Master's Thesis of Public Health

Association between Community Water Fluoridation Implementation and Bone Health:

A Natural Experiment in Cheongju

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Abstract

Association between Community Water Fluoridation Implementation and Bone Health:

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Objectives: The community water fluoridation (referred to as "CWF") was conducted in Cheongju City in South Korea from 1982 to 2004. The purpose of this study was to evaluate epidemiologically the risk of CWF for adverse health effect, specifically bone related diseases (hip fracture, osteoporosis, and bone cancer).

Design: This study was an ecological study based on natural experiment design.

Methods: Study participants were residents in Cheongju from 2004 to 2013 and data were collected by National Health Insurance Service database. Hip fracture, osteoporosis, and bone cancer among adverse health diseases were selected. We ensured the trend of medical use trend after CWF ceased in Cheongju and analyzed the prevalence of selected disease to evaluate the risk of CWF. The Hierarchical

Bayesian spatio-temporal Poisson regression model which consider spatial and temporal correlation was performed to analyze the association between implementation of CWF and the prevalence of selected diseases of residents in Cheongju. Conditional autocorrelation (CAR) which is frequently used to control spatial correlation was applied in this analysis. The calculation method for Bayesian estimation was based on the R-INLA.

Results: After CWF ceased in Cheongju, we observed increasing trend in hip fracture, osteoporosis and bone cancer in both areas (fluoridated and non-fluoridated areas). However, there was no statically significant difference in the prevalence of selected bone diseases in CWF area (RR = 0.95, 95% CrI: 0.87-1.05; RR = 0.94, 95% CrI: 0.87-1.02; RR = 1.20 95% CrI: 0.89-1.61, respectively).

Conclusions: We used a spatiotemporal method to analyze the medical use of selected bone diseases from 2004 to 2013 in Cheongju with small area unit by using National Health Insurance Service data. Our study verified that there was no statistically different in prevalence of selected bone disease between CWF and non-CWF areas after CWF was ceased. With this results, we confirmed that fluoridation has no negative impacts on adverse health effects. There was no clear evidence that exposure of CWF increased the risk on health effects. Our study provided one of the scientific evidence and it is necessary to research and develop as a public health prevention program continuously.

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Keywords: Community water fluoridation, adverse health effect, natural experiment, spatiotemporal analysis, small-area studies, environmental epidemiology

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List of Abbreviations

AIC	Akaike Information Criterion
CAR	Conditional AutoRegressive
CDC	Centers for Disease Control and prevention
CWF	Community Water Fluoridation
DIC	Deviance Information Criterion
DMFT	Decayed, Missing, and Filled Teeth
ICD	International Classification of Diseases
INLA	Integrated Nested Laplace Approximations
MCMC	Markov Chain Monte Carlo
MeSH	Medical Subject Headings
MIDS	MicroData Integrated Service
NHIS	National Health Insurance Service
RR	Relative Risk
SIR	Standardized Incidence Ratios
WHO	World Health Organization

CHAPTER 1. INTRODUCTION

1.1 Background information

Definition of community water fluoridation and history

Community water fluoridation (refer as "CWF") is public health prevention program that prevents dental caries by adjusting the amount of fluoride level in community water system that is not harmful to human (CDC, 2016). In January of 1945, CWF was implemented first in the world in Grand Rapids, Michigan and Newburgh, New York in the United States with concentration of 1ppm (1.0 parts of per million) as part of case study (Crawford, 1995). In the same year in May, it began in Brantford, Ontario in Canada (Rabb-Waytowich, 2015). After the results of the effects of these programs were published between 1950s to 1960s, many countries such as Australia, Brazil, Ireland, New Zealand, the United Kingdom, and elsewhere has been implemented CWF program (Hutton et al., 1951; Ludwig, 1965; Jones et al., 2005). With seventy-years history of CWF, fluoridation of drinking water has been declared the ten greatest public health achievements of the 20^{th} century by the Centers for Disease Control (CDC). CWF considered as the safest and highest cost-effectiveness methods of preventing tooth decay regardless of socioeconomic status and it actively conducted by many developed countries, as it is recommended by the World Health Organization (WHO) (Klein et al., 1985).

Debate continues over community water fluoridation

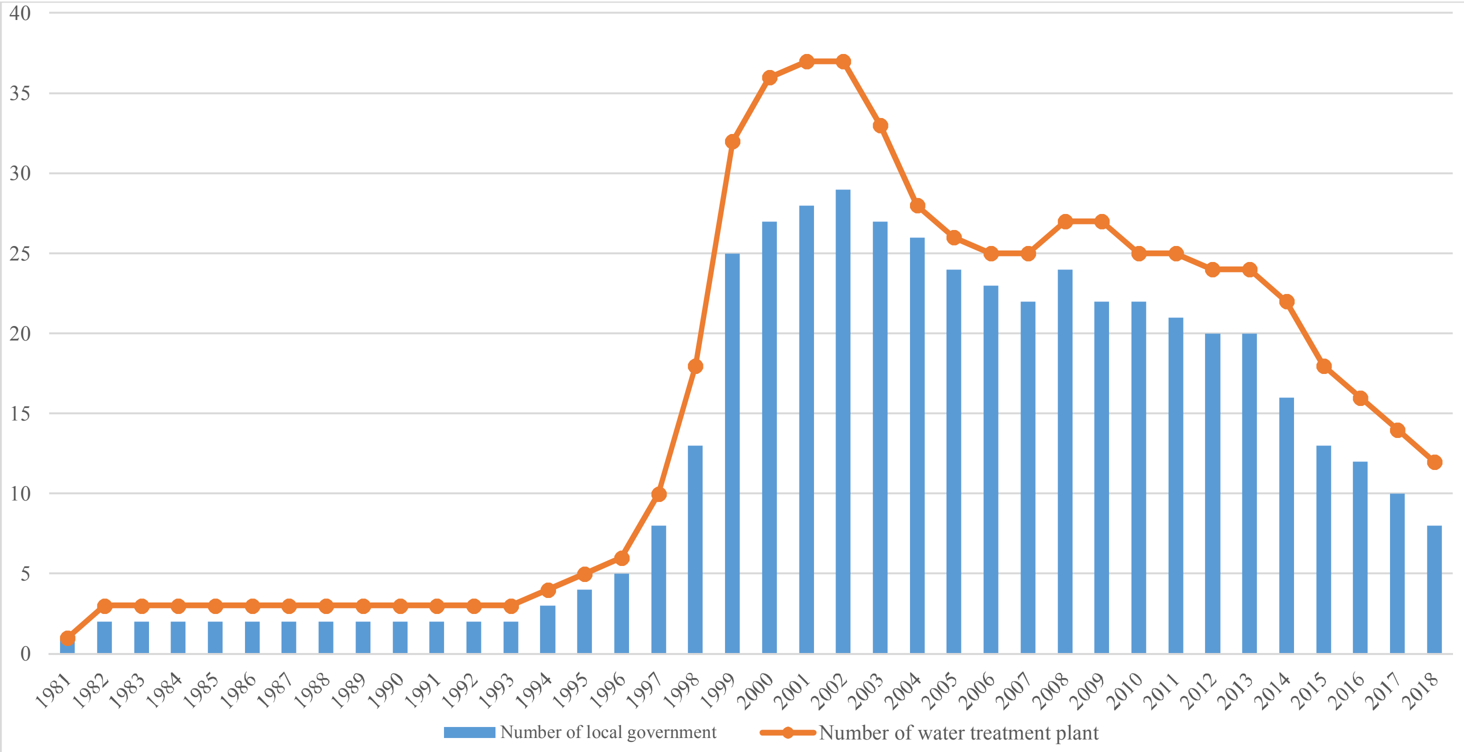
The positive effects of CWF program already has been confirmed in published in many scientific literatures in various of countries. With health and economic benefits, fluoridation is the most effective way of preventing and controlling dental caries and many countries has already been proved effectiveness of water fluoridation (Kanduti et al., 2016). Considering the effect of prevention of dental caries and efficiency, it is the minimum national prevention program for oral health and can ease the financial burden of the state (Moore et al., 2017). The fact that CWF has been proven safe as a public health prevention program was revealed in the global implementation status. For the meantime, a systematic review of CWF and health impacts through 25 databases conducted and it concluded that there was no evidence of potential adverse effects, although decrease in dental caries ought to be considered with increase of dental fluorosis at the same time (McDonagh et al, 2000). Despite numerous studies and countless tests were performed over the seventy-years records, opponents claimed for cessation with growing on the premise of negative outcomes or adverse health effects through accumulation of fluoride in bone (Whitford, 1989; Levy et al., 2014)

History and current status of community water fluoridation in Korea

The Ministry of Health and Welfare of the Republic of Korea enacted the provisions of fluoridation in community water sources in 1980. Since then, in April 1981, CWF has implemented in Jinhae City in Gyeonsangnam-do Province, and Cheongju City in Chungcheongbuk-do Province in February 1982 as case studies (Kim et al., 1996). As the effectiveness and safety of CWF known to the public, it has expanded in earnest. Later, the government expanded to 37 water treatment plants (include 32 local governments) and covered 4.43 million populations in 2002 (roughly 9.4% of the Korean population) in 2002 (Kim et al., 2019).

Previous studies on the prevention effect of dental caries due to fluoridation have been widely published in Korea. A survey on children (6 to 11 years old) who have lived in Cheongju (CWF area) or Seongnam (non-CWF area), showed that the rate of permanent dental caries prevention was 35.4% (Kim et al., 1997). Another study reported that children’s dental caries reduced in Ansan (CWF area) compared to Geoje (non-CWF area) (Han et al., 2011). As such, there were many studies that have shown the effect of preventing dental caries by comparing children in CWF and non-CWF areas. In addition, many epidemiological studies have been conducted on human health effects and number of studies have been reported on bone density and fractures. Many previous studies confirmed that there was no significant risk of safety and adverse health effects such as bone related disease (fractures, bone mineral density, osteosarcoma studies). Even so, anti-fluoridation activities have intervened, and they argued for cessation of CWF in Korea with following reasons: 1) Fluoride classified as a neurotoxin, 2) CWF can cause dental fluorosis, 3) Safety issues regard with adverse health effects has not been properly evaluated, 4) It violates individual’s option by putting fluoride in public water system.

The pros and cons of CWF are still debating and open discussion are performing. Many local governments had ceased CWF by anti-fluoridation activities and considered the claims of local residents. This situation considered as “opportunist epidemiology” which result an unplanned break cause of opponents (Burt et al., 2000). In [Figure 1], it displays the number of operating water treatment plants and local governments in Korea. Based on the information, only 8 local governments out of 226 (3.5% of local governments, include 12 water treatments plants) are operating CWF program in Korea (Ministry of Health and Welfare, 2018).



Source: Ministry of Health and Welfare, 2018

Figure 1. Status of community water fluoridation implementation in South Korea, from 1981 to 2018

1.2 Literature review

A systematic review was conducted to identify the association between CWF and bone diseases. Also, we conducted a literature review about ecological studies, especially, focusing on natural experiment design to review previous studies. All the processes of literature search were based on the PRISMA, a systematic review and meta-analysis research report format. We searched PubMed and Embase as international databases (search date: 2019.5.1. ~2019.5.5.), and Korean Medical database (KM base), National Digital Science Library (NDSL), and Research Information Sharing Service (RISS) were used as national databases (search date: 2019.5.6. ~2019.5.7.).

Association between bone diseases and community water fluoridation

In international and national databases, detailed searches (advanced) were used to search for key terms related to "*water fluoridation*" in "all fields" tap and "*bone*" such as "*fracture*" or "*osteoporosis*" or "*bone mineral density*" in this study [Table 1]. Through screening 1, we excluded not relevant topics, non-article formats such as abstract, letters, review, supplementary, commentary. In screening 2, we excluded ineligible outcomes and animal studies. With this process, 40 studies were relevant to our study [Figure 2].

We summarized each previous studies relate with water fluoridation and bone diseases [Appendix. A]. We arranged the studies in yearly order, defined study country, study design, population by number of participants, disease outcome, outcome measurements, and presence of risk (if the study reported the risk than marked as yes (Y), otherwise no (N)). The study designs used included 11 case-control (include matched case-control) studies, 6 cohorts (prospective or retrospective or multicenter prospective) studies, 8 cross-sectional studies, 13 ecological studies and 2 hybrids (ecological cohort and ecological prospective) studies. In 40 studies, the outcome of 9 studies were osteosarcoma (most common form of bone cancer), rest of 31 studies were observed fractures include hip, wrist, ankle with measurement of bone mineral density. Most of studies were compared the residents' health outcome between fluoridated and non-fluoridated areas or patients who have lived in a community with low concentration rate of fluoride.

Throughout the systematic review, most studies have found that there was no significant association between CWF and bone diseases. Many studies have been linked to fractures with bone mineral density. In our study, we will specifically focus on the risk of hip fracture, osteoporosis and bone cancer in fluoridated drinking water.

Table 1. Search terms in international and national databases relate with bone diseases.

Database		Search terms
International	PubMed	(“Fluoridation”[MeSH] OR “CWF” OR “water fluoridation” OR “Fluoride”[MeSH]) AND (“Hip fracture”[MeSH] OR “Fracture” OR “Bone cancer” OR “Osteosarcoma”[MeSH] OR “Osteoporosis”[MeSH] OR “Bone Density”[MeSH] OR “Bone strength” OR “Bone fragility”) AND (“Public health” [MeSH] OR “Epidemiology” [MeSH] OR “Health” [MeSH] OR “Disease”[MeSH])
	Embase	#1 (‘Fluoridation’ OR ‘water fluoridation’ OR ‘CWF’) AND (‘Hip fracture’ OR ‘Fractures’ OR ‘Bone cancer’ OR ‘Osteosarcoma’ OR ‘Osteoporosis’ OR ‘Bone Density’ OR ‘Bone strength’ OR ‘Bone fragility’) AND ('Public health'/exp OR ‘public health’ OR ‘epidemiology’/exp OR ‘epidemiology’ OR ‘Health’ OR ‘Disease’) #2 #1 AND ‘article’/it
National	KM base	“Fluoridation” AND “Bone”
	NDSL	(‘Water fluoridation’|‘Fluoridation’|‘Community water fluoridation’) <AND> (‘Fracture’|‘Bone density’|‘Osteoporosis’|‘Osteosarcoma’|‘Bone’)
	RISS	(‘Water fluoridation’|‘Fluoridation’|‘Community water fluoridation’) <AND> (‘Fracture’|‘Bone density’|‘Osteoporosis’ |‘Osteosarcoma’|‘Bone’)

Note.

· Abbreviations: MeSH, Medical Subject Headings

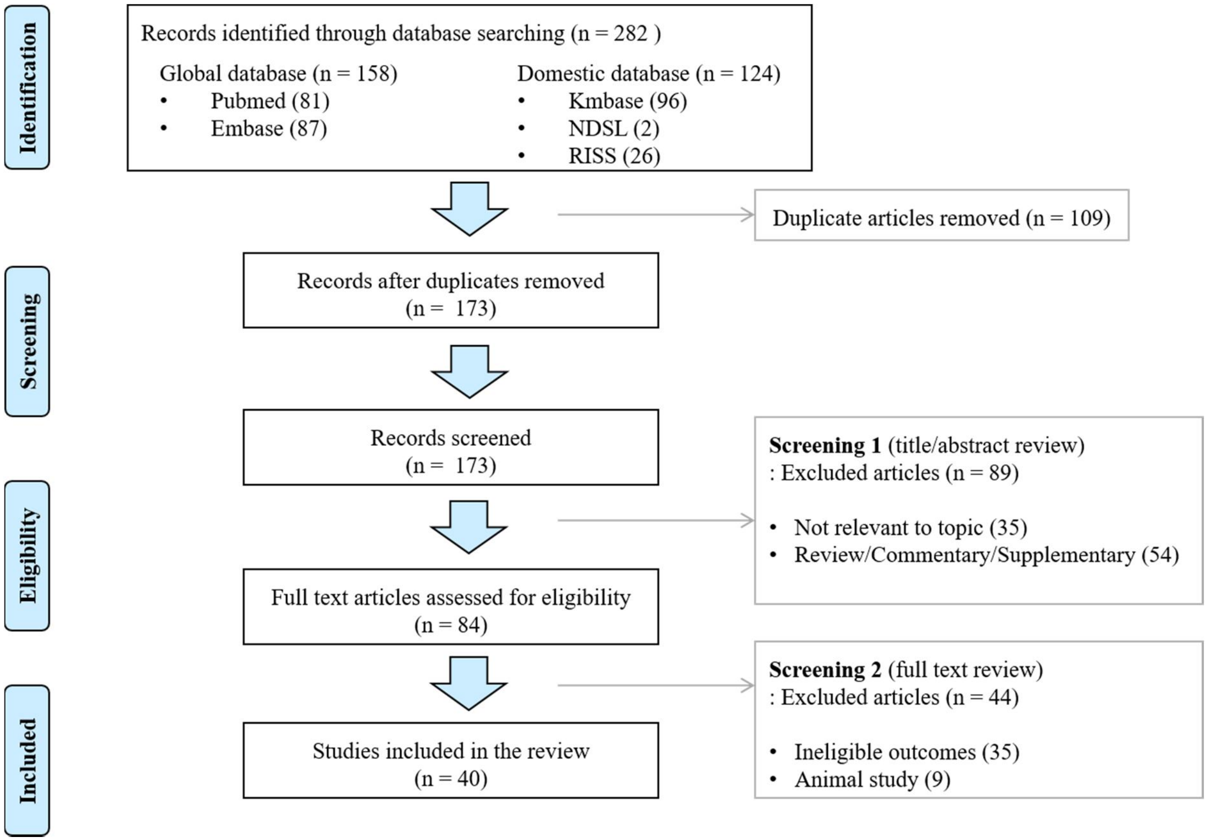


Figure 2. Flow diagram of literature and selection criteria about bone diseases.

Community water fluoridation with natural experiment

In international and national databases, detailed searches (advanced) were used to search for terms related to "*water fluoridation*" in "all fields" tap and "*natural experiment*" [Table 3].

We found 13 studies in the databases but since natural experiment related to CWF considered as rare case, we only had 4 studies after removed duplicate articles. Thus, we conducted one time of screening in this review. Then, we excluded studies that were not relevant to topic, and with this process, we have found that 2 studies were relevant to our study [Figure 3].

In [Table 3], we summarized the previous studies that were relevant to water fluoridation with natural experiment design. We arranged the studies in yearly order, defined study country, study design, population by number of participants, outcome, measurements and association of risk. Reviewed studies were compared the health outcome, focused on dental caries by compare fluoridated and non-fluoridated areas. In Brazil study, they investigated dental outcomes with a population-based cohort study names *EpiFloripa* and matched with participant's residency to tract the exposure of fluoridated water. The study reported that adults with lower the lifetime access to fluoridated water had the higher rate of decayed, missing, and filled teeth (DMFT): lifetime access to fluoridated water for less than 50% (RR: 2.70, 95% CI: 2.01-3.63) was higher than 50% to 70% (RR: 1.93, 95% CI: 1.39-2.68) on DMFT rate ratio (Peres et al., 2016). The study result was consistent with a recent Cochrane DB of systematic review on the effectiveness of water fluoridation on adult dental caries (Iheozor‐Ejiofor et al., 2015). In Canada study, they examined dental caries incidences among children with a pre-post cross-sectional design with comparison CWF cessation area and continued area. They have found an increase in primary teeth mean deft as 37% (RR: 1.37, 95% CI: 1.25-1.51) in cessation area (McLaren et al., 2017).

With the systematic review of studies, we have found that selected studies were related to fluoridation with natural experiment design have been limited to dental caries only and reported that there was no statistically significant risk in drinking fluoridated water. To be differentiate, our study, we will investigate the association of bone health with natural experiment design.

Table 2. Search terms in international and national databases relate with natural experiment.

Database		Search terms
International	PubMed	(“Fluoridation”[Mesh] OR “Community water fluoridation” OR “CWF” OR “water fluoridation” OR “Fluoride”[Mesh]) AND (“Natural experiment”)
	Embase	(‘Fluoridation’ OR ‘Community water fluoridation’ OR ‘CWF’ OR ‘water fluoridation’) AND (‘Natural experiment’)
National	KM base	“Natural experiment”
	NDSL	(‘Water fluoridation’|‘Fluoridation’|‘Community water fluoridation’) <AND> (‘Natural experiment’)
	RISS	(‘Water fluoridation’|‘Fluoridation’|‘Community water fluoridation’) <AND> (‘Natural experiment’)

Note.

· Abbreviations: MeSH, Medical Subject Headings

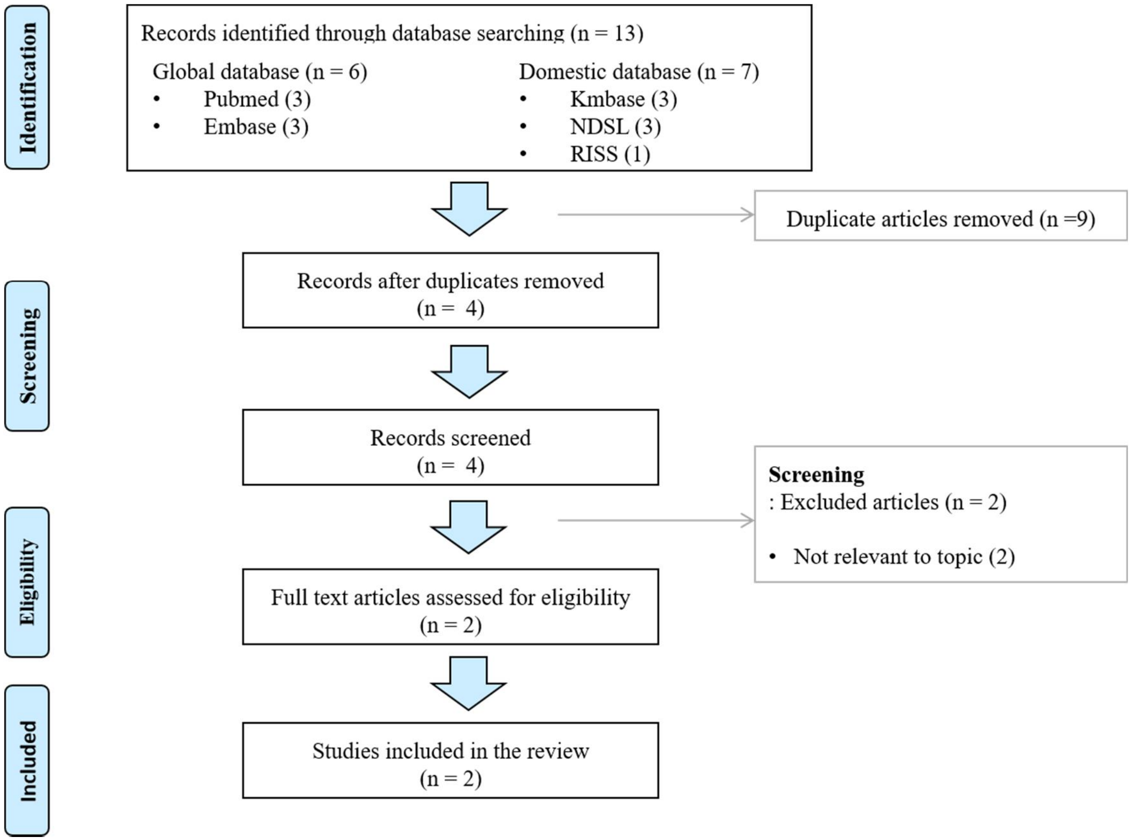


Figure 3. Flow diagram of literature and selection criteria about natural experiment.

Table 3. Summary of the previous studies on CWF and natural experiment.

Year	Author	Country	Study design	Study population; N	Outcome	Outcome Measurement	Risk (Y/N)	Remarks
2016	Peres MA, et al	Brazil	Natural Experiment	Population aged 20 to 59 year old, in Florianopolis; N=209	Decayed, missing, and filled teeth (DMFT)	Risk ratio	N	-
2017	McLaren L, et al	Canada	Pre-post cross-sectional	Grade 2 children in 2004/05 and2013/14 in Calgary and Edmonton; N=12,408	Decayed, missing, and filled teeth (DMFT)	Crude rate	N	

1.3 Study objective

There are limited current epidemiological studies that have assessed the adverse health effects of water fluoridation. The purpose of this study is to analyze the adverse health effects of CWF based on the prevalence of bone diseases (hip fracture, osteoporosis, bone cancer).

The study is conducted in three successive objectives, each building on the previous ones.

***Objective 1**:* Identify the current status and adverse health outcome of water fluoridation in Korea through recent literature reviews.

***Objective 2**:* To compare the prevalence of selected bone diseases (hip fracture, osteoporosis, and bone cancer) among the residents in Cheongju.

***Objective 3**:* Epidemiologically, investigated the risk of health outcome through fluoridation with spatio-temporal method.

CHPATER 2. METHODS

2.1 Study design, and setting

This is an ecological study in the form of natural experiment design. We chose Cheongju as study area because naturally experimental situations occurred without researcher's intervention or control of the area. Cheongju was the second area where CWF program was conducted on a trial case in Korea, and implemented for about 22 years from 1982 to 2004. Cheongju consists of 23 towns and residents has been supplied community water source from two local water treatment plants: Yeong-un and Ji-buk. In two water treatment plants, 14 towns were supplied with fluoridated water and 9 towns were supplied with non-fluoridated water. We mapped the status of CWF in Cheongju [Figure 4]. In [Figure 4 (A)], it indicates the province of Cheongju (Chungcheongbuk-do) in Korea and in [Figure 4(B)], it indicates Cheongju in the province. In [Figure 4 (C)], it showed the status of CWF in Cheongju. Light pink areas represented that CWF implemented for 22 years from 1982 to 2004, and the dark red areas implemented CWF for 7 years from 1997 to 2004. Rest of regions colored in white represented the area where CWF never conducted.

In order to investigate the risk of CWF, a control group was needed who have similar population characteristics as case group but never exposed to fluoridated water to compare adverse health effects. Cheongju was divided into two regions where fluoridation and non-fluoridation area within the same area, unlikely other areas where conduct CWF program in whole region. Consequently, Cheongju considered as the most suitable area for present study and perfect condition of natural experiment design.

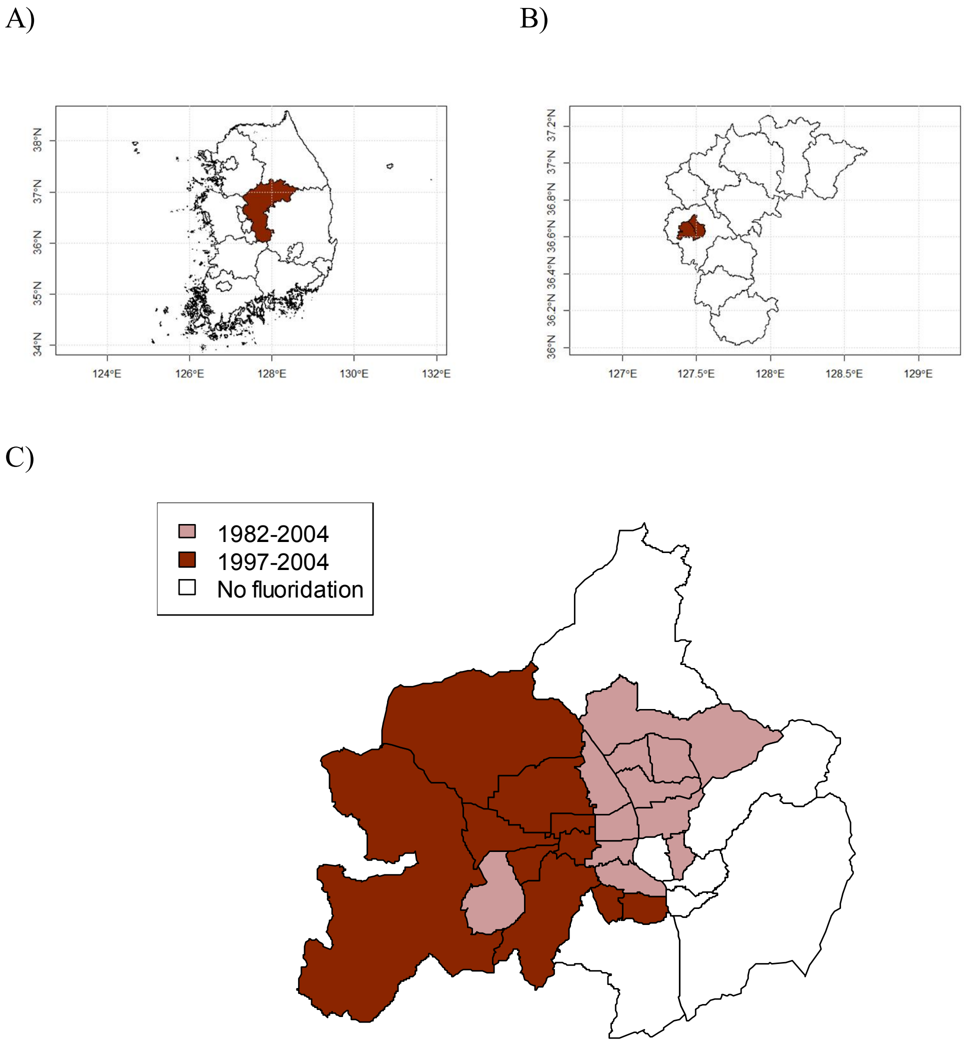


Figure 4. Status of Community water fluoridation implementation in Cheongju from 1982 to 2004.

2.2 Data descriptions and study subjects

In our study, we examined the adverse health effects of residents in Cheongju. We extracted data from 2004 to 2013 from the National Health Insurance Service (NHIS) database. The NHIS is Korean healthcare insurance of governmental organization under the Ministry of Health and Welfare (Chung et al., 2018). We requested the customized database for academic research purpose and it included information regarding medical utilization information in smallest administrative unit, town (i.e., Eup/Myeon/Dong in Korea). This claims data represents the whole population in Korea since 98% of the population is covered by the national health insurance (Lee et al., 2018). Since we have requested customized data from NHIS, there were no missing information and obtained each of the selected diseases in the form of frequency by gender, year, age, and address in town.

The study population were all residence in Cheongju, obtained medical utilization information of patients were obtained from NHIS. Among them, we have used residents who were diagnosed with hip fracture or osteoporosis or bone cancer. Medical utilization information of selected disease was collected in the form of frequency by age and gender group and, twenty-year intervals were used for age categorization in the analysis.

2.3 Variables

We have chosen bone disease as outcome variables. The most common findings of the results of adverse health effects related to CWF were bone diseases. Most studies have been published that there was no association or risk between CWF and bone diseases (fracture, bone density, osteoporosis, osteosarcoma, and others) through systematic reviews but since there were lack of epidemiological studies with natural experiments design, we have targeted bone diseases that are most likely to be associated with fluoride and adverse health effects. Among the diseases classified by the KCD-7 based on the International Classification of Diseases (ICD)-10, three types of bone diseases that were known to be relevant to CWF were selected: hip fracture (S72), osteoporosis (M80-82), and bone cancer (C40-41) (WHO, 1992) [Table 4]. For three selected diseases, age-sex standardized rates per 10,000 person-years were calculated with the corresponding population in fluoridated and non-fluoridated areas and we applied 2010 Census in Korea as standard population.

For the independent variables, we set the time variable from 2004 to 2013 and spatial variable which was designated based on CWF implementation status. In addition, general variables such as gender, age, population density, and number of towns were used to compare the characteristics between CWF and non-CWF areas. Also, we used the variables related to the exposure of fluoridation such as period of residence, source of water, and types of drinking water. We obtained theses customized data from Korean Microdata Integrated Service (MIDS) of statistics

Korea (MicroData, 2018). Microdata represents the data that is modified the errors and basis of data processing such as statistical tables. Among these, we extracted questionnaire that is related with exposure of fluoride of household information in the 2010 Census data.

Table 4. Classification of disease that were used as outcome variables

Classification	KCD-7*	Disease codes
Hip fracture	S72	Fracture of femur
Osteoporosis	M80	Osteoporosis with pathological fracture
	M81	Osteoporosis without pathological fracture
	M82	Osteoporosis in diseases classified elsewhere
Bone cancer	C40	Malignant neoplasm of bone and articular cartilage of limbs
	C41	Malignant neoplasm of bone and articular cartilage of other and unspecified sites

*: Korean Standard Classification of Disease

2.4 Statistical analysis

Space-time correlation

In order to check the space and time correlation in prevalence of three bone diseases, we measured the disease risk by calculating standardized incidence ratios (SIRs) which consider as the one of simple measure of disease risk in areas (Moraga, 2018). An observed count in each areal unit i expressed as $\mathrm{Y} = (Y_1, \ldots, Y_n)$ and a set of expected disease counts in area i is given by $\mathrm{E} = (E_1, \ldots, E_n)$. These expected counts calculated based on the age and sex demographics of population within each areal unit. An estimate for the SIRs is than given by

$$\mathrm{SIR}_i = \frac{Y_i}{E_i} \tag{1}$$

A value of SIR higher than 1 represents that an area has a higher disease risk than expected, while a value of SIRs under 1 suggests a lower risk compare to expected. In some conditions, SIRs might have the disease's spatial variability and extreme values with small sample sizes (Anderson et al., 2017; Gelfand et al., 2010). We mapped the average value of the SIRs in three different years to observe the space and time correlation [Figure 5]. SIR for different towns were shown to be different over time, and bone cancer was found to have relatively lower SIRs compared to the two different diseases. We plotted the temporal trends for three selected diseases after adjusting age and sex using 2010 Census from 2004 to 2013. (Figure 3). Overall, selected diseases tend to increase year to year, but the trend of hip fracture and osteoporosis were similar in CWF and non-CWF regions. For bone cancer, it appears to be different due to the number of patients was so small so it was not statistically significant. Therefore, to analyze this disease count data, a statistical model considering space and time may be appropriate.

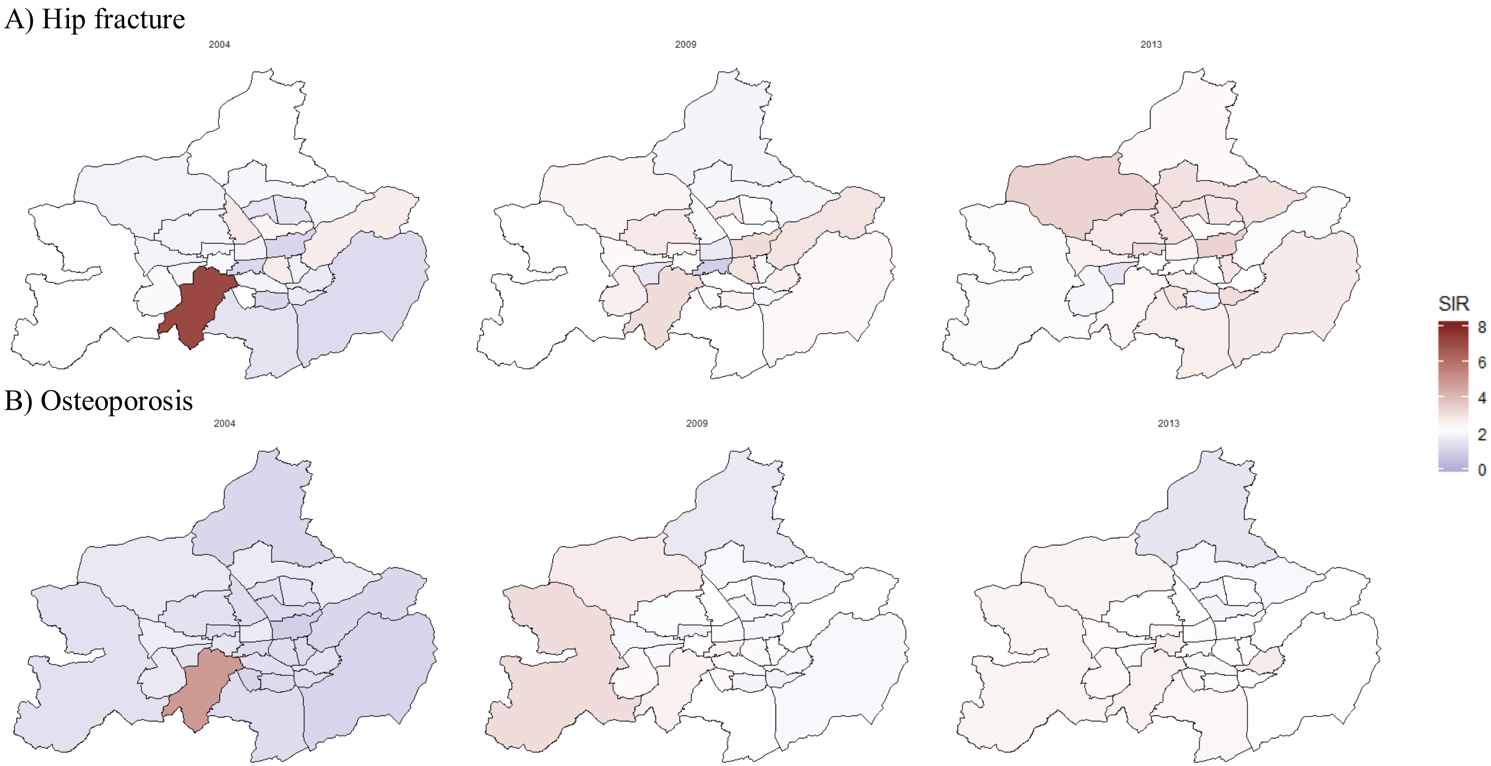


Figure 5. Standardized incidence ratios (Y_i/E_i) in three different years; 2004, 2009 and 2013

C) Bone cancer

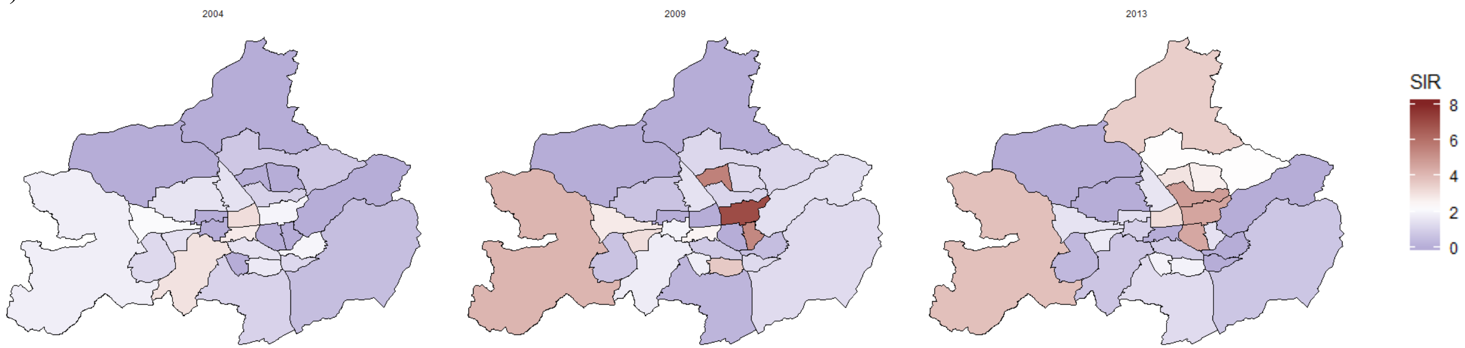


Figure 5. Standardized incidence ratios (Y_i/E_i) in three different years; 2004, 2009 and 2013. *(Continued)*

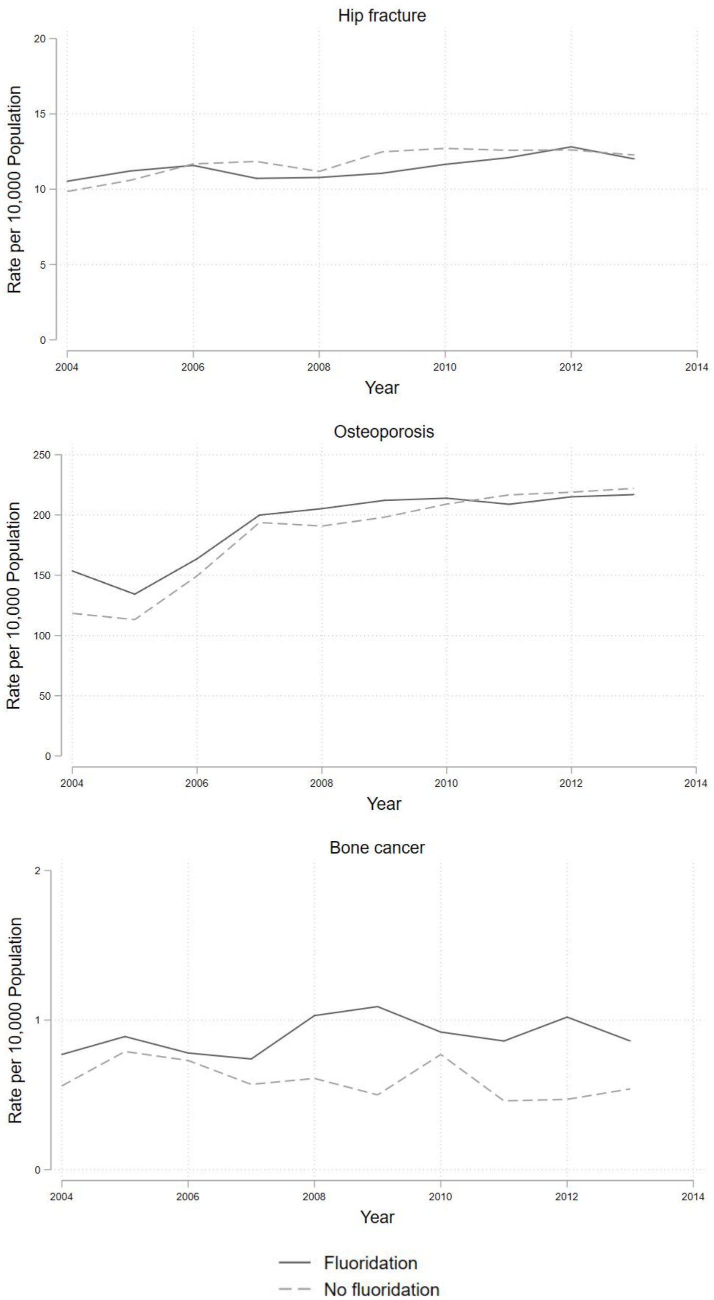


Figure 6. Age-sex adjusted standardized rates for three selected diseases, 2004-2013.

Bayesian Spatio-temporal model

In our study, we conducted a hierarchical Bayesian Poisson regression model that takes into account space and time correlations to model the relationship between CWF and the standardized prevalence of three selected diseases among Cheongju residents. Bayesian spatio-temporal models were developed from many authors, and we adapted the general time trend model proposed by Knorr-Held since our study consider temporal development of the association between three selected disease and water fluoridation through space and time interactions (Bernardinelli et al., 1995; Knorr-Held, 2000; Blangiardo et al., 2015).

We used observed and expected count data in yearly of three bone diseases in Cheongju. The Poisson regression model, which takes into account spatial correlation and time trends, is used to calculate the relative risk and 95% credible interval. The Conditional Autoregressive (CAR) model was applied to control spatial correlation. In this paper, we used an integrated nested Laplace approximation (INLA) in R package to estimate Bayesian inference in latent Gaussian models (Schrödle, 2011). We also used the Deviance Information Criterion (DIC) to compare the quality of the model fit. Generally, DIC is a Bayesian analogue of the Akaike Information Criterion (AIC) and test the goodness-of-fit and complexity (Luan et al., 2016). The best fitting model consider as the one with the lowest value of the absolute scale of DIC with reasonable computational time (Lunn et al., 2012). The equation of DIC is shown where $\overline{D}$ is the mean deviance which favors a good fit and p_D is effective number of parameters.

$$\mathrm{DIC} = p_D + \overline{D} \quad (2)$$

$$p_D = \overline{D} + \widehat{D}$$

To describe each type of integration, for Type 1 interaction, if two unstructured main effects υ and ϑ are expected to interact δ, then all interaction parameters δ_{it} is a priori independent. Type 2 is to combine random walk main effect α with the unstructured block ϑ, then each $\delta_i = (\delta_1, \ldots, \delta_{iT})', \mathrm{i} = 1, \ldots, \mathrm{n}$ follows random walk apart from other counties. In the case of type 3, the main effects γ and θ interact, then Type 3, $\delta_i = (\delta_1, \ldots, \delta_{nt})', \mathrm{t} = 1, \ldots, \mathrm{T}$, (independently) follows an intrinsic autoregression. Finally, Type 4 yields two dependent main effects, the random walk and the intrinsic autoregression, ϑ, as the most interesting interaction type from a theoretical point of view. R-INLA coding for four types of interaction is presented in [Appendix C]. To find the best fitted model, we presented the value of DIC for each type of interactions in three bone diseases using R-INLA [Table 5]. Among the four models described above, the more suitable model selected Type 1 according to the principle that it has a smaller DIC value. In the case of osteoporosis, type 2, 3, and 4 were too large, and for bone cancer, type 3 has small DIC value. Overall, Type 1 interaction is most appropriate.

With number of observed data in each Cheongju (town unit, i = 1,…,28) and time period in year (t = 1,…,10), we present a Poisson distribution of spatio-temporal model based on Knorr-Held as follows:

$$Y_{ij} \sim Poisson\left(\mathrm{E}_{ij}\mu_{ij}\right), i, j = 1, \dots, n, t = 1, \dots, T,$$

$$E\left(y_{ij}\right) = \lambda_{ij} = e_{ij}\theta_{ij}, \quad (3)$$

$$\log\left(\mu_{ij}\right) = x_{ij}^{T}\beta + \mu_{i(j)} + v_j + \gamma_t + \varphi_{jt}$$

where $x_{ij}^{T}\beta$ is an overall risk level, $\mu_{i(j)}$ represents the spatial level for the i-th area (town unit, i = 1,…,28) which consider the spatial correlation, and v_j has the same meaning as $\mu_{i(j)}$, which represents the spatial level for the j-th area (town unit, j = 1,…,28) that equivalent to unique regional variations. γ_t represents temporal effects from 2004 to 2013 (t=1,…,10), and φ_{jt} represents space x time interaction.

Sensitivity analysis

Also, we used CARBayesST package in R based on Markov chain Monte Carlo (MCMC) simulation to compared several models which applied the spatial temporal interaction. Sensitivity analysis can explain similarities and differences between models. We have used models that take into account spatial and temporal correlations. CARBayesST is the first proprietary software package for spatio-temporal unit modeling with CAR prior (Lee et al., 2018). We compared the DIC value in two different packages in order to ensure that the model we chose to describe the best of our data. The models were compared in three key criteria: calculation time, p_D and model fit. The quality of the model fit is defined using DIC (Equation (2)). Model with the lowest DIC can be considered to provide the closest fit to the observed data (Lunn et al., 2012; Anderson et al., 2017).

Ethics Statement

This study was approved by the Institutional Review Board of the Seoul National University (IRB No. E1903/003-006).

Table 5. The DIC values for type comparison with selected bone diseases

Interaction	Parameter interacting	Hip fracture	Osteoporosis	Bone cancer
			DIC	
Type 1	v_i and φ_t	**2158.1**	**3241.2**	**1021.6**
Type 2	v_i and γ_t	2403.5	11441.6	2774.0
Type 3	φ_t and u_i	2398.3	11442.2	1031.6
Type 4	u_i and γ_t	2404.0	11440.4	$2.42e^{37}$

Note.

· Bold number represents the lowest DIC value in the table.

· Supplementary programming code (R-INLA) is in Appendix B.

CHAPTER 3. RESULTS

3.1 General characteristics of study population

In [Table 6], we showed the general characteristics of study population in Cheongju and observed the regional difference between CWF and non-CWF areas. All variables except population density and number of towns are expressed as frequency and percentage (%). Intuitively, number of population was about twice higher in CWF than non-CWF, but proportion of gender was about the same in both areas. By age group, 20-39 years old (33.4%) was highest group in CWF area and 40-59 years old (35.8%) was highest in non-CWF area. In the case of population density, CWF area was about 1.5 times higher than non-CWF area, and number of towns in CWF area was 2.3 times higher than non-CWF area. In both regions, drinking tap water had the highest portion (CWF: 47.8%, non-CWF: 45.5%). This directly shows that both regions were exposed to fluoridated water at a similar rate. There was no significant regional difference in education level, source of water and types of drinking water.

Table 6. The distribution of general characteristics in CWF and non-CWF areas from 2004 to 2013.

Variables	CWF		non-CWF	
	No. of residents	%	No. of residents	%
Total	4,406,021		2,270,959	
Gender				
Male	2 200 104	49.9	1 126 495	49.6
Female	2 205 917	50.1	1 144 464	50.4
Age (years)				
< 20	1 135 966	25.8	603 984	26.6
20 – 39	1 473 753	33.4	650 749	28.7
40 – 59	1 292 255	29.3	813 074	35.8
60 – 79	445 321	10.1	177 593	7.8
80 ≥	58 726	1.33	25 559	1.13
Population density (people per km^2)	5.1		3.4	
Number of towns (N)	21		9	
Education level*				
Middle school or lower	1 689	36.8	2 541	34.9
High school	1 433	31.2	2 140	29.4
College or higher	1 469	32.0	2 607	35.8

Table 6. Distribution of general characteristics in CWF and non-CWF regions from 2004 to 2013. *(Continued)*

Variables	CWF		non-CWF	
	No. of residents	%	No. of residents	%
Period of residence*				
> 1 year	324	23.5	691	34.1
1 – 5 years	493	35.8	1 002	49.4
5 – 10 years	397	28.9	462	22.8
10 – 25 years	362	26.3	461	22.7
< 25 years	124	9.01	104	5.13
Source of water*				
Community water system	4 363	98.8	2 681	98.6
Village water (temporal)	6	0.14	0	0.00
None	49	1.11	39	1.43
Types of drinking water				
Drinking tap water	812	47.8	1 237	45.5
Purified tap water	524	30.9	860	31.6
Bottled water	238	14.0	427	15.7
Others	124 691	7.30	196	7.21

Note.
* indicate that data obtain from Microdata Integrated Service of 2010 Korean Census

3.2 Comparison of crude and age-sex standardized rates

Present study analyzed 7,751 cases of hip fracture (male: 2,830, female: 4,921), 128,211 cases of osteoporosis (male: 11,595, female: 116,616), and 528 cases of bone cancer (male:312, female: 216) [Table 6]. Depending on CWF implementation status, we categorized into gender and age distribution (under or above 80 years old) for each selected disease and calculated the crude rate per 10,000 person-years. In terms of gender, the number of observed counts was higher in female with hip fracture and osteoporosis regardless exposure of fluoridation, and the crude rate was about twice higher in female than male. In the case of bone cancer, both regions had higher rate in male (CWF: 1.11 in male, 0.73 in female; non-CWF: 0.59 in male, 0.47 in female). Based on the age of 80 years old, the crude rate of over 80 years old was higher than patients who were under 80 years old in all diseases, which it is commonly known that bone strength or bone density getting weaker as they become older (Ringertz et al., 1997).

To describe the data, we plotted the temporal trends for three selected diseases after adjust age and sex using 2010 Census as the standard population from 2004 to 2013. The shape of age-sex adjusted standardized rates per 10,000 person-years for all diseases tend to increase year to year [Figure 5]. For hip fracture, age-sex standardized rates are higher in non-CWF area and for osteoporosis, it was increasing in non-CWF as time goes. Compared to the other diseases, the trend for bone cancer was higher in CWF than non-CWF area. However, there was no statistically significant difference since number of diagnosed patients were very small. In both regions, the prevalence of three selected diseases were tend to increase over the period of time, but this can interpret as natural phenomenon include many other risk factors, not typically impact of CWF.

Table 7. Number of cases, crude rates per 10,000 person-years of three selected diseases in CWF and non-CWF areas.

Variables	CWF		non-CWF	
	No. of patients	**Crude rate***	**No. of patients**	**Crude rate***
Hip fracture				
Male	1,965	8.9	865	7.7
Female	3,366	15.3	1,555	13.6
Under 80 years old	3,746	8.62	1,715	7.64
Above 80 years old	1,585	269.90	705	275.83
Osteoporosis				
Male	8,025	36.5	3,570	31.7
Female	82,667	374.8	33,949	296.6
Under 80 years old	83,111	191.18	34,306	152.78
Above 80 years old	7,581	1290.91	3,213	1257.09
Bone cancer				
Male	245	1.11	67	0.59
Female	162	0.73	54	0.47
Under 80 years old	386	0.89	118	0.53
Above 80 years old	21	3.58	3	1.17

Note.
*: Crude rate per 10,000 person-years

3.3 Comparison of the relative risk of selected diseases

We used the Bayesian spatio-temporal regression using the R-INLA package to determine whether each bone diseases increases with fluoridation exposure period. From [Table 8], in the case of hip fracture, the relative risk in CWF is 0.94 (95% CrI: 0.86-1.04), and for osteoporosis, it was 0.94 (95% CrI: 0.87-1.02). Relative risk in hip fractures and osteoporosis are less than 1 indicate that the risk of CWF did not increased. On the other hand, the relative risk of bone cancer was 1.20 (95% CrI: 0.89-1.61), which was relatively higher than other diseases but the result of bone cancer was difficult to interpret as statically significant because the number of patients was very small since it considers as a rare case.

We compared the relative risk by gender. The relative risk for hip fracture in male and female were 0.88 and 0.99, and for osteoporosis were 0.86 and 0.95, respectively. Particularly, hip fractures and osteoporosis were significantly higher in females than in males. This because hormone's changes in men were not as large as in women, and women have higher bone loss due to menopause which is not equivalent that loss of testosterone and E-level with age in men (Khosla et al., 1998). Additionally, previous study reported that fluoride reduce the risk of fractures by increasing bone mass and it use as one of therapy of male osteoporosis (Tuck et al., 2007). That explains why the relative risk for hip fracture and osteoporosis were higher in female than in male.

In addition, we calculate the relative risk by time difference [Appendix D]. On the contrary, the relative risk was higher in the long-term (conducted from 1982 to 2004) than short-term (conducted from 1997 to 2004) exposure area. This indicates that exposure to fluoridation for long periods of time does not increase the risk to human health. In the case of bone cancer, the relative risk has different aspects than other two diseases, but this was not statistically significant with small number of cases.

Table 8. Posterior distribution of relative risks with 95% credible intervals in total, male and female.

	Total	Male	Female
		RR* (95% CrI)**	
Hip Fracture	0.94 (0.86 - 1.04)	0.88 (0.75 – 1.01)	0.99 (0.89 - 1.09)
Osteoporosis	0.94 (0.87 – 1.02)	0.86 (0.76 – 0.97)	0.95 (0.87 - 1.03)
Bone Cancer	1.20 (0.89 - 1.61)	1.26 (0.84 – 1.88)	1.03 (0.87 – 1.22)

Note.
* RR: Relative risk
** 95% CrI: 95% Credible Interval
· Supplementary programming code (R-INLA) is in Appendix B.

3.4 Disease mapping of selected diseases

Three-year period (2004, 2009, and 2013) between 2004 to 2013 were used to map the posterior distribution of relative risk for the selected disease [Figure 6]. The results of disease mapping reflect time trend from 2004 to 2013 and primarily focused on change in prevalence of selected bone diseases over the time. The area marked with bold line was the region where CWF was implemented, and the other area was classified as non-CWF area where CWF was never conducted. On the right side of the map, legend of the relative risk value is displayed from 0.85 to 1.80 and the color of blue represented a relatively lower risk and the red color represented a higher risk. Overall, the color of the map represents the prevalence of selected disease increased over time, but we ensured that intuitively there was no significant difference between CWF and non-CWF areas which is consistent with previous results conducted by R-INLA [Table8].

In addition, we also present disease mapping that divided into three different regions depend of duration of the period of time of CWF [Appendix E]. One area (yellow dotted line) was the area where CWF conducted from 1982 to 2004 (consider as long-term exposure), the other area (purple bold line) was the area where CWF conducted from 1997 to 2004 (consider as short-term exposure) and rest of region never implemented CWF. Likewise, the prevalence of all selected diseases tend to increase but the disease risk reveals no difference in the period of time (short and long-term exposure).

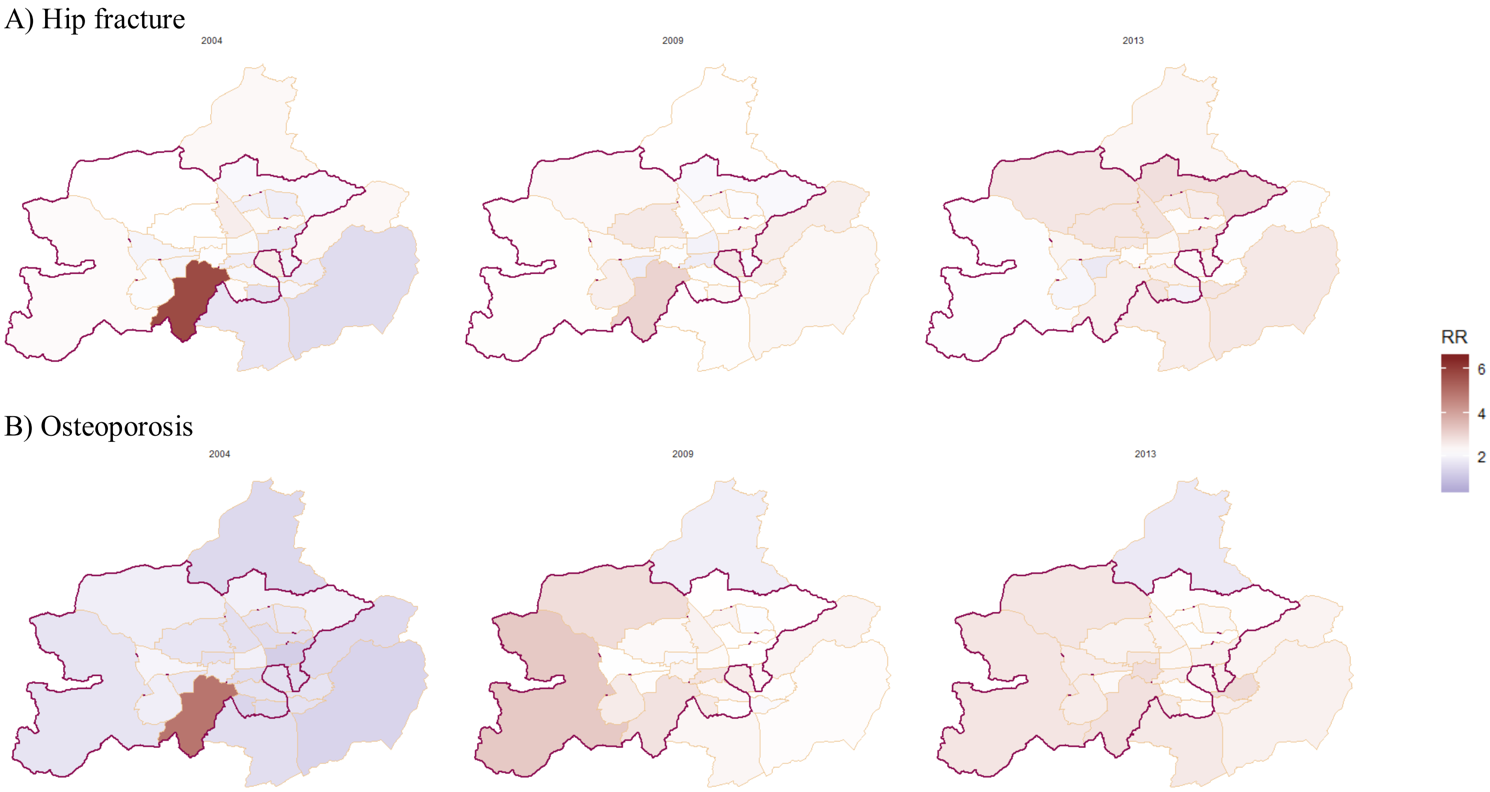
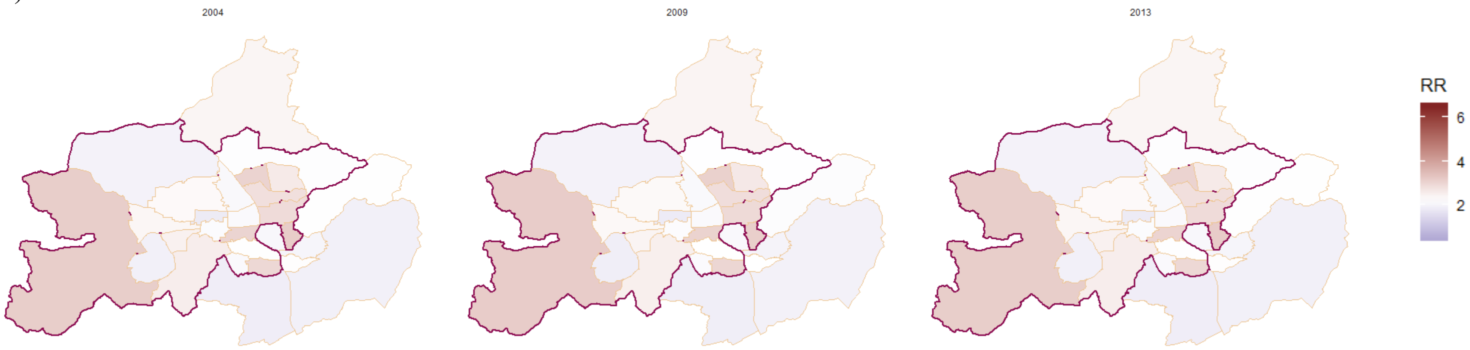


Figure 7. Spatial distribution of posterior relative risk by town and year in 2004, 2009, and 2013.

C) Bone cancer



Note.
· Bold line region: CWF was conducted and rest of region: CWF never implemented

Figure 7. Spatial distribution of posterior relative risk by town and year in 2004, 2009, and 2013. *(Continued)*

3.5 Comparison of the performance of the models

We applied Model 1 to 5 to the dataset using the CARBayesST software in R and displayed the result of computation time, DIC value, effective number of parameters (p_D) for each of the five selected models [Table 9]. We have added a reference to the five models and summarized table shown in [Appendix F] (Lee et al., 2018). Each model was fitted to calculate DIC generated by a MCMC simulation, and in each case, 50,000 interactions were discarded as burn-in. In terms of p_D, small relative to the number of data points will be approximately equal to the actual number of parameters and it consider as spatial and temporal autocorrelation of our dataset (Best et al., 2005; Luan et al., 2016).

For hip fracture, the best fitting model by the DIC criterion is Model 4since it has lowest DIC value of 2007.7 with 545.3 seconds. Next, the best model is DIC value of 2029.2 with 389.9 second in Model 5. Followed by Model 3 with 2102.4, and lastly DIC value for Model 1 is 2118.5. For osteoporosis, Model 4 has lowest DIC with a value of 2001.8 with 478.9 seconds and the next best value of DIC is 2029.3 in Model 5. Then, Model 3 (3272.0), Model 1 (3821.7) and then Model 2 (6163.7). For bone cancer, Model 3 has lowest DIC value of 1011.2 with 100.6 seconds. Followed by, Model 2 with 1026.1, and then Model 1 with 1029.3, and then Model 4 (2004.9), and Model 5 (2027.5), respectively.

Although Model 4 has lowest DIC value in hip fracture and osteoporosis but it took a longer computational time. Consequently, Model 1 appears to be best choice over all in all three diseases since the DIC value is consistent with previous R-INLA results in [Table 8] and it has reasonable computation time compare to other models.

Table 9. Comparison of the values of DIC between the models for selected bone diseases.

R package	Model	Hip fracture			Osteoporosis			Bone cancer		
		Time(s)	**DIC**	p_D *	**Time(s)**	**DIC**	p_D *	**Time(s)**	**DIC**	p_D *
CARBayesST	Model 1: CARanova	142.9	2118.5	171.8	147.1	3821.7	353.7	162.3	1029.3	29.4
	Model 2: CARlinear	132.2	2123.8	52.7	127.9	6163.7	65.3	141.1	1026.1	24.4
	Model 3: CARar	98.5	2102.4	151.6	102.8	3272.0	323.6	100.6	1011.2	42.3
	Model 4: CARadaptive	545.3	2007.7	74.2	478.9	2001.8	72.3	480.8	2004.9	72.0
	Model 5: CARlocalised	389.9	2029.2	109.6	374.3	2029.3	108.8	388.2	2027.5	109.3
R-INLA	Type 1 interaction	3.23	2100.1	159.7	2.76	3212.3	304.8	2.24	1021.7	21.9

Note.

* p_D : Effective number of parameters

· Supplementary programming code is in Appendix C.

CHAPTER 4. DISCUSSION

4.1 Summary of results: A new finding of this study

To our knowledge, our study has attempted to investigate the association between exposure of fluoridation and adverse health effect, specifically bone diseases with natural experiment design. Ecological analysis used high-quality population based on NHIS data which are considered to be representative of the Korea's population. As a result of spatio-temporal analysis with town unit, prevalence of all three selected diseases in Cheongju showed a tendency to increase from year to year, however it was not statistically significant difference in CWF area compared to non-CWF area. This study results confirmed that there was no clear evidence of adverse health effects associated with residence in areas with water fluoridation.

4.2 Comparison with previous studies

A large number of results of studies on fluoride exposure and bone diseases were mainly focused on fractures. These findings are generally consistent with previous study results. Meta-analysis confirmed that chronic fluoride exposure from drinking water does not significantly increase the risk of hip fracture and in the United States, long term exposure to fluoridated drinking water does not increase the risk of fracture (Yin et al., 2015; Phipps et al., 2000). In addition to Ireland study, there was no significant relationship between water fluoridation and bone health among older adults (O' Sullivan et al., 2015). Likewise, our study consistent with previous results that the risk of bone disease has not increased since the prevalence did not increased in those residents who exposed to fluoridated water (Public Health England, 2014). Moreover, the benefits associated with preventing dental caries from conducting CWF in town were evident in previous study in Cheongju (Kim et al., 2014). Our study presented not only hip fracture but also prevalence of osteoporosis and bone cancer, and the epidemiological analysis by natural experimental design is a distinction from other studies.

4.3 Strengths and Limitations of this study

There are several important limitations in this study. First, on the exposed side, it was not clear to find out how much of residents are exposed to fluoridated water in CWF area. Non-differential misclassification can occur because individual exposure is unknown, and it may be appearing that there is no difference in prevalence between the two areas due to toward null. However, the ratio of drinking tap water in both regions was about the same (CWF: 47.8%, non-CWF: 45.5%). This means that small amount of fluoride in one region has also been less exposed in another region, so there will be no error in the interpret the consequences of bias. Second, exposure should be long enough depending on the dose-response relationship in order to develop the disease in relation to fluoridation. Though, the percentage of people who lived in the region for more than twenty-five years is small at 9.01% in

CWF and 5.13% in non-CWF, respectively, which can cause no difference in the prevalence. Despite the difference in the proportion of people who have lived long between the two regions, it would be difficult to see a difference in prevalence even when there are actually more people exposed for a long time. Third, our study could not measure the individual level of intakes of fluoride compared to Brazilian studies by the same natural experimental design (Peres et al., 2016). Given the source of water and types of drinking water, there was no difference in fluoride exposure between the two areas, so it would be difficult to see the understatement or overstatement of measurement. Fourth, since we used the national claim data from NHIS for the diseases, a single disease occurrence can result in limitations such as the use of multiple institutions or the accuracy of diagnosis names, and part of the definition of hip fracture may also worsen specificity or have a greater effect on estimates of the sensitivity (Berry et al., 2017). On the other hand, we analyze small areas in the region with claim data, hence it will not affect the results.

Strengths of our study is that it was designed to be a natural experiment without the intervention of researchers and we compared adverse health effects in the CWF and non-CWF areas. Internal comparisons within the same population group on a small area unit can provide a clear evidence of the effect on adverse health effects from the CWF. Further, the spatiotemporal analysis allowed us to observe the difference between the CWF and non-CWF areas and adverse health effects by visualizing the prevalence of disease.

4.4 Public health implication

Prevention effect of dental caries by CWF have already been proven through a lot of studies and it substantially improved many nation's dental health. Despite this, a small but highly vocal opposition repeatedly against the fluoridation and now many countries are in the situation of ceasing water fluoridation program which is a great loss in nationwide since a preventive program for many people around the world, including social minorities, to maintain oral health for a long time at low cost. Furthermore, opponents are in the vanguard of anti-scientific activities such as anti-vaccination, anti-fluoridation and other forms of science denial for similar reasons (Morabia, 2016). If CWF program stopped, they will conduct anti-scientific movement such as avoid vaccination and this could eventually lead to the failure of public health prevention service collapsing like dominoes.

The nation's local government is vulnerable to the voices of opponents, and they repeatedly bring up opposition to the community water fluoridation program in worldwide. In Korea, the CWF is on the verge of a complete halt, and to prevent this state, the Ministry of Health and Welfare need to address the public's uneasiness by presenting it on the basis of a paper published into professional journals. The participation of experts from each local government is urgently needed, and although the effectiveness and benefits of public health prevention programs are evident, due to opposition from groups, polices and institutional supplementation that the local government arbitrarily decides to suspend are absolutely necessary.

CHAPTER 5. CONCLUSION

Through our study, we conclude that there was no significant association between CWF and bone diseases (hip fracture, osteoporosis, and bone cancer). With spatio-temporal Poisson regression analysis, implementation of water fluoridation program did not increase the risk of adverse health effect compared to areas where never implemented CWF program.

Fluoride, consider as a double-edged sword (Unde et al., 2018). Although our study results consistent to previous studies, well-design epidemiological studies of adverse health effect or large case-control studies that linked to spatiotemporal method are recommended. One of the study suggested CATFISH project (Cumbrian Assessment of Teeth a Fluoride Intervention Study for Health) to evaluate reintroduction of a water fluoridation scheme (Goodwin et al., 2016). This study result will provide not only scientific evidence but also evidence for policy decision on resume or discontinue of community water fluoridation program.

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APPENDIX A. Summary of systematic review results

Table A. Summary of the previous studies on water fluoridation and bone diseases.

Year	Author	Country	Study design	Study population; N	Outcome	Outcome Measurement	Risk (Y/N)	Remarks
1965	Goggin JE, et al	USA	Ecological	Women aged 60 years or older; N=420	Fracture	Crude rate	N	-
1969	Korns RF	USA	Ecological	Aged 40 years or older; N=429	Hip fracture, Wrist fracture	Crude rate	N	-
1980	Alhava EM, et al	Finland	Case-control	Case: Kuopio residents, Control: samples from outside Kuopio; N=53	Bone strength, Bone mineral density	Bone mineral density	N	-
1983	Madans J, et al	USA	Ecological	Patients diagnosed with hip fracture from National Health Interview Surveys of 1973-1977; N=596	Hip fracture, Osteoporosis	Incidence rate	N	-
1985	Simonen O, et al	Finland	Case-control	Case: aged 50 years or older in Kuopio, Control: Jyväskylä; N=133,398	Bone fragility, Femoral-neck fracture, Osteoporosis,	Incidence rate	N	-
1986	Arnala I, et al	Finland	Case-control	Case: patients with a hip fracture, Control: matched for age and sex; N=18	Osteofluorosis	Incidence rate	N	-
1990	Cooper C, et al	United Kingdom	Cross-sectional	Aged 45 years or older residents in 39 county districts; N=20,393	Hip fracture	Correlation coefficient	N	-

Table A. Summary of the previous studies on water fluoridation and bone diseases. *(Continued)*

Year	Author	Country	Study design	Study population; N	Outcome	Outcome Measurement	Risk (Y/N)	Remarks
1991	Sowers MF, et al	USA	Cohort (Prospective)	Women aged 20-80 in three Lowa communities; N=684	Bone mass, Fracture	Relative risk	N	-
1991	Mahoney MC, et al	USA	Ecological	Patients diagnosed in bone cancer; N=3166	Osteosarcoma	Relative risk	N	-
1991	McGuire SM, et al	USA	Case-control (Matched)	Case: patients diagnosed between 1980-1990 and younger than 40, Control: matched; N=54	Osteosarcoma	Odds ratio, Relative risk	N	-
1992	Jacobsen SJ, et al	USA	Ecological	Aged 65 years or older; N=218951	Hip fracture	Relative risk	N	-
1992	Danielson C, et al	USA	Hybrid (Ecological+ Cohort)	Patients with hip fracture who were 65 years and older	Hip fracture	Relative risk	Y	Low level of fluoride(1ppm) may increase the risk in elderly
1993	Suarez-Almazor ME, et al	Canada	Ecological	Aged 45 years or older residing in Edmonton or Calgary who were admitted to hospitals in 1981-1987; N=5,267	Hip fracture	Standardized rate, Rate ratio	N	-
1993	Jacobsen SJ, et al	USA	Ecological	Aged 50 years and older in Rochester; N=651	Hip fracture	Incidence rate	N	-

Table A. Summary of the previous studies on water fluoridation and bone diseases. *(Continued)*

Year	Author	Country	Study design	Study population; N	Outcome	Outcome Measurement	Risk (Y/N)	Remarks
1994	Kröger H, et al	Finland	Cross-sectional	Women aged 47-56 years old residing in Kuopio; N=3,222	Ankle factures, Writs fractures, others	Bone mineral density	N	-
1995	Lan CE, et al	Taiwan	Cross-sectional	Women aged 46-65 years old in Taiwan; N=248	Bone mineral density	Bone mineral density	N	-
1995	Cauley JA, et al	USA	Hybrid (Ecologic+ Prospective)	Women aged 65 years and older; N=2,076	Bone mass, Osteoporotic fractures	Relative risk	N	-
1995	Moss ME, et al	USA	Case-control	Case: 167 osteosarcoma, Control: 989matched cancer referent; N=1,156	Osteosarcoma	Odds ratio	N	-
1995	Gelberg KH, et al	USA	Case-control	Case: 130 osteosarcoma patients between 1978-1988, at age 24 years or younger, Control: matched on year of birth and sex; N=260	Osteosarcoma	Odds ratio	N	-
1996	Karagas MR, et al	USA	Ecological	Individuals who aged 65-92 years old in 1986-1990.; N= 59,383	Fracture(Ankle, Distal forearm, Hip, Proximal humeru)	Rate ratios	N	-

Table A. Summary of the previous studies on water fluoridation and bone diseases *(Continued)*

Year	Author	Country	Study design	Study population; N	Outcome	Outcome Measurement	Risk (Y/N)	Remarks
1997	Arnold CM, et al	Canada	Cross-sectional	Females aged 18 to 25 years who live in Regina and Saskatoon; N=57	Bone mineral density	Bone mineral density	N	-
1998	Phipps KR, et al	USA	Cross-sectional	3 rural communities with different concentration level, all adults age 60 and over; N=670	Bone mineral density	Bone mineral density	N	-
1998	Lehmann R, et al	Germany	Cohort (Retrospective)	Halle and Chemnitz populations from 35-85 years old; N=556	Bone mineral density, Hip fracture	Incidence rate, Odds ratio	N	-
1998	Feskanich D, et al	USA	Case-control (Matched)	Case: 30-55 years of women in Nurses' Health Study(53), forearm fracture(188), Controls: 241; N=482	Fracture (Hip, Distal forearm)	Odds ratio, Relative risk	N	-
1998	Jacqmin-Gadda, H, et al	France	Cohort (Prospective)	People aged 65 years and older; N=3,216	Hip fractures	Odds ratio	N	-
1999	Fabiani L, et al	Italia	Cross-sectional	Local Health Unit of Avezzano and Bracciano zones; N=1,125	Fractures, Osteoporosis	Relative risk	N	-

Table A. Summary of the previous studies on water fluoridation and bone diseases *(Continued)*

Year	Author	Country	Study design	Study population; N	Outcome	Outcome Measurement	Risk (Y/N)	Remarks
2000	Hillier S, et al	United Kingdom	Case-control	Case: 50 years and older in Cleveland, Control: hip fracture patients; N=2,110	Hip fractures	Odds ratio	N	-
2000	Phipps KR, et al	USA	Cohort (Multicenter prospective)	ambulatory women without bilateral hip replacements in 1986-1988; N=9,704	Bone mineral density, Hip fracture	Relative risk	N	-
2001	Li Y, et al	China	Cross-sectional	Six groups of subjects≥50 years of age were randomly selected; N=8,266	Bone fractures	Odds ratio	Y	With 4.32ppm or higher concentration
2005	Sowers MF, et al	USA	Case-control	Case: women, aged 20-92 years old who live in high calcium and high fluoride communities, Control: community; N=1,300	Bone mineral density, Fractures	Risk ratio	N	-
2006	Bassin EB, et al	USA	Case-control (Matched)	103 cases under age of 20 and 215 matched controls; N=318	Osteosarcoma	Odds ratios	Y	During childhood among males but not consistent with females

Table A. Summary of the previous studies on water fluoridation and bone diseases *(Continued)*

Year	Author	Country	Study design	Study population; N	Outcome	Outcome Measurement	Risk (Y/N)	Remarks
2008	Han YJ, et al	Korea	Ecological	Residents in Ansan and Shiwa ;N=785	Bone mineral density	Multivariate analysis	N	-
2008	Park EY, et al	Korea	Ecological	Residents(>65 years old) in Cheongju, Chungju, Chuncheon, Suwon, Wonju ;N=80,558	Hip fracture	Crude rate, Relative risk	N	-
2011	Comber H, et al	Ireland	Ecological	Northern Ireland cancer registry and national cancer registry of Ireland on osteosarcoma incidence from 1994 - 2006; N=1,686,962	Osteosarcoma	Standardized rate ratio	N	-
2012	Levy M, et al	USA	Ecological	1999-2006 from US Cancer Statistics, 5-19 years old; N=935	Osteosarcoma	Incidence rate, risk ratio	N	-
2013	Nasman P, et al	Sweden	Cohort (Retrospective)	all individuals born in Sweden between Jan 1, 1900 and December 31, 1919; N=473,277	Hip fracture	Hazard ratios, Incidence rate	N	-
2014	Levy SM, et al	USA	Cohort (Prospective)	Longitudinal Lowa Fluoride study, birth to 15years; N=358	Bone mineral density	Bone mineral density	N	-

Table A. Summary of the previous studies on water fluoridation and bone diseases *(Continued)*

Year	Author	Country	Study design	Study population; N	Outcome	Outcome Measurement	Risk (Y/N)	Remarks
2014	Blakey K, et al	Great Britain	Ecological	0-49 years in GB during 1980-2005; N=2566(Osteosarcoma)+1650(Ewing sarcoma)	Osteosarcoma, Ewing sarcoma	Relative risk	N	-
2015	Young N, et al	England	Cross-sectional	Hip fracture/all-cause mortality > 65years old from 2010 ONS , renal calculi>25 years old , bladder cancer and osteosarcoma >=50years; N=32482	Hip fracture, renal calculi, all-cause mortality, bladder cancer, osteosarcoma, Down syndrome	Crude rate, Incidence rate ratio	N	-
2016	Archer NP, et al	USA	Case-control	Case: Texas children and adolescents < 20years, Control: sampled from central nervous system tumors or leukemia during same time frame; N=397	Osteosarcoma	Crude rate, Adjusted OR	N	-

APPENDIX B. R-INLA coding

```
> fom1_hfx = hfx_case ~ f(region, model='bym', graph=cheongju) +
                        f(time, model="rw2") +
                        f(time1, model="iid") +
                        f(region.time, model="iid") +
                        flo

> result1_hfx= inla(fom1_hfx, family="poisson", data=dat,
                        E=dat$hfx_exp,
                        control.compute=list(dic=TRUE, cpo=TRUE,
                        graph=TRUE, mlik=TRUE) )



> fom2_hfx = hfx_case ~ f(region, model='bym', graph=cheongju) +
                        f(time, model="rw2") +
                        f(time1, model="iid") +
                        f(region.int, model="iid",group=time.int,
                        control.group=list(model="rw2")) +
                        flo


> fom3_hfx = hfx_case ~ f(region, model='bym', graph=cheongju) +
                        f(time, model="rw2") +
                        f(time1, model="iid") +
                        f(time.int, model="iid", group=region.int,
                        control.group=list(model="besag",
                                           graph=cheongju)) +
                        flo


> fom4_hfx = hfx_case ~ f(region, model='bym', graph=cheongju) +
                        f(time, model="rw2") +
                        f(time1, model="iid") +
                        f(region.int, model="besag",
                        graph=cheongju, group=time.int,
                        control.group=list(model="rw2")) +
                        flo
```

These R codes are for fitting each type of formula with hip fracture. We did not include other selected diseases (osteoporosis, bone cancer) because it also performed in the same way.

APPENDIX C. CARBayesST coding

Model comparison for hip fracture
[CARBayesST]

```
> m1_hfx = CARBayesST::ST.CARanova(f_hfx, data=dat, W=W.mat,
                           family="poisson",interaction=TRUE,
                           burnin=50000, n.sample=200000, thin=5)


> m2_hfx = CARBayesST::ST.CARlinear(f_hfx, data=dat, W=W.mat,
                           family="poisson",burnin=50000, n.sample=200000,
                           thin=5)


> m3_hfx = CARBayesST::ST.CARar(f_hfx, data=dat, W=W.mat,
                           family="poisson",burnin=50000, n.sample=200000,
                           thin=5)


> m4_hfx = CARBayesST::ST.CARadaptive(f_hfx, data=dat, W=W.mat,
                           family="poisson",burnin=50000, n.sample=200000,
                           thin=5)


> m5_hfx = CARBayesST::ST.CARlocalised(f_hfx, data=dat, W=W.mat,
                           family="poisson", G=3,burnin=5000,
                           burnin=50000, n.sample=200000, thin=5)
```

These CARBayesST codes was used in R. We did not include other diseases (osteoporosis and bone cancer) codes since the codes structure are same with different data.

APPENDIX D. Compare the relative risk

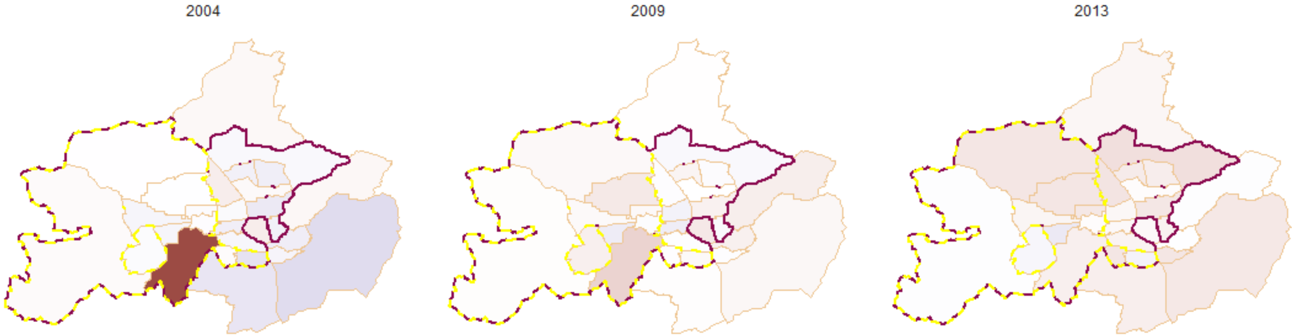
Table B. Posterior distribution of relative risks (RR) with 95% credible intervals in different period of time.

	1982-2004	1997-2004
	RR* (95% CrI)**	
Hip Fracture	0.96 (0.87 – 1.05)	1.07 (0.97 - 1.16)
Osteoporosis	0.96 (0.89 – 1.03)	1.10 (1.02 - 1.19)
Bone Cancer	1.20 (0.89 – 1.62)	0.96 (0.73 – 1.25)

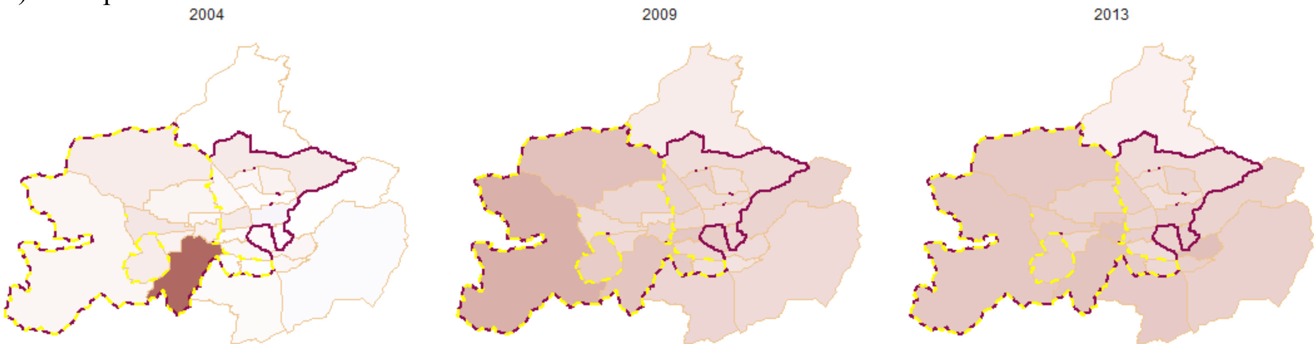
Note.
* RR: Relative risk
** 95% CrI: 95% Credible Interval

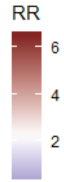
APPENDIX E. Disease mapping with three different regions

A) Hip fracture

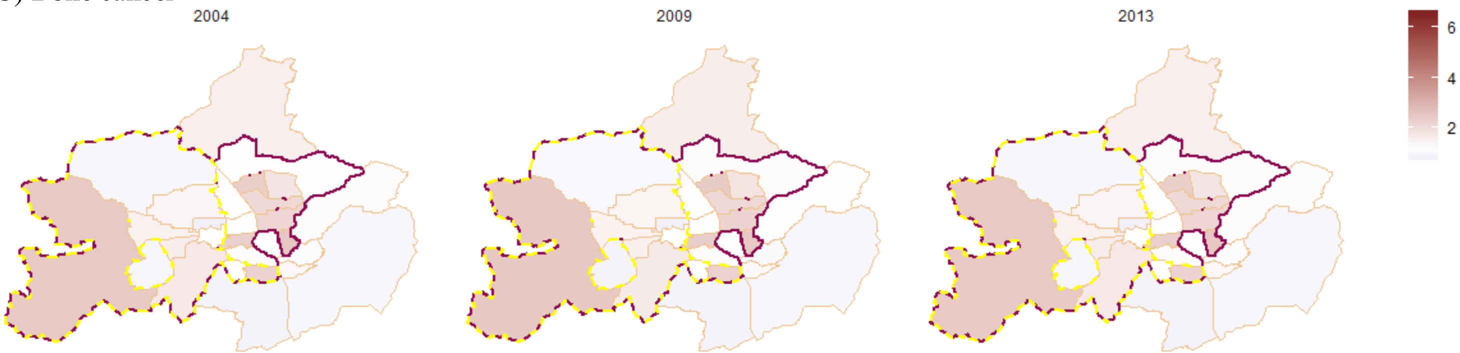


B) Osteoporosis





C) Bone cancer



Note.

· Purple bold line region: CWF was conducted from 1982 to 2004 (long-term exposure)
· Yellow dotted line region: CWF was conducted from 1997 to 2004 (short-term exposure)
· Rest of region: CWF never implemented

APPENDIX F. Outline of the methods

Table C. Outline the six models compared in this study

Model	Paper	Software
Model 1	Knorr-Held (2000)	ST.CARanova
Model 2	Bernardinelli et al (1995)	ST.CARlinear
Model 3	Rushworth et al (2014)	ST.CARar
Model 4	Rushworth et al (2017)	ST.CARadaptive
Model 5	Lee and Lawson (2016)	ST.CARlocalised
Model 6	Knorr-Held (2000)	R-INLA

Source: Lee et al., (2018)

APPENDIX G. RECORD statement

Table D. The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data

	Item Number	STROBE Items	RECORD Items	Page No
Title and Abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract. (b) Provide in the abstract an informative and balanced summary of what was done and what was found. RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and time frame within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	(a) Indicate the study's design with a commonly used term in the title or the abstract. (b) Provide in the abstract an informative and balanced summary of what was done and what was found. RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and time frame within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Page i,ii
Introduction				
Background rationale	2	Explain the scientific background and rationale for the investigation being		Page 1-4

		reported.		
Objectives	3	State specific objectives, including any prespecified hypotheses.		Page 15
Methods				
Study Design	4	Present key elements of study design early in the paper.		Page 16
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.		Page 16-18
Participants	6	(a) Cohort study: Give the eligibility criteria and the sources and methods of selection of participants. Describe methods of follow-up. Case-control study: Give the eligibility criteria and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. Cross-sectional study: Give the eligibility criteria and the sources and methods of selection of participants. (b) Cohort study: For matched studies, give matching criteria and number of exposed and unexposed. Case-control study: For matched studies, give matching criteria and the number of controls per	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the	Page 19

		case.	number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Page 20-21
Data sources /measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.		Page 19
Bias	9	Describe any effort to address potential sources of bias.		N/A
Study size	10	Explain how the study size was arrived at.		Page 19
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.		Page 20-21
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examine subgroups and interactions. (c) Explain how		Page 23-25, 28-31

		missing data were addressed. (d) Cohort study: If applicable, explain how loss to follow-up was addressed. Case-control study: If applicable, explain how matching of cases and controls was addressed. Cross-sectional study: If applicable, describe analytical methods taking account of sampling strategy. (e) Describe any sensitivity analyses		
Data access and cleaning methods	13	N/A	RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	N/A
Linkage	14	N/A	RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Page 18
Results				
Participants	15	(a) Report the numbers of individuals	RECORD 13.1: Describe in detail the	Page

		at each stage of the study (e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed). (b) Give reasons for nonparticipation at each stage. (c) Consider use of a flow diagram.	selection of the persons included in the study (i.e., study population selection), including filtering based on data quality, data availability, and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	33
Descriptive data	16	(a) Give characteristics of study participants (e.g., demographic, clinical, and social) and information on exposures and potential confounders. (b) Indicate the number of participants with missing data for each variable of interest. (c) Cohort study: summaries follow-up time (e.g., average and total amount).		Page 33-35
Outcome data	17	Cohort study: Report numbers of outcome events or summary measures over time. Case-control study: Report numbers in each exposure category or summary measures of exposure. Cross-sectional study: Report numbers of outcome events or summary measures.		Page 387
Main results	18	(a) Give unadjusted estimates and, if applicable, confounder-adjusted		Page 41-44

		estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries when continuous variables were categorized. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.		
Other analyses	19	Report other analyses done—e.g., analyses of subgroups and interactions and sensitivity analyses.		Page 47, 68-70
Discussion				
Key results	20	Summarize the key results with reference to study objectives.		Page 48
Limitations	21	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Page 48-49
Interpretation	22	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses,		Page 48-51

		results from similar studies, and other relevant evidence .		
Generalisability	23	Discuss the generalizability (external validity) of the study results.		N/A
Other Information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.		N/A
Accessibility of protocol, raw data, and programming code		N/A	RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Page 66-67

Note.
Abbreviations: N/A, not applicable
Source. Benchimol et al., 2015

Abstract (Korean)

수돗물불소농도조정사업 시행과 골 건강과의 연관성: 청주시 자연실험

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연구목적: 수돗물불소농도조정사업 (이하, 수불사업)은 청주시에 1982년부터 2004년까지 시행되었다. 본 연구는 뼈와 관련된 질환 (고관절 골절, 골다공증, 골암)에 대한 수불사업의 위해를 역학적으로 평가하고자 한다.
연구설계: 본 연구는 자연실험 설계를 기반으로 한 생태학적 연구이다.
연구방법: 2004년부터 2013년 사이의 청주시 주민등록인구기반 거주자를 연구 대상자로 선정하여 국민건강보험공단 국민건강자료에서 맞춤형 DB를 사용하였다. 전신건강질환 중 고관절 골절, 골다공증, 골암을 관심질환으로 선정하였으며 관심질환 의료의용의 환자 건수를 이용하여 자연실험으로 설계된 청주시에서의 수불사업 중단 이후 의료이용 추이를 분석하고 질병 발생의 경향과 수불사업의 위해에 대하여 분석하였다. 읍면동별 불소화 시행 여부와 청주시 거주민들의 관심질환의 표준화 유병률과의 관계를 모형화 하는데 시공간적 상관성을 고려한 계층적 베이지안 시공한 포아송 회귀모형을 사용하여 분석하였다. 공간적 상관성을 통제하

는데 자주 사용되는 조건부 자기회귀모형(CAR)을 적용하였다. 베이지안 추론을 위한 계산 방법은 R-INLA 패키지를 사용하였다.

연구결과: 수불사업이 중단된 이후, 수불사업이 시행되었던 지역과 한번도 시행하지 않은 지역을 비교하였을 때 관심질환의 유병률이 통계적으로 유의한 차이가 없음을 확인하였다 (고관절 골절: RR=0.94, 95% CrI [0.86-1.04], 골다공증: RR=0.94, 95% CrI [0.87-1.02], 골암: RR=1.20, 95% CrI [0.89-1.61]).

결론: 국민건강보험자료를 이용하여 청주시 소지역(읍면동) 단위로 2004년부터 2013년까지 관심질환의 의료이용에 대한 시간과 공간을 고려한 시공간 분석을 수행하였다. 수불사업 중단 이후, 시행지역과 미시행지역 간의 의료이용에 차이가 없었음을 확인하였으며 시행지역이 미시행지역에 비해 골질환 유병률이 특별히 증가하는 추세를 발견하지 못하였다. 따라서, 수불사업으로 인한 위해가 없었음을 확인하였다. 본 연구결과는 자연실험을 통한 역학연구로서 수불사업의 인체위해성에 대한 과학적 근거자료로 제공 될 수 있으며, 공중보건사업으로 꾸준히 연구하고 발전시켜 나아가야할 필요성을 제시한다.

주요어: 수돗물불소농도조정사업, 전신건강영향, 자연실험, 시공간 분석, 환경역학

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