^b
Other dermatitis					
0–9	48.50	70.38	250.64	430.41	0.98 (0.85, 1.12) ^b
10–29	35.14	41.82	85.25	98.10	1.03 (0.89, 1.19)
30–59	60.78	65.78	96.51	92.71	0.84 (0.75, 0.94) ^b
60–	18.14	22.04	104.86	108.95	0.84 (0.71, 0.99) ^b
Unspecified dermatitis					
0–9	10.47	8.18	54.36	49.91	0.79 (0.60, 1.04) ^b
10–29	13.86	17.64	33.88	40.89	2.49 (1.24, 4.99) ^b
30–59	38.83	42.46	61.78	60.71	2.27 (1.29, 4.00) ^b
60–	15.34	19.47	86.83	96.45	1.36 (1.03, 1.79) ^b
Asthma					
0–9	117.38	84.34	588.40	514.55	1.37 (1.10, 1.71) ^b
10–29	39.16	30.51	96.31	71.47	1.00 (0.75, 1.32) ^b
30–59	76.53	88.12	121.87	124.79	1.18 (0.95, 1.48) ^b
60–	35.19	33.58	207.37	166.62	0.89 (0.73, 1.07) ^b
Vasomotor and allergic rhinitis					
0–9	169.07	185.84	864.30	1133.03	1.35 (1.17, 1.56) ^b
10–29	198.64	144.74	486.79	337.69	1.15 (0.98, 1.36) ^b
30–59	309.78	242.18	494.69	343.57	1.05 (0.90, 1.22) ^b
60–	48.52	55.88	285.69	277.63	1.21 (1.01, 1.45) ^b
Fracture of forearm					
0–9	9.78	5.73	50.11	34.93	0.71 (0.54, 0.94)
10–29	18.78	16.43	45.72	38.40	1.06 (0.87, 1.28)
30–59	10.34	11.78	16.47	16.62	1.01 (0.79, 1.27)
60–	8.76	10.38	51.81	51.36	1.03 (0.78, 1.37)

^a Monthly incidence rate is calculated by dividing number of monthly incidence case with total number of annual population.^b Breusch-Godfrey test revealed serial autocorrelation. Therefore, robust standard errors are used to calculate 95% confidence intervals.

factory also supports the hypothesis that occupational exposure as one of the explanations for our study findings.

On the other hand, the entire city residents can be exposed to relatively low levels of heavy metal dust after the operation of the ferronickel factory. In this case, our situation might be more similar to natural meteorological events, such as an Asian dust, which affect large

numbers of the population with low levels of airborne heavy metals. Asian dust usually occurs during the spring or fall in the East Asian region. The dust which originates from the Chinese and Mongolian deserts adsorbs diverse anthropogenic materials such as environmental pollutants, microbiological materials, and heavy metals during their transportation (Onishi et al., 2012).

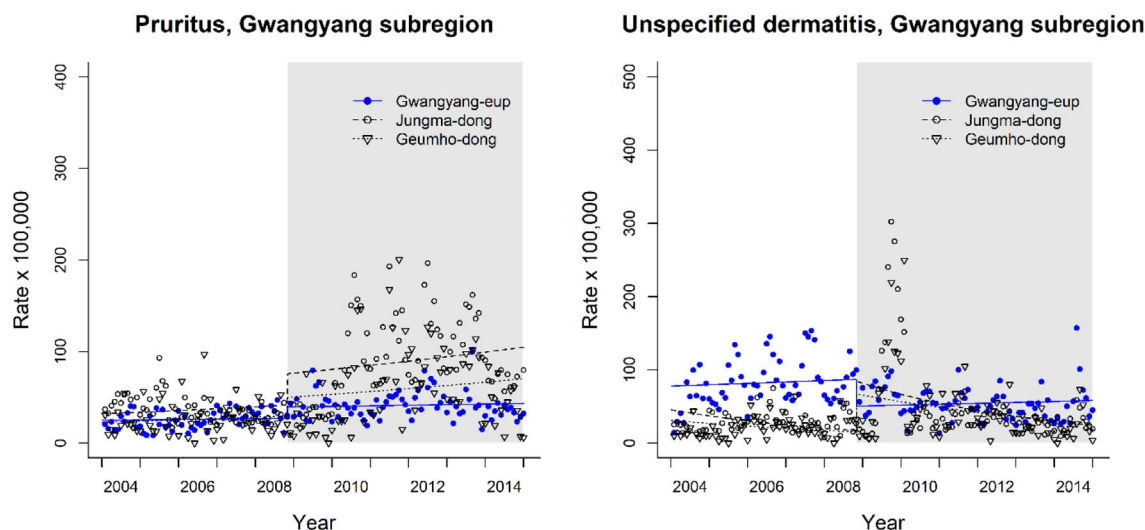


Fig. 3. The association between the operation of the ferronickel factory (2008.11–) and the monthly incidence of pruritus and unspecified dermatitis in the sub-regions of Gwangyang City. Data points represent the monthly incidence rates of each disease in the sub-regions of Gwangyang. Jungma-dong and Geumho-dong are located within 10 km from the ferronickel factory and Gwangyang-eup is located over 15 km from the ferronickel factory. Straight lines represent fitted estimates using a linear step change model. White and gray backgrounds represent periods before (2004.01–2008.10) and after (2008.11–2014.12) the operation of the ferronickel factory.

Asian dust exposure is associated with diverse forms of acute allergy-related conditions such as skin symptoms, allergic rhinitis, asthma, and conjunctivitis (Otani et al., 2012). Allergic reactions after Asian dust exposure are believed to be derived from the heavy metal particles bound to the dust (Otani et al., 2012). Particularly, nickel contents are highly associated with skin symptoms and subjects with skin symptoms after Asian dust exposure showed the tendency for nickel allergies (Onishi et al., 2012, 2015; Otani et al., 2012). In addition, exposure to Asian dust particles was associated with increased respiratory inflammation in rats (Lei et al., 2004). In vitro studies, metallic components of Asian dust were associated with respiratory inflammation, and particularly, nickel showed a high affinity for the horny layer and inner root sheath of hairs of normal skin (Shin et al., 2013; Wells, 1956). 5% nickel sulfate and 1% cobalt chloride caused irritation in individuals under the occlusion patch tests (Kalimo and Lammintausta, 1984), and 0.1% nickel sulfate solution caused irritation on scarified skin after exposure once daily for 3 days (Frosch and Kligman, 1976). The threshold of nickel chloride solution for skin irritancy was 1% with occlusion and 10% without occlusion when the solution was applied to the back of subjects for 48 h (Vandenberg and Epstein, 1963).

Therefore, it is biologically plausible to explain that exposure to the heavy metal-containing dust originating from the ferronickel factory and ferronickel slag disposal site may have increased the incidence of irritant or allergic disease among residents. However, there are several findings which need additional explanation. First, the monthly incidence of pruritus showed a marked increase since early 2010, thereby showing about 1-year time lag after the operation of the ferronickel factory. Although nickel-induced contact dermatitis needs sensitization before the occurrence of skin symptoms and exposure to nickel in ambient air has been associated with nickel sensitization among children (Mann et al., 2010), we were unable to find similar study which explains a possible association between heavy metal dust exposure and pruritic skin symptoms with such a time lag. In addition, overall patterns of monthly incidence of allergic dermatitis (ICD-code: L23.X) which contains allergic contact dermatitis due to metals (L23.0) did not show any marked change after the factory operation, which suggests that pruritic skin symptoms of Gwangyang City residents may not have appeared as typical Nickel or Chromium related allergic contact dermatitis (Supplemental Figs. S3 and S4).

Second, statistically significant increase in pruritus incidence after the ferronickel factory operation in Yeosu City residents are unexpected

results. Although we selected nearest industrial City, Yeosu to increase overall comparability, Yeosu City residents may not serve as an absolute counterfactual scenario of Gwangyang City residents (what if the disease incidence changed in Gwangyang City residents if there was no ferronickel factory opening in Gwangyang) due to the spillover effects of ferronickel factory and comparability issues. Two to Three sub-regions of Yeosu City may be close enough to be affected from the ferronickel factory. In addition, there could be specific situations which may have been occurred at Yeosu City. Therefore, to conclude causal association between ferronickel factory operation and increase of allergic and irritant disease of local residents in our study, follow up studies with sub-regions of Yeosu City and epidemiological survey for Gwangyang City residents are needed in the future.

There are several limitations in our study. First, there could be other time-varying variables which may have affected the incidence patterns of asthma, allergic rhinitis, and dermatitis among Gwangyang City residents (Bernal et al., 2017). For example, air pollution including particulate matter concentration and other socioeconomic variables of Gwangyang City residents could have changed during the ten-year study period. In addition, accessibility to the hospital may be increased if the number of hospitals and doctors were simultaneously increased with the operation of the factory. However, to minimize the effects of other unknown time-varying confounders, we added a control region and control outcome in our interrupted time series design. Furthermore, additional adjustment for monthly PM₁₀ concentration in Gwangyang City did not change our main study results (results not shown) and number of doctors and hospitals did not changed with the operation of the ferronickel factory in the Gwangyang City (Supplemental Fig. S5). However, even with our study design, there is the possibility that circumstances unique to Gwangyang City may have affected our study findings. For example, we do not have detailed daily heavy metal content information of particulate matter or meteorological data (wind speed, direction, temperature, and humidity) in the sub-regions of Gwangyang City during our study period which might have affected the results of the sub-regional level analysis. Second, in our subgroup analysis, several subgroups comprised of relatively small populations may produce unstable incidence rates. This could lead to a reduction in the statistical precision of our estimates in the subgroup analysis. Third, although we used ICD-10 codes to determine the incident cases of asthma, allergic rhinitis, and dermatitis, the diagnostic accuracy of each disease had not been confirmed in the health insurance claim data. However, these potential non-differential

misclassifications may not have affected our study conclusion seriously, since such misclassifications are more likely to pull the results toward the null. Fourth, because we used health insurance claim data for over 10 years of the study period, changes in administrative procedure may have affected the registered data. However, we found relatively stable incidence patterns in several allergic diseases such as allergic dermatitis and the control outcome, fracture of the forearm, which suggests minimal effects of instrumentation in our study.

Even if the validity of our study is threatened by the above limitations, there are two important findings which support the causal association between the ferronickel factory operation and the changes in the disease incidence patterns among Gwangyang City residents. First, the monthly incidence of pruritus and vasomotor and allergic rhinitis had increased in Gwangyang City after the opening of the ferronickel factory, and these increases were significant even after accounting for the changes of the corresponding disease incidence of the comparison city, Yeosu. Second, there was an unusual short-term increase in unspecified dermatitis in the summer of 2009, and this increase was seen among residents from Gwangyang's sub-regions near the factory site but not in the sub-regions far from the factory or in the comparison city.

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Disclosure of potential conflict of interest

All authors have no conflicts of interest to declare.

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This study used the customized database of the National Health Insurance Service for policy and academic research. The aim and conclusion of this study are irrelevant to the National Health Insurance Service, Republic of Korea. The research number of this study is NHIS-2016-1-105.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2018.02.045>.

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Supplemental Material

Title

Adverse health effects of ferronickel manufacturing factory on local residents: An interrupted time series analysis

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Supplemental Table S3. Characteristics of Gwangyang and Yeosu Cities in 2014 (All the data are gathered from Statistics Korea).

Supplemental Table S4. Number of eligible person who retained eligibility criteria for the health insurance service.

Supplemental Table S5. Difference-in-difference (DID) analysis to evaluate the association between operation of the ferronickel factory (2008.11-) and the incidence of allergic disease in Gwangyang and Yeosu City (Men).

Supplemental Table S6. Difference-in-difference (DID) analysis to evaluate the association between operation of the ferronickel factory (2008.11-) and the incidence of allergic disease in Gwangyang and Yeosu City (Women).

Supplemental Table S7. The association between the operation of the ferronickel factory and the incidence of allergic disease in the sub-regions of Gwangyang. Jungma-dong and Geumho-dong are located within 10 km from the ferronickel factory and Gwangyang-eup is located over 15 km from the ferronickel factory.

Supplemental Figure S1. Location of monitoring stations of Supplementary Table S2

Supplemental Figure S2. Map of the Republic of Korea, including the study area, Gwangyang City, and the comparison city, Yeosu

Supplemental Figure S3. The association between the operation of the ferronickel factory (2008.11-) and the incidence of allergic disease in Gwangyang and Yeosu City among men

Supplemental Figure S4. The association between the operation of the ferronickel factory (2008.11-) and the incidence of allergic disease in Gwangyang and Yeosu City among women

Supplemental Figure S5. Temporal trends in yearly number of doctors and hospitals in Gwangyang City from 2002 to 2014

Supplemental Table S1. Heavy metal contents in granulated and air-cooled ferronickel slag from the Gwangyang ferronickel factory.

Types of Ferronickel Slag	Cd	Cu	Pb	Zn	Ni	As	Hg	Cr (6 ⁺)									
By NIER ^a (mg/kg)																	
Granulated slag	0.94	2.4	14.3	95.1	881.4	N.D ^c	N.D	0.5									
Air cooled slag	0.37	1.9	8.0	57.7	477.0	N.D	N.D	0.9									
	SiO ₂	Fe ₂ O ₃	MgO	CaO	Al ₂ O ₃	MnO	Cr ₂ O ₃	SO ₃	P ₂ O ₅	ZnO	TiO ₂	NiO	K ₂ O	V ₂ O ₅	Co ₃ O ₄	NaO	Cl
By GIST ^b (%)																	
Granulated slag	41.74	21.83	18.36	7.85	5.79	1.02	1.00	0.75	0.44	0.32	0.25	0.25	0.22	0.05	0.04	0.03	0.02
Air cooled slag	51.72	14.98	27.81	0.32	1.56	0.50	1.55	0.44	0.01	0.04	0.03	0.13	0.04	0.02	0.03	0.70	0.11

^aNIER: National Institute of Environmental Research

^bGIST: Gwangju Institute of Science and Technology

^cN.D: Not Detected

Supplemental Table S2. Heavy metal contents of particulate matter in the year 2016 at Gwangyang and Yeosu (ng/m³)^a. This table was constructed based on reports from the National Institute of Environmental Research (National Institute of Environmental Research (NIER) 2017).

Heavy metals	Gwangyang		Yeosu	
	Taein-dong	Geumho-dong	Haesan-dong	Jusam-dong
As	11.0	11.2	5.7	7.9
Be	N.D ^b	N.D	N.D	N.D
Cd	0.5	0.6	0.5	0.7
Co	1.1	0.4	0.3	0.4
Cr	47.4	48.7	9.9	10.4
Fe	2327.4	2340.3	1249.1	1498.8
Mn	56.1	54.5	34.9	41.0
Ni	22.0	22.5	12.2	15.0
Pb	35.7	39.7	36.4	37.7
Zn	1478.0	1485.5	546.1	560.6
V	N.D	N.D	N.D	N.D

^a Heavy metal contents were analyzed by Inductively Coupled Plasma/Atomic Emission Spectrometer

^b N.D: Not detected

Supplemental Table S3. Characteristics of Gwangyang and Yeosu Cities in 2014 (All the data are gathered from Statistics Korea^a).

	Sub-regions of Gwangyang				
	Gwangyang	Yeosu	Gwangyang-eup	Jungma-dong	Geumho-domg
Area (km ²)	460	510	55	10	21
Mid-year registered residents (number)					
Total	151,261.0	289,248.5	48,974	53,440	14,429
Less than 9 years, n(%)	16,310 (10.78)	25,439.5 (8.80)	5,517 (11.27)	7,476 (13.99)	996 (6.9)
10 to 29 years, n(%)	40,888 (27.03)	71,366 (24.67)	12,496 (25.52)	15,417 (28.85)	5,334 (36.97)
30 to 59 years, n(%)	72,905 (48.20)	133,716 (46.23)	23,446 (47.87)	27,487 (51.44)	6,978 (48.36)
Equal to or more than 60 years of age, n(%)	21,158 (13.99)	58,727 (20.30)	7,515 (15.34)	3,060 (5.73)	1,121 (7.77)
Population density (thousands/km ²)	0.33	0.57	0.89	5.34	0.69
Gross regional domestic product per capita (1,000,000 Korean Won)	9,950,509	18,262,290			
Meteorological factors (Annual mean)					
Temperature (°C)	14.4	14.7			
Relative Humidity (%)	63.8	60.0			
Characteristics related to hospital use					
General hospital (Number)	1	3	0	1	0
Hospital (Number)	3	6	1	2	0
Clinic (Number)	51	139	16	24	1
Number of doctors	106	372	20	72	4

^a <http://kostat.go.kr/portal/korea/index.action>

Supplemental Table S4. Number of eligible person who retained eligibility criteria for the health insurance service.

Year	Total	Age group, N (%)								
		0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-
Gwangyang City										
2002	135304	24620 (18.2)	20006 (14.79)	18887 (13.96)	28588 (21.13)	19765 (14.61)	9387 (6.94)	8004 (5.92)	4362 (3.22)	1685 (1.25)
2003	134479	22998 (17.1)	20214 (15.03)	18213 (13.54)	28034 (20.85)	20723 (15.41)	9819 (7.3)	8124 (6.04)	4533 (3.37)	1821 (1.35)
2004	135989	22048 (16.21)	20926 (15.39)	17861 (13.13)	27890 (20.51)	21661 (15.93)	10744 (7.9)	8129 (5.98)	4871 (3.58)	1859 (1.37)
2005	137149	20387 (14.86)	21957 (16.01)	17774 (12.96)	26965 (19.66)	22834 (16.65)	11942 (8.71)	8058 (5.88)	5281 (3.85)	1951 (1.42)
2006	137070	19198 (14.01)	22625 (16.51)	17324 (12.64)	25682 (18.74)	23887 (17.43)	12647 (9.23)	7986 (5.83)	5716 (4.17)	2005 (1.46)
2007	146340	18219 (12.45)	24307 (16.61)	19019 (13)	25040 (17.11)	25623 (17.51)	13922 (9.51)	10124 (6.92)	7569 (5.17)	2517 (1.72)
2008	148937	17601 (11.82)	24994 (16.78)	19348 (12.99)	24005 (16.12)	27153 (18.23)	14928 (10.02)	10220 (6.86)	7981 (5.36)	2707 (1.82)
2009	150932	16924 (11.21)	25332 (16.78)	19368 (12.83)	23556 (15.61)	28157 (18.66)	16035 (10.62)	10195 (6.75)	8391 (5.56)	2974 (1.97)
2010	145591	16194 (11.12)	24842 (17.06)	17695 (12.15)	22770 (15.64)	28172 (19.35)	17377 (11.94)	8846 (6.08)	6838 (4.7)	2857 (1.96)
2011	148462	16067 (10.82)	24314 (16.38)	18784 (12.65)	22866 (15.4)	28764 (19.37)	18873 (12.71)	8989 (6.05)	6851 (4.61)	2954 (1.99)
2012	151174	16356 (10.82)	23890 (15.8)	18751 (12.4)	22803 (15.08)	29057 (19.22)	20304 (13.43)	9432 (6.24)	7303 (4.83)	3278 (2.17)
2013	152106	16372 (10.76)	22903 (15.06)	18745 (12.32)	22502 (14.79)	29190 (19.19)	21717 (14.28)	9769 (6.42)	7429 (4.88)	3479 (2.29)
2014	152738	16221 (10.62)	21743 (14.24)	19368 (12.68)	21967 (14.38)	28975 (18.97)	22665 (14.84)	10651 (6.97)	7426 (4.86)	3722 (2.44)
Gwangyang-eup										
2002	40412	6506 (16.1)	6041 (14.95)	6632 (16.41)	7393 (18.29)	6145 (15.21)	3212 (7.95)	2614 (6.47)	1337 (3.31)	532 (1.32)
2003	41291	6366 (15.42)	6160 (14.92)	6640 (16.08)	7590 (18.38)	6528 (15.81)	3355 (8.13)	2675 (6.48)	1390 (3.37)	587 (1.42)
2004	42807	6456 (15.08)	6395 (14.94)	6597 (15.41)	8032 (18.76)	6826 (15.95)	3701 (8.65)	2710 (6.33)	1506 (3.52)	584 (1.36)
2005	43434	6161 (14.18)	6589 (15.17)	6606 (15.21)	7975 (18.36)	7109 (16.37)	4044 (9.31)	2711 (6.24)	1626 (3.74)	613 (1.41)
2006	43370	5920 (13.65)	6596 (15.21)	6338 (14.61)	7798 (17.98)	7322 (16.88)	4243 (9.78)	2713 (6.26)	1795 (4.14)	645 (1.49)
2007	44006	5655 (12.85)	6939 (15.77)	6309 (14.34)	7710 (17.52)	7563 (17.19)	4486 (10.19)	2773 (6.3)	1846 (4.19)	725 (1.65)
2008	44610	5517 (12.37)	7022 (15.74)	6216 (13.93)	7508 (16.83)	7836 (17.57)	4828 (10.82)	2911 (6.53)	1981 (4.44)	791 (1.77)
2009	44729	5349 (11.96)	7065 (15.8)	6049 (13.52)	7315 (16.35)	7909 (17.68)	5201 (11.63)	2950 (6.6)	2062 (4.61)	829 (1.85)
2010	44232	4962 (11.22)	6908 (15.62)	5642 (12.76)	7039 (15.91)	7704 (17.42)	5751 (13)	3083 (6.97)	2212 (5)	931 (2.1)
2011	44693	5056 (11.31)	6636 (14.85)	5898 (13.2)	7079 (15.84)	7776 (17.4)	6014 (13.46)	3073 (6.88)	2234 (5)	927 (2.07)
2012	47192	5206 (11.03)	6684 (14.16)	6156 (13.04)	7368 (15.61)	8219 (17.42)	6746 (14.29)	3323 (7.04)	2432 (5.15)	1058 (2.24)
2013	48339	5355 (11.08)	6472 (13.39)	6242 (12.91)	7511 (15.54)	8467 (17.52)	7270 (15.04)	3388 (7.01)	2491 (5.15)	1143 (2.36)
2014	49360	5499 (11.14)	6286 (12.74)	6422 (13.01)	7482 (15.16)	8676 (17.58)	7497 (15.19)	3748 (7.59)	2536 (5.14)	1214 (2.46)

Jungma-dong

2002	33125	9285 (28.03)	4168 (12.58)	3782 (11.42)	10047 (30.33)	3576 (10.8)	1116 (3.37)	698 (2.11)	317 (0.96)	136 (0.41)
2003	32881	8673 (26.38)	4524 (13.76)	3511 (10.68)	9792 (29.78)	3995 (12.15)	1192 (3.63)	712 (2.17)	330 (1)	152 (0.46)
2004	33943	8460 (24.92)	5018 (14.78)	3515 (10.36)	9849 (29.02)	4494 (13.24)	1347 (3.97)	732 (2.16)	380 (1.12)	148 (0.44)
2005	35708	7959 (22.29)	5844 (16.37)	3782 (10.59)	9818 (27.5)	5253 (14.71)	1671 (4.68)	778 (2.18)	447 (1.25)	156 (0.44)
2006	37889	7881 (20.8)	6578 (17.36)	4056 (10.7)	9813 (25.9)	6096 (16.09)	1941 (5.12)	840 (2.22)	519 (1.37)	165 (0.44)
2007	45189	7653 (16.94)	7390 (16.35)	4866 (10.77)	9876 (21.85)	7276 (16.1)	2997 (6.63)	2962 (6.55)	1756 (3.89)	413 (0.91)
2008	48856	7736 (15.83)	8167 (16.72)	5507 (11.27)	9916 (20.3)	8447 (17.29)	3527 (7.22)	3084 (6.31)	1995 (4.08)	477 (0.98)
2009	51617	7682 (14.88)	8649 (16.76)	5818 (11.27)	10132 (19.63)	9366 (18.15)	4031 (7.81)	3143 (6.09)	2206 (4.27)	590 (1.14)
2010	48688	7696 (15.81)	9202 (18.9)	5531 (11.36)	10102 (20.75)	10085 (20.71)	3803 (7.81)	1262 (2.59)	733 (1.51)	274 (0.56)
2011	49153	7481 (15.22)	9239 (18.8)	5677 (11.55)	9740 (19.82)	10388 (21.13)	4249 (8.64)	1336 (2.72)	751 (1.53)	292 (0.59)
2012	51829	7704 (14.86)	9415 (18.17)	5945 (11.47)	10125 (19.54)	11101 (21.42)	4894 (9.44)	1496 (2.89)	813 (1.57)	336 (0.65)
2013	52297	7567 (14.47)	9186 (17.57)	6044 (11.56)	9759 (18.66)	11391 (21.78)	5534 (10.58)	1620 (3.1)	847 (1.62)	349 (0.67)
2014	53539	7476 (13.96)	9000 (16.81)	6493 (12.13)	9626 (17.98)	11690 (21.83)	6186 (11.55)	1825 (3.41)	871 (1.63)	372 (0.69)

Geumho-domg

2002	19692	3834 (19.47)	4334 (22.01)	1560 (7.92)	4490 (22.8)	4200 (21.33)	893 (4.53)	133 (0.68)	170 (0.86)	78 (0.4)
2003	19097	3375 (17.67)	4345 (22.75)	1544 (8.09)	4146 (21.71)	4199 (21.99)	1087 (5.69)	150 (0.79)	162 (0.85)	89 (0.47)
2004	18731	2891 (15.43)	4467 (23.85)	1615 (8.62)	3728 (19.9)	4195 (22.4)	1384 (7.39)	172 (0.92)	182 (0.97)	97 (0.52)
2005	18114	2429 (13.41)	4535 (25.04)	1608 (8.88)	3199 (17.66)	4176 (23.05)	1682 (9.29)	193 (1.07)	193 (1.07)	99 (0.55)
2006	17372	2002 (11.52)	4521 (26.02)	1616 (9.3)	2695 (15.51)	4163 (23.96)	1878 (10.81)	211 (1.21)	191 (1.1)	95 (0.55)
2007	21358	1566 (7.33)	4660 (21.82)	2521 (11.8)	2289 (10.72)	4495 (21.05)	2290 (10.72)	1471 (6.89)	1604 (7.51)	462 (2.16)
2008	20677	1306 (6.32)	4608 (22.29)	2482 (12)	1821 (8.81)	4607 (22.28)	2376 (11.49)	1358 (6.57)	1626 (7.86)	493 (2.38)
2009	20226	1098 (5.43)	4537 (22.43)	2571 (12.71)	1580 (7.81)	4591 (22.7)	2450 (12.11)	1209 (5.98)	1650 (8.16)	540 (2.67)
2010	16048	937 (5.84)	4331 (26.99)	1970 (12.28)	1305 (8.13)	4309 (26.85)	2534 (15.79)	345 (2.15)	186 (1.16)	131 (0.82)
2011	15543	864 (5.56)	4000 (25.74)	2152 (13.85)	1210 (7.78)	3999 (25.73)	2605 (16.76)	403 (2.59)	181 (1.16)	129 (0.83)
2012	15467	895 (5.79)	3707 (23.97)	2277 (14.72)	1213 (7.84)	3821 (24.7)	2705 (17.49)	540 (3.49)	181 (1.17)	128 (0.83)
2013	14929	936 (6.27)	3356 (22.48)	2239 (15)	1219 (8.17)	3513 (23.53)	2696 (18.06)	665 (4.45)	173 (1.16)	132 (0.88)
2014	14495	994 (6.86)	2945 (20.32)	2420 (16.7)	1256 (8.67)	3097 (21.37)	2654 (18.31)	828 (5.71)	178 (1.23)	123 (0.85)

Supplemental Table S5. Difference-in-difference (DID) analysis to evaluate the association between operation of the ferronickel factory (2008.11-) and the incidence of allergic disease in Gwangyang and Yeosu City (Men).

Disease	Mean number of monthly incidence cases		Mean monthly incidence rate X 100,000		DID estimates ^a
	Gwangyang	Yeosu	Gwangyang	Yeosu	Relative risk (95% CI)
Pruritus					
2006.11-2008.10	27.96	54.88	36.04	35.75	ref
2008.11-2010.10	32.63	70.71	51.25	45.91	1.08 (0.85-1.37)
2010.11-2012.10	45.58	64.79	76.56	43.73	1.69 (1.34-2.13)
2012.12-2014.10	41.92	71.58	66.3	50.37	1.27 (1.01-1.60)
Acute Bronchitis					
2006.11-2008.10	404.83	834.54	588.4	593.89	ref
2008.11-2010.10	382.71	678.96	582.33	519.56	1.07 (0.85-1.36)
2010.11-2012.10	371.75	597.88	582.97	490.04	1.14 (0.90-1.45)
2012.12-2014.10	352.29	495.92	522.21	428.95	1.17 (0.91-1.50)
Allergic dermatitis					
2006.11-2008.10	306.33	503.92	430.59	360.55	ref
2008.11-2010.10	281.54	456.88	401.86	343.66	1.02 (0.84-1.24)
2010.11-2012.10	284.38	435.46	401.96	331.8	1.06 (0.87-1.29)
2012.12-2014.10	245.21	386.13	351.25	298.95	1.03 (0.84-1.26)
Atopic dermatitis					
2006.11-2008.10	77.29	127.29	143.49	134.99	ref
2008.11-2010.10	71.67	107.96	142.29	125.22	1.13 (0.99-1.29)
2010.11-2012.10	64.88	91.71	127.68	118.83	1.07 (0.93-1.23)
2012.12-2014.10	52.63	83.29	101.53	112.05	0.90 (0.78-1.04)
Seborrheic dermatitis					
2006.11-2008.10	56.75	153.79	73.72	99.13	ref
2008.11-2010.10	57.5	144.21	75.54	92.75	0.98 (0.87-1.11)
2010.11-2012.10	62.71	148.08	80.2	97.74	0.99 (0.88-1.12)
2012.12-2014.10	60.42	137.46	78.49	92.79	1.02 (0.90-1.16)
Irritant dermatitis					
2006.11-2008.10	59.21	219.92	85.67	151.72	ref
2008.11-2010.10	49.5	163.08	76.9	121.56	1.03 (0.87-1.23)
2010.11-2012.10	58.13	165.33	90.53	131.4	1.12 (0.95-1.33)
2012.12-2014.10	57	163.88	87.79	132.05	1.09 (0.92-1.28)
Other dermatitis					
2006.11-2008.10	88.08	167.21	137.04	118.96	ref
2008.11-2010.10	80.33	164.75	134.44	120.3	1.03 (0.89-1.20)
2010.11-2012.10	95.38	171.79	167.51	131.24	1.18 (1.03-1.36)
2012.12-2014.10	104.04	187.96	184.53	154.67	1.10 (0.97-1.26)
Unspecified dermatitis					
2006.11-2008.10	36.46	63.38	49.35	44.55	ref
2008.11-2010.10	54.58	54.08	68.57	35.69	1.72 (1.29-2.31)
2010.11-2012.10	31.38	64	41.48	45.04	0.83 (0.61-1.12)
2012.12-2014.10	26.54	59.5	35.77	42.69	0.75 (0.55-1.03)
Asthma					
2006.11-2008.10	95.38	346.96	157.19	279.92	ref
2008.11-2010.10	111.83	297.21	196.53	263.04	1.03 (0.83-1.27)
2010.11-2012.10	105.83	224.08	181.84	226.8	1.10 (0.88-1.38)
2012.12-2014.10	100.63	170.63	175.16	186.2	1.29 (1.02-1.63)
Vasomotor and allergic					

rhinitis					
2006.11-2008.10	321.63	614.29	479.53	458.61	ref
2008.11-2010.10	340.63	544.13	539.96	420.55	1.12 (0.91-1.37)
2010.11-2012.10	313.58	408.33	494.84	349.37	1.24 (1.00-1.53)
2012.12-2014.10	273.42	392.13	437.82	356.71	1.07 (0.86-1.33)
Humerus Fx					
2006.11-2008.10	27.96	45.25	43.05	36.6	ref
2008.11-2010.10	25.17	41.04	35.95	33.73	0.89 (0.72-1.11)
2010.11-2012.10	25.21	37.42	36.98	31.17	0.99 (0.80-1.24)
2012.12-2014.10	21.88	38.75	32.89	32.88	0.84 (0.67-1.04)

^a DID estimates are derived from following model.

$$\log [\mu_t] = \beta_0 + \beta_1 R + \beta_2 T_t + \beta_3 P_1 + \beta_4 P_2 + \beta_5 P_3 + \beta_6 R * P_1 + \beta_7 R * P_2 + \beta_8 R * P_3 + \varepsilon$$

R as an indicator variable for region ($R=1$ Gwangyang city, $R=0$ Yeosu city), T_t as the time elapsed since the start of the study (in month unit), P_x as an indicator variable for study period after the ferronickel factory operation ($P_1= 2008.11-2010.10$; $P_2= 2010.11-2012.10$; $P_3= 2012.11-2014.10$), and $R * P_x$ as an interaction term between region and period indicators.

the ferronickel factory (2008.11-) and the incidence of allergic disease in Gwangyang and Yeosu City (Women).

Disease	Mean number of monthly incidence cases		Mean monthly incidence rate X 100,000		DID estimates
	Gwangyang	Yeosu	Gwangyang	Yeosu	Relative risk (95% CI)
Pruritus					
2006.11-2008.10	25.46	58.04	30.93	35.07	ref
2008.11-2010.10	37.21	78.96	56.23	48.45	1.23 (0.97-1.57)
2010.11-2012.10	50.71	87.08	82.55	56.51	1.55 (1.24-1.94)
2012.12-2014.10	47.29	94.83	69.26	64.7	1.14 (0.91-1.42)
Acute bronchitis					
2006.11-2008.10	447.21	867.75	669.09	636.36	ref
2008.11-2010.10	396.71	688.38	622.77	550.64	1.03 (0.81-1.30)
2010.11-2012.10	370.79	561.96	626.18	498.87	1.14 (0.90-1.45)
2012.12-2014.10	340.71	441.38	558.92	410.4	1.24 (0.96-1.60)
Allergic dermatitis					
2006.11-2008.10	353.54	618.33	506.13	436.09	ref
2008.11-2010.10	313.38	540.58	456.21	401.42	1.01 (0.84-1.22)
2010.11-2012.10	299.88	506.71	446.85	392.35	1.01 (0.84-1.22)
2012.12-2014.10	256.75	418.63	387.76	332.25	1.04 (0.85-1.27)
Atopic dermatitis					
2006.11-2008.10	79.79	133.42	154.33	145.53	ref
2008.11-2010.10	78.08	115.54	155.5	133.59	1.16 (1.04-1.29)
2010.11-2012.10	66.54	103.79	133.33	136.35	0.97 (0.87-1.09)
2012.12-2014.10	55.42	83.88	107.84	112.59	0.95 (0.84-1.07)
Seborrheic dermatitis					
2006.11-2008.10	52.5	136.67	72.93	92.84	ref
2008.11-2010.10	52.96	137.13	75.78	96.52	0.93 (0.82-1.05)
2010.11-2012.10	55.5	133.46	80.45	97.5	0.97 (0.86-1.10)
2012.12-2014.10	57.38	125.46	82.28	96.3	1.01 (0.89-1.14)
Irritant dermatitis					
2006.11-2008.10	83.29	257.46	118.73	173.52	ref
2008.11-2010.10	67.92	209.17	103.75	152.67	0.89 (0.75-1.06)
2010.11-2012.10	91.71	205.17	139.24	161.16	1.14 (0.96-1.34)
2012.12-2014.10	81.58	195	123.25	157.95	1.03 (0.87-1.21)
Other dermatitis					
2006.11-2008.10	91.04	187.08	145.56	131.75	ref
2008.11-2010.10	87.88	184.17	145.21	132.76	1.04 (0.87-1.24)
2010.11-2012.10	118.5	195.17	199.59	152.27	1.25 (1.06-1.47)
2012.12-2014.10	113.75	210.79	200.03	175.04	1.09 (0.92-1.28)
Unspecified dermatitis					
2006.11-2008.10	45.29	82.67	59.06	56.28	ref
2008.11-2010.10	70	72.71	86.06	47.25	1.63 (1.19-2.24)
2010.11-2012.10	43.46	96.38	55.61	63.67	0.78 (0.57-1.08)
2012.12-2014.10	40.63	84.33	52.73	60.59	0.78 (0.56-1.08)
Asthma					
2006.11-2008.10	114.83	430.63	176.2	325.9	ref
2008.11-2010.10	139.79	372.96	231.24	305.01	1.08 (0.86-1.35)
2010.11-2012.10	132.42	269.13	211.62	244.93	1.23 (0.97-1.56)
2012.12-2014.10	120.42	189.04	194.12	192.2	1.44 (1.12-1.85)
Vasomotor and allergic rhinitis					

2006.11-2008.10	354.83	709.67	550.45	516.39	ref
2008.11-2010.10	366.29	611.83	596.33	472.91	1.10 (0.89-1.35)
2010.11-2012.10	317.29	446.83	536.94	382.82	1.22 (0.98-1.52)
2012.12-2014.10	277	407.67	475.5	376.39	1.10 (0.88-1.38)
Humerus Fx					
2006.11-2008.10	19.5	41.71	26.56	26.16	ref
2008.11-2010.10	19.58	43.42	25.71	25.28	0.97 (0.79-1.19)
2010.11-2012.10	19.38	41.96	24.86	23.61	1.00 (0.81-1.24)
2012.12-2014.10	21.54	44.29	25.46	24.25	1.00 (0.81-1.23)

Supplemental Table S7. The association between the operation of the ferronickel factory and the incidence of allergic disease in the sub-regions of Gwangyang. Jungma-dong and Geumho-dong are located within 10 km from the ferronickel factory

and Gwangyang-eup is located over 15 km from the ferronickel factory.

Disease	Mean number of monthly incidence cases		Mean monthly incidence rate ^a x 100,000		Relative risk (95% CI)
	Before (2004.01-2008.10)	After (2008.11-2014.12)	Before (2004.01-2008.10)	After (2008.11-2014.12)	Step change
Pruritus					
Gwangyang-eup	11.55	19.69	25.96	41.28	1.51 (1.19, 1.92) ^b
Jungma-dong	14.26	38.72	36.62	89.62	1.93 (1.32, 2.83) ^b
Geumho-dong	5.14	5.91	26.11	59.68	1.81 (1.09, 3.01) ^b
Acute Bronchitis					
Gwangyang-eup	381.93	279.92	930.77	693.63	0.84 (0.71, 1.00) ^b
Jungma-dong	346.33	328.70	901.90	704.80	0.97 (0.82, 1.15) ^b
Geumho-dong	114.40	63.16	638.91	619.62	0.94 (0.69, 1.28) ^b
Allergic dermatitis					
Gwangyang-eup	201.33	189.62	468.06	435.75	0.99 (0.88, 1.12) ^b
Jungma-dong	228.09	219.89	582.99	455.16	1.02 (0.91, 1.16) ^b
Geumho-dong	85.29	59.07	468.38	432.62	1.10 (0.93, 1.30) ^b
Atopic dermatitis					
Gwangyang-eup	56.67	41.18	176.35	133.36	1.08 (0.94, 1.23) ^b
Jungma-dong	62.93	57.84	170.39	139.69	1.21 (1.07, 1.37)
Geumho-dong	22.02	10.11	155.60	108.82	0.89 (0.69, 1.14)
Seborrheic dermatitis					
Gwangyang-eup	37.41	38.05	83.06	84.86	0.88 (0.76, 1.03) ^b
Jungma-dong	28.81	41.08	70.49	82.01	1.11 (0.97, 1.27)
Geumho-dong	12.97	13.74	66.54	82.15	1.16 (0.90, 1.49)
Irritant dermatitis					
Gwangyang-eup	74.28	67.04	179.20	168.39	0.92 (0.80, 1.05)
Jungma-dong	23.62	30.68	61.39	66.83	1.00 (0.84, 1.19)
Geumho-dong	9.05	8.09	53.91	63.18	0.80 (0.58, 1.12) ^b
Other dermatitis					
Gwangyang-eup	41.83	65.28	101.53	176.48	1.09 (0.96, 1.24)
Jungma-dong	57.40	75.66	147.31	174.81	0.85 (0.75, 0.97)
Geumho-dong	18.43	19.65	113.66	185.99	0.94 (0.74, 1.19)
Unspecified dermatitis					
Gwangyang-eup	38.47	26.16	82.40	54.23	0.65 (0.52, 0.81) ^b
Jungma-dong	10.57	24.76	28.79	47.87	5.58 (2.37, 13.13) ^b
Geumho-dong	3.55	7.39	22.07	43.89	4.90 (2.39, 10.03) ^b
Asthma					
Gwangyang-eup	79.09	69.01	214.72	175.80	0.89 (0.71, 1.10) ^b
Jungma-dong	88.50	104.65	242.65	241.63	1.48 (1.15, 1.90) ^b
Geumho-dong	31.09	17.22	207.85	171.90	1.15 (0.76, 1.75) ^b
Vasomotor and allergic rhinitis					
Gwangyang-eup	181.19	208.76	438.53	535.50	0.99 (0.84, 1.17) ^b
Jungma-dong	293.95	286.18	736.62	624.45	1.23 (1.08, 1.41) ^b
Geumho-dong	98.72	65.93	549.62	575.25	0.99 (0.84, 1.18) ^b
Humerus Fracture					
Gwangyang-eup	12.34	12.85	30.93	28.66	0.99 (0.79, 1.26)
Jungma-dong	13.41	14.20	38.15	30.84	0.87 (0.72, 1.06)
Geumho-dong	6.90	5.51	41.31	34.33	0.79 (0.55, 1.13)

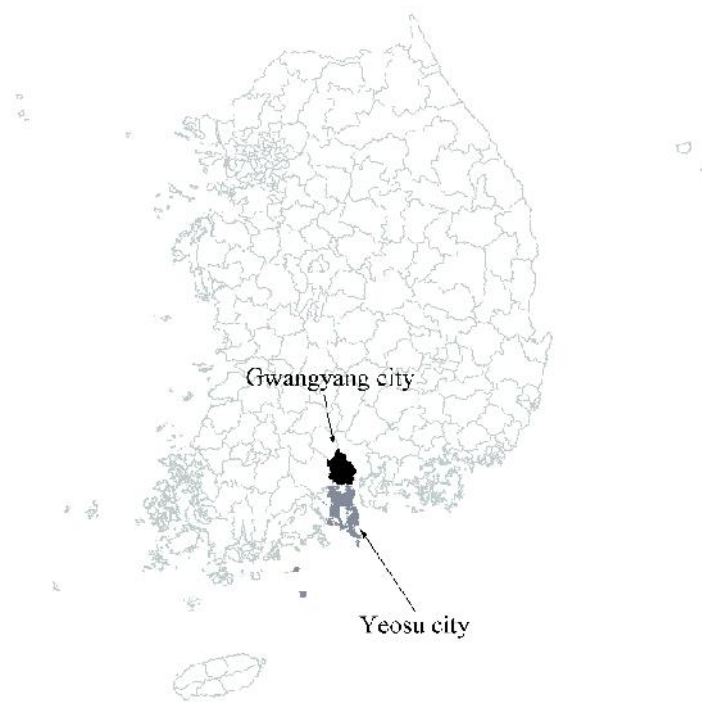
^aAge standardised according to WHO standard population

^bBreusch-Godfrey test revealed serial autocorrelation. Therefore, robust standard errors are used to calculate 95% confidence

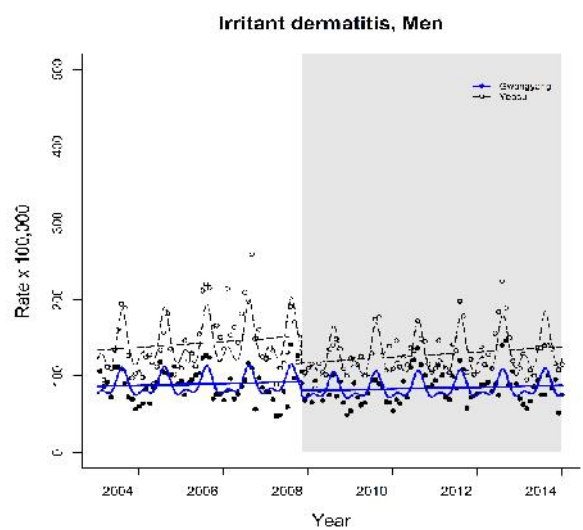
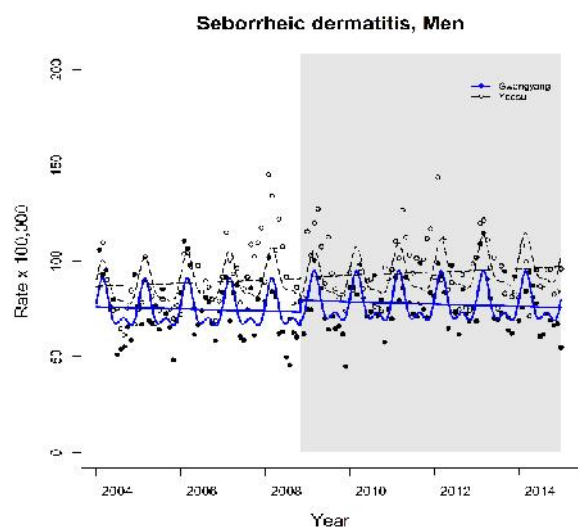
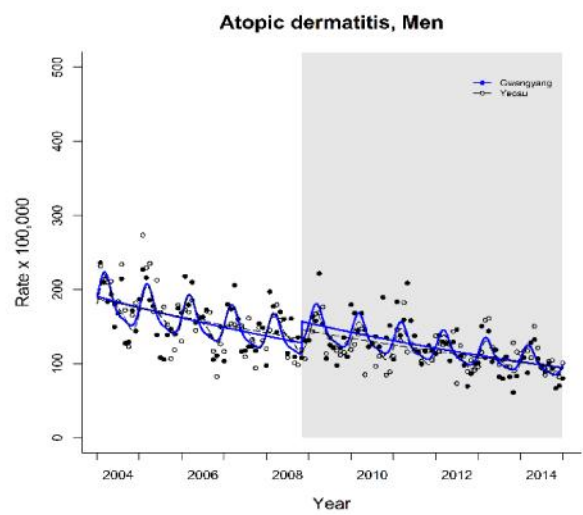
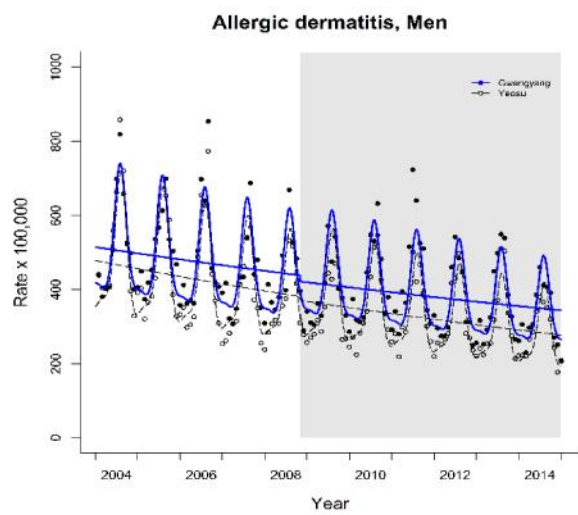
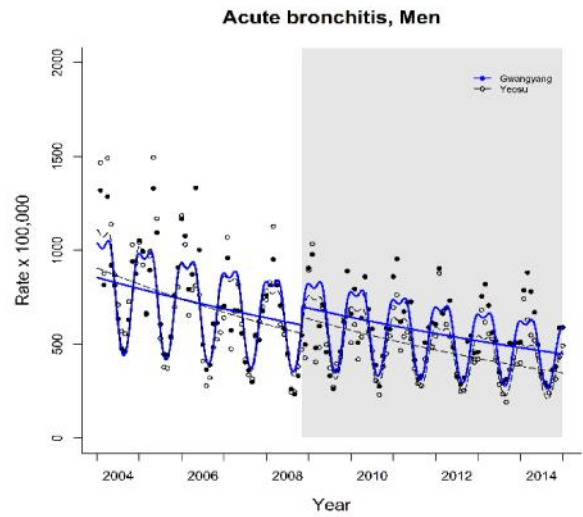
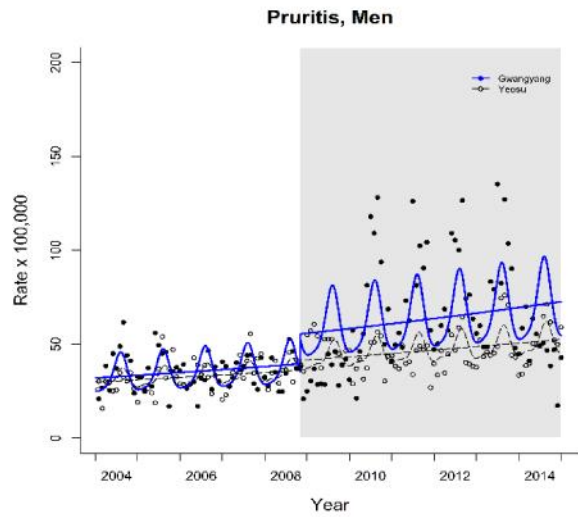
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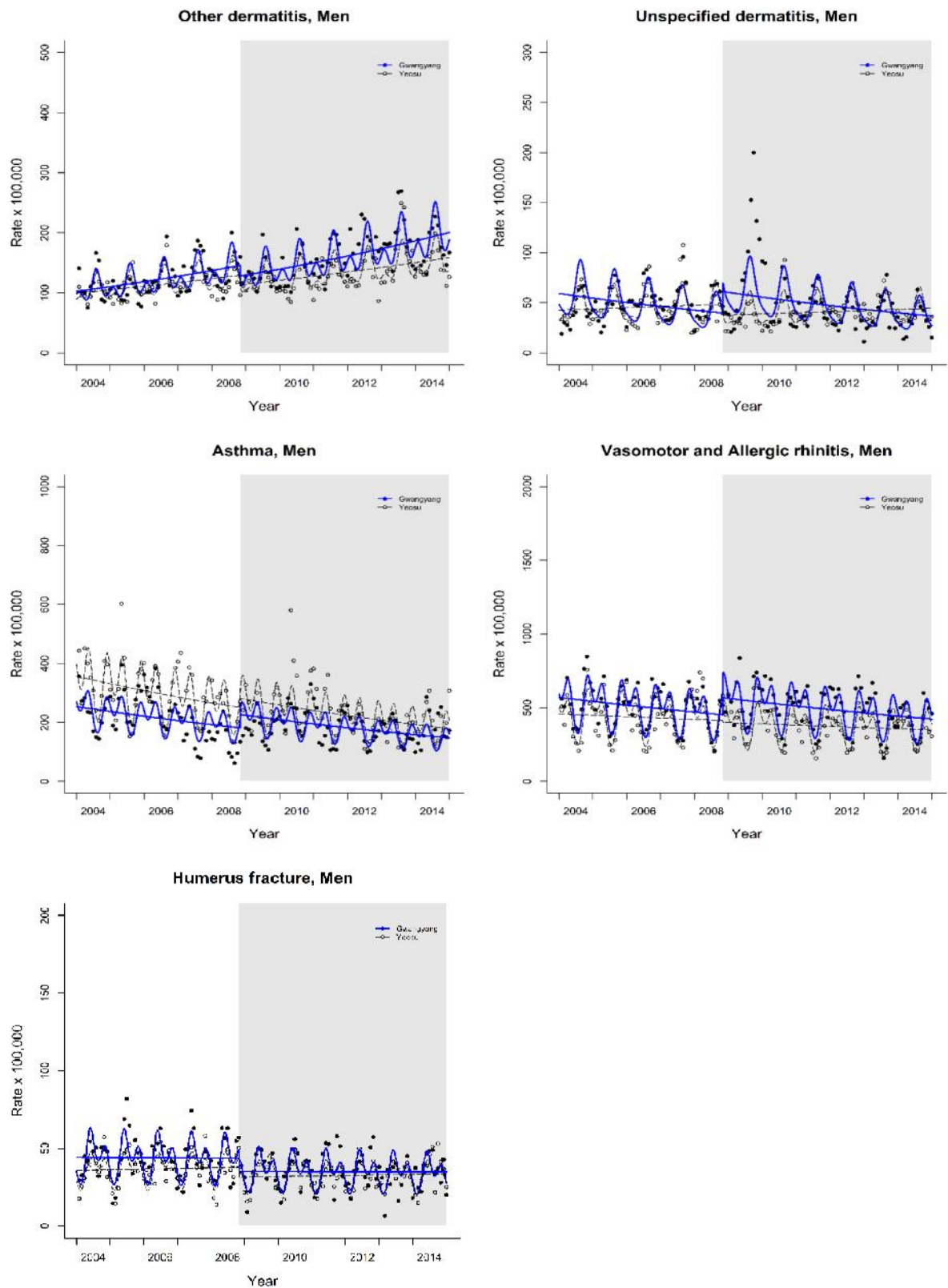


Supplemental Figure S1. Location of monitoring stations of Supplementary Table S2

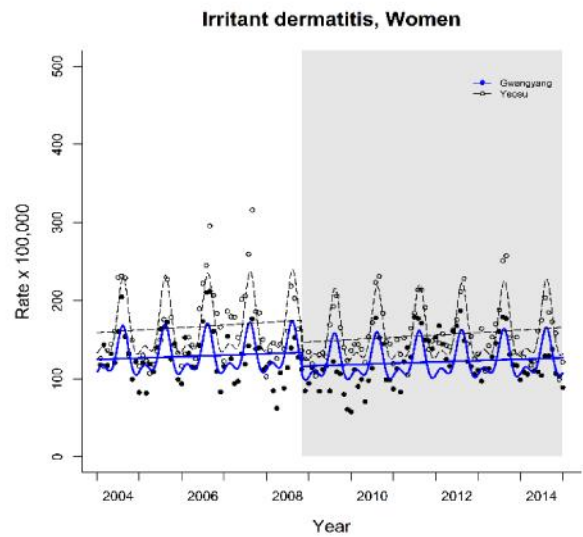
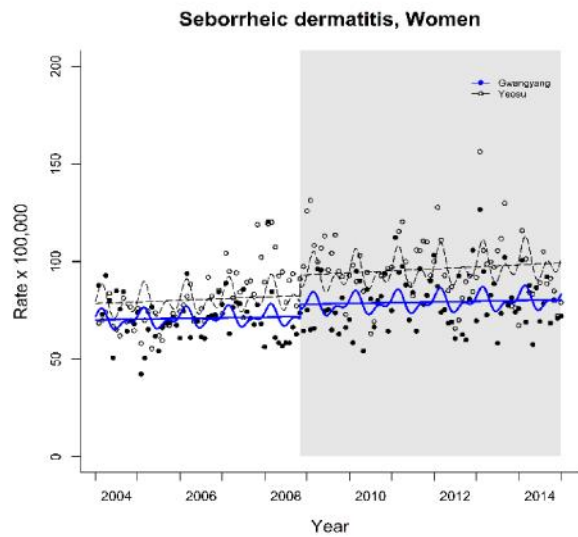
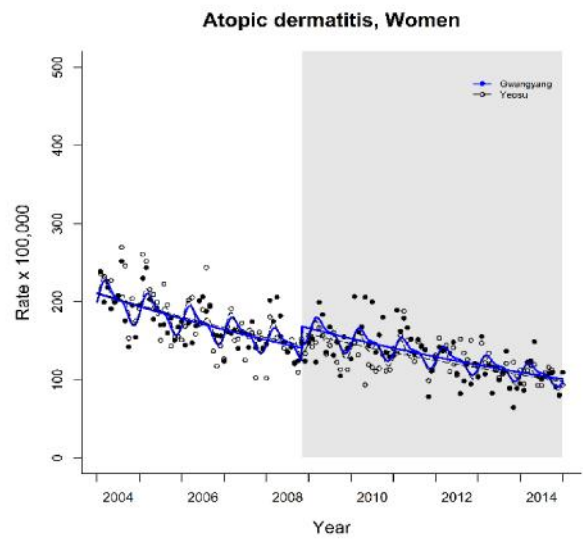
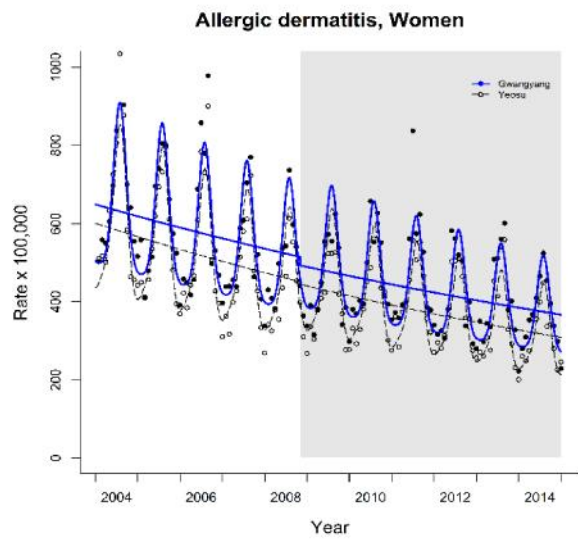
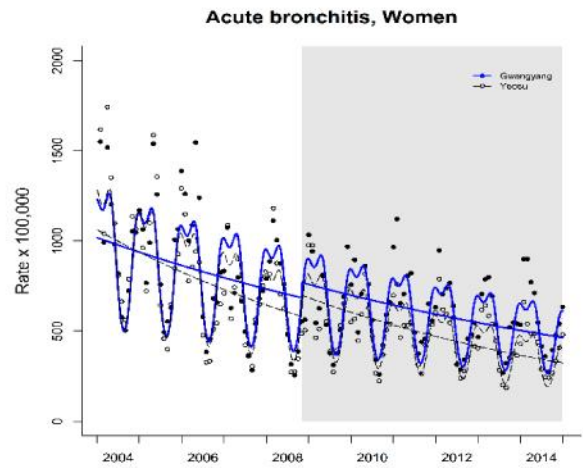
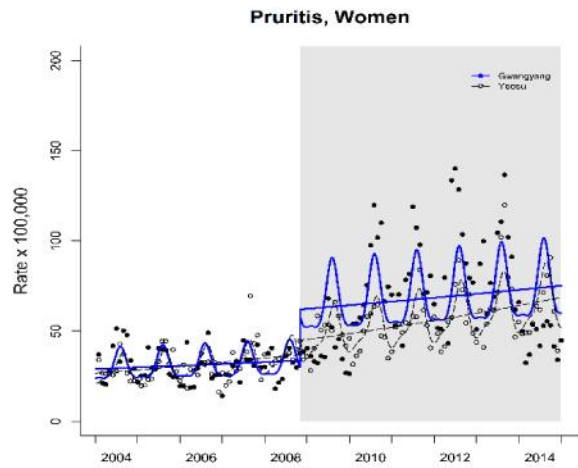


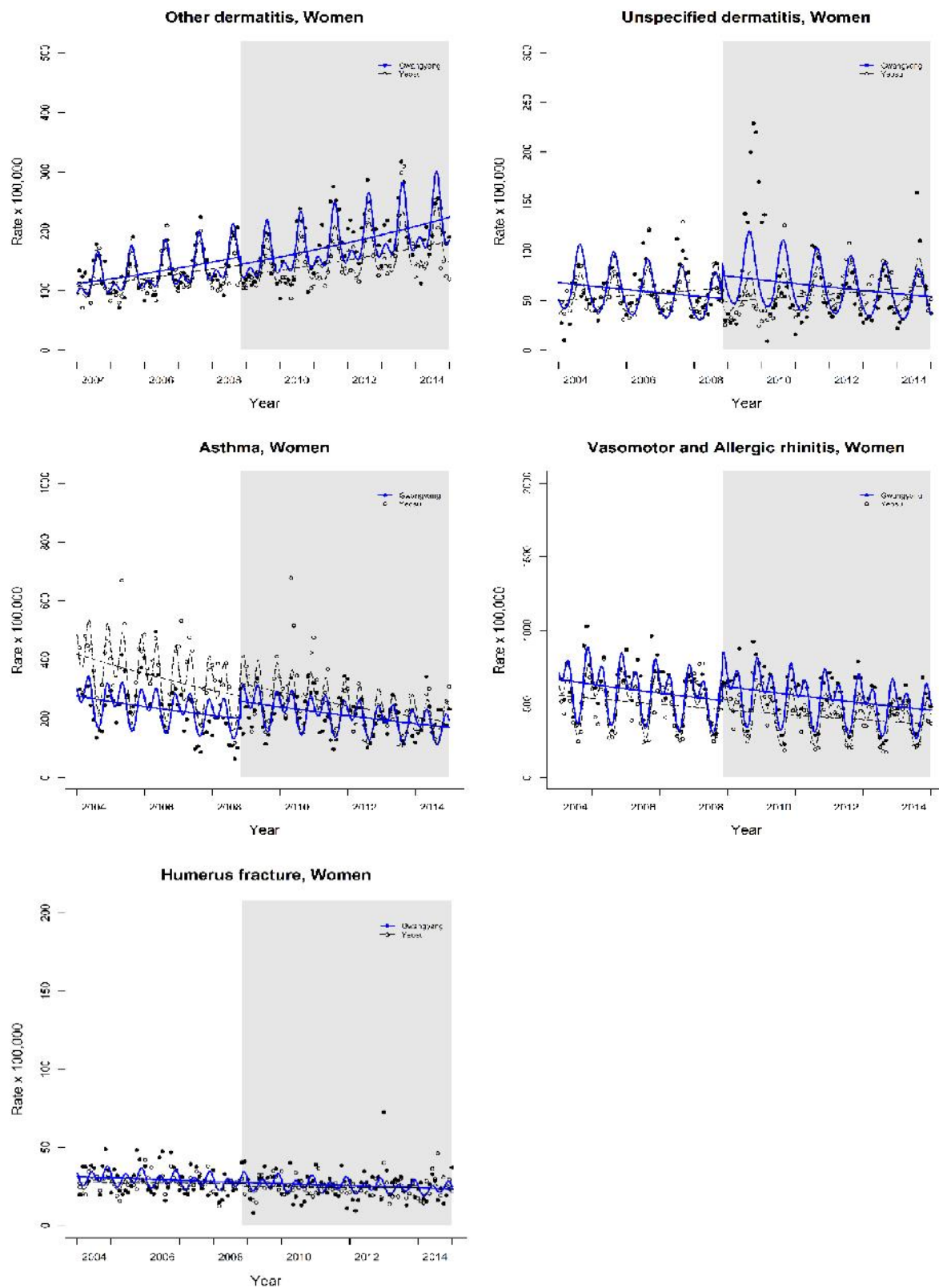
Supplemental Figure S2. Map of the Republic of Korea, including the study area, Gwangyang City, and the comparison city, Yeosu



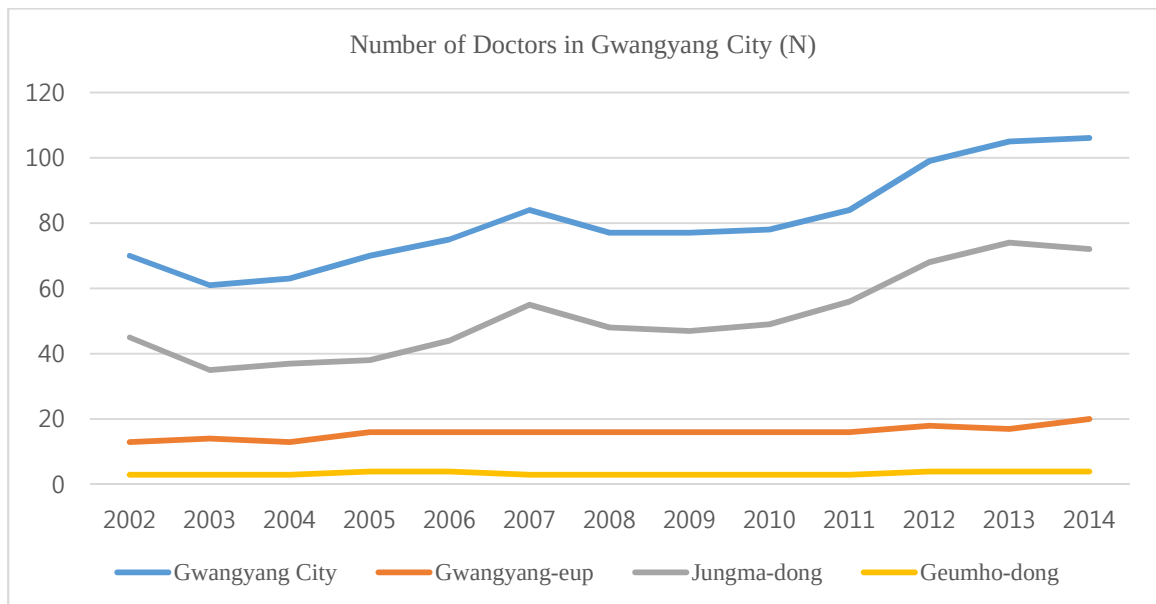
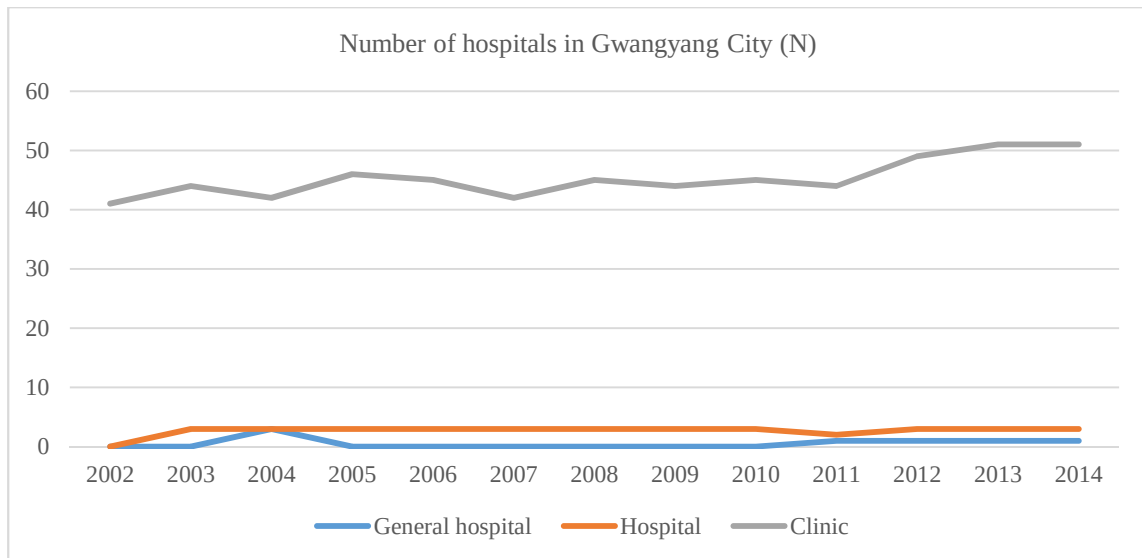


Supplemental Figure S3. The association between the operation of the ferronickel factory (2008.11-) and the incidence of allergic disease in Gwangyang and Yeosu City among men





Supplemental Figure S4. The association between the operation of the ferronickel factory (2008.11-) and the incidence of allergic disease in Gwangyang and Yeosu City among women



Supplemental Figure S5. Temporal trends in yearly number of doctors and hospitals in Gwangyang City from 2002 to 2014