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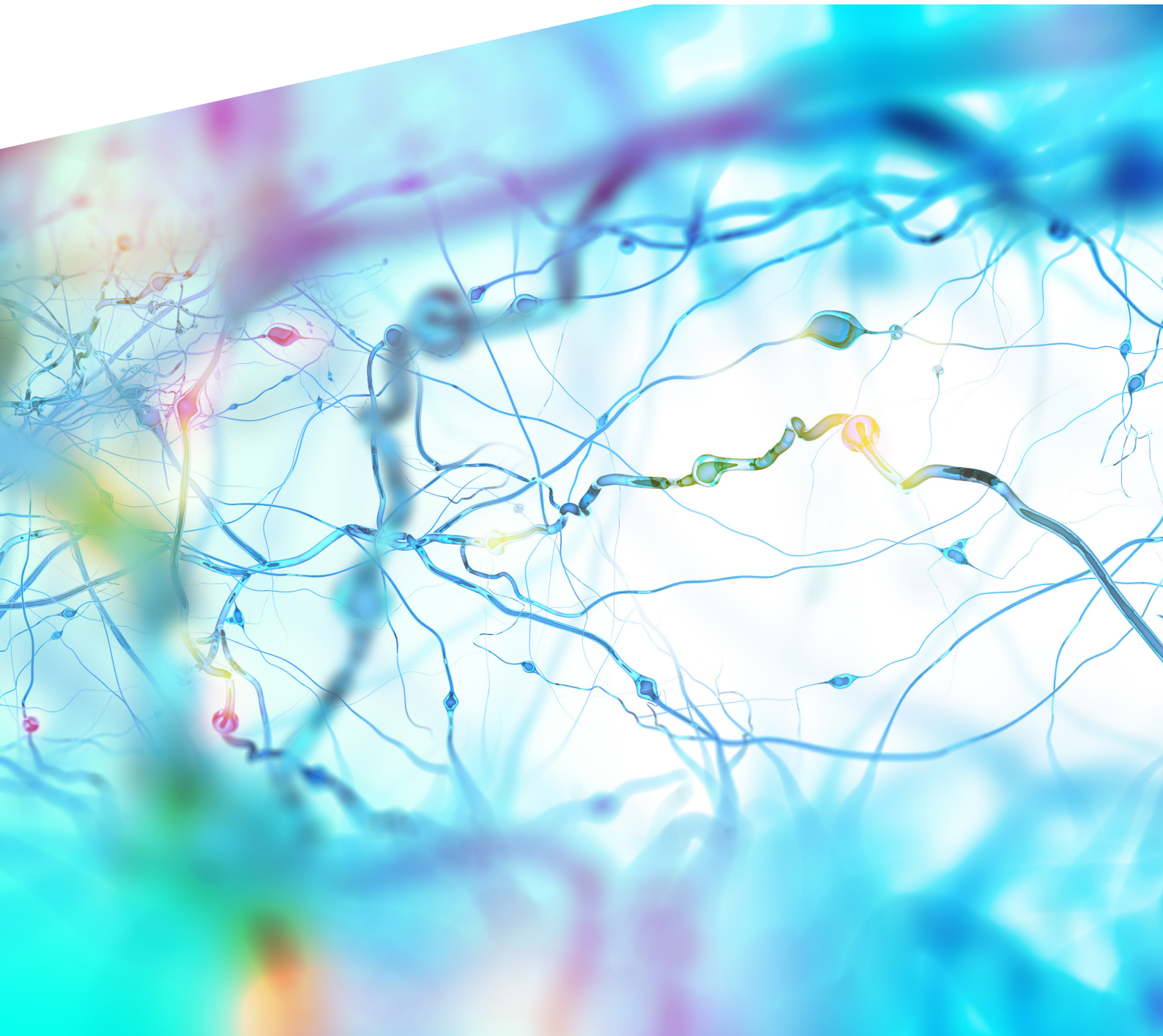

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## Aims & Scope

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Editorial office Ewha Medical Research Institute
25, Magokdong-ro 2-gil, Gangseo-gu, Seoul 07804, Korea
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# Editorial Board

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## Review Articles: Special Drafts for Colorectal and Anal Diseases



## Review Article



## Original Article



## Case Reports



## Perspective

Review Article

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# Update on Diagnosis and Treatment of Colorectal Cancer

**Chan Wook Kim**

Department of Colon and Rectal Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

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**Corresponding author**
Chan Wook Kim
Department of Colon and Rectal Surgery, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: 82-2-3010-3928
Fax: 82-2-3010-6710
E-mail: crscwkim@amc.seoul.kr

**Key Words**
Colorectal neoplasms; Screening; Metastatic; Neoadjuvant therapy; Precision medicine

The rate of colorectal cancer (CRC) has altered. Early-onset CRC patients are increasing, and it is one of the main causes of cancer-related death. Based on epidemiologic change, the CRC screening program needs to be changed. To increase compliance, non-invasive screening techniques are developed. Although CRC survival has increased, the oncologic prognosis of metastatic CRC is remains poor. Even in metastatic CRC, which is the most difficult to treat, attempts are being made to increase the survival rate by active surgical therapy with the creation of chemotherapeutic regimens and targeted treatment based on genomic information. Due to the introduction of aggressive chemotherapy regimens, targeted therapy based on genomic features, and improvements in surgical technique, the role of surgical treatment in metastatic CRC has expanded. Metastatic CRC surgery was indicated for liver, lung, and even peritoneal seeding. Local ablation therapy was also effectively used for liver and lung metastasis. Cytoreductive surgery and intraperitoneal chemotherapy were tried for peritoneal seeding and demonstrated good results in a subgroup of patients, although the right indication was carefully assessed. At the same time, one of the key goals of treatment for CRC was to maintain functional outcomes. Neoadjuvant treatment, in particular, helped rectal cancer patients preserve functional results while maintaining oncologic safety. Rectal cancer organ preservation techniques are now being researched heavily in a variety of neoadjuvant treatment settings, including immunotherapy and whole neoadjuvant therapy. Precision medicine based on patient and disease characteristics is currently being used for the diagnosis and treatment of CRC.

## Introduction

In 2019, cancer is the leading cause of death in Korea, and colorectal cancer (CRC) is one of the most prevalent malignancies worldwide [1,2]. CRC is the second leading cause of cancer-related death and the third most prevalent malignancy globally [2]. Thyroid, lung, stomach, colorectal, and breast cancer were the five most frequently diagnosed malignancies in Korea in 2019 according to statistics from the National Cancer Registration Project of the Central Cancer Registry of Korea. After stomach and lung cancer in males and breast and thyroid cancer in women, CRC is the third most frequent malignancy in both sexes [1]. Since 1999, the incidence of CRC has been consistently rising; however, it has been slowly declining since about 2011. Both rectal and colon cancers exhibit the same incidence trend (Fig. 1). Although adenocarcinoma makes up the majority of CRC cases, neuroendocrine tumors are the most common non-adenocarcinoma [3]. A feature worth observing is the lowering of the age of onset, and it has

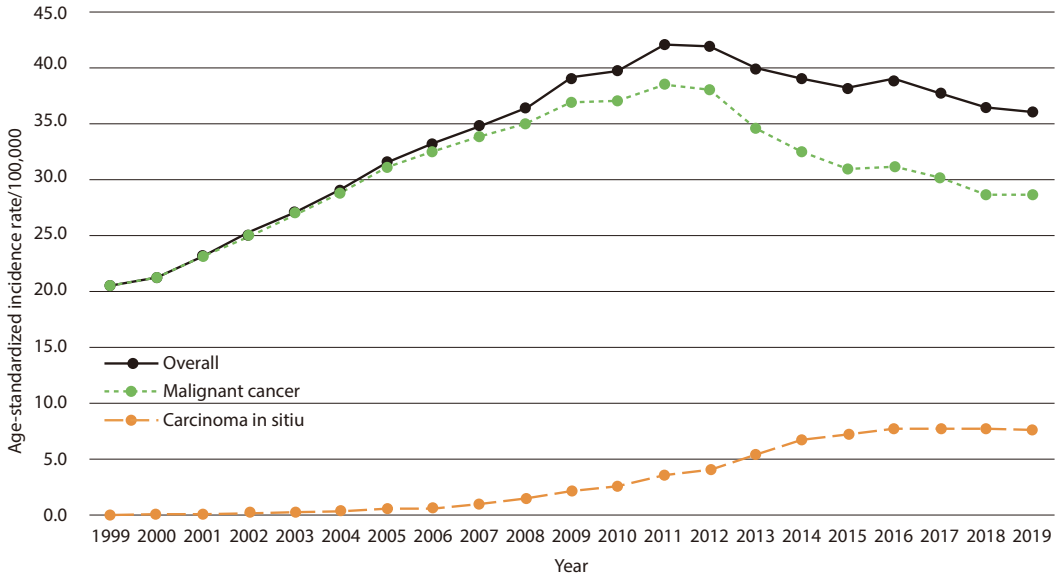


**Fig. 1.** Age-standardized incidence rates of colorectal cancer in Korea, 1999–2019. Adapted from Kang et al. [1] with CC-BY-NC.

been observed that in industrialized nations, the prevalence of early-onset CRC in those under 50 is rising, increasing social awareness It is very obvious that CRC incidence is rising among the elderly. The growing older population in good health appears to be the cause. A national investigation on the treatment strategy for advanced CRC seems necessary given the current trend toward an aging society [1,2,4].

Overall survival (OS) rates for CRC patients in Korea are extremely high, and the relative OS rate for CRC patients is reported to be 74.3% of patients diagnosed between 2015 and 2019 [1]. In Korea, the OS rate of CRC varies by gender, with men having a greater rate than women. The increased survival rate in men is thought to be due to the average age of CRC diagnosis being older in women than in men and the presence of more right-sided CRC in women, despite the fact that the precise mechanism is unknown [1,2,5]. Although the survival rate for CRC in stages I-III is increasing, there is still an issue because the increase in the OS rate for CRC with metastatic disease is not significant.

## Advances in Colorectal Cancer Screening and Diagnosis

The cost, compliance, sensitivity, and specificity of the test, as well as other factors, are taken into account while choosing the screening test to be used. Fecal occult blood test, an immunochemical test method, is now employed in Korea as the first line screening test for national health screening. Although there is still debate regarding the accuracy of the diagnosis of polyps or CRC, the non-invasive test has the significant advantage of high compliance. There will not be any debate on the importance of colonoscopy in the timely diagnosis and treatment of precancerous lesions and early CRC. Due to the invasiveness and low compliance of the colonoscopy as a primary screening test, it is crucial to weigh this option [6,7]. Fecal occult blood testing every one to two years for asymptomatic persons aged 45 to 80 is the current CRC screening prescription in Korea, and colonoscopies are only occasionally conducted according on individual risk. The question of whether colonoscopy can be used as a primary screening test


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is being investigated in Korea as a pilot project, but it is still necessary to make decisions about potential complications and costs, whether the examination can be restricted based on bowel preparation, and how to assess the operator's skill. In particular, the screening test may only be used and assessed for effectiveness after extensive research and development on how to improve patient compliance.

More accurate non-invasive screening methods have been developed in an effort to replace the fecal occult blood test, which is the current screening method [8–10] (Table 1). The test that seeks to identify tumor epithelial DNA in feces in order to diagnose CRC is now coming the closest to clinical application. An assay for mutant *KRAS*, methylation *BMP3*, methylated *NDRG4*, and a fecal immunochemical test for hemoglobin were all included in the FDA-approved multi-target fecal DNA test [8]. In a research involving 9,989 average-risk people having colonoscopy, the multi-target fecal DNA test demonstrated better sensitivity for the diagnosis of CRC (92% vs. 74%) and advanced adenoma (42% vs. 24%) when compared with fecal immunochemical test test. In 2018, the Ministry of Food and Drug Safety in Korea approved the EarlyTect fecal DNA test (Genomic Tree, Daejun, Korea), which only examines the methylation of one gene, the syndecan-2 gene [10]. The findings are significant since we are carrying out a prospective multicenter study with a focus on the asymptomatic general population over 60 or in the high-risk category. Due to its excellent disease prediction, non-invasiveness, and high compliance, this fecal DNA detection test is projected to be used as a screening tool. The poor identification rate of pre-cancerous lesions is a challenge; thus it is important to watch with greater skepticism what kind of outcomes will be seen in the long-term impact of CRC prevention in the future.

Changes to CRC screening are required in light of the rising incidence of CRC in people under the age of 50 [1,2,11] and the growing elderly population. Although the US Preventive Services Task Force and the Multi-Specialty Task Force currently recommend starting screening at age 50, the American Cancer Society published guidelines in 2018 with a qualified recommendation to lower the starting age for CRC screening from 50 to 45 years of age in the average-risk adult population [12]. Few empirical studies have been conducted on the effectiveness of screening in younger, average-risk persons [13,14], and it is unknown which screening method is best for this age group.

According to the US Preventive Services Task Force's most recent CRC screening recommendation for individuals aged 76 to 85, the choice to test for CRC should be made individually, taking into account the patient's general health and screening history [15]. According to the recommendation, screening is best recommended for people who have never been screened, are healthy enough to get treatment if CRC is found, and do not have significantly shortened life expectancies. Due to conflicting sources of death, screening is not advised for persons 86 years of age and older. Although further research is needed, healthcare professionals should participate in shared decision-making when evaluating people over 75 years old and take into account factors like life expectancy, patient risk, values, and preferences.

**Table 1.** Clinically available non-invasive screening method with stool DNA detection for colorectal cancer diagnosis

| Product name | Target | Sensitivity, cancer | Specificity, cancer | Sensitivity, advanced adenoma detection |
|---|---|---|---|---|
| Cologuard [8] | *NDRG4*, *BMP3* DNA methylation, KRAS mutation, hemoglobin | 92.3% | 89.8% | 42.4% |
| EarlyTect [10] | *SDT2* methylation, hemoglobin | 90.2% | 90.2% | 66.7% |

*NDRG4*, N-myc downstream-regulated gene 4; *BMP3*, bone morphogenetic protein 3; *KRAS*, Kirsten rat sarcoma virus; *SDT2*, synthecan 2.


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It is crucial to advise when to halt screening in future research.

## Development Surgical Treatment of Metastatic Colorectal Cancer

Despite a significant improvement in treatment outcomes for CRC, metastatic CRC therapy outcomes remain remarkably poor [1,2]. Therefore, we have worked hard to actively treat patients with metastatic disease in an effort to increase the OS of CRC patients.

Chemotherapy is the major treatment for CRC that has spread to other organs, and surgery is only occasionally employed. However, with advancements in systemic therapy, increased use of genetic information, and the development of surgical techniques, more individuals with metastatic CRC can benefit from curative-intent surgical surgery [16–18].

Liver metastasis, common metastasis of CRC, is known as metastatic CRC that can improve the prognosis with surgery. Liver resection with or without local ablation therapy, such as radiofrequency ablation and stereotatic radiation (SBRT), can be used for curative treatment in CRC patients with liver metastases [19–21]. Numerous prognostic factors and key drivers of resectability have included the size and location of liver metastases, as well as their distribution throughout the liver and the existence of extrahepatic metastatic lesions [20,22,23]. However, today, even in situations with multiple liver metastases, surgery is used when the likelihood of resection is verified through earlier chemotherapy, and in some instances, secondary resection is carried out in specific patients [23–25]. In metastatic CRC patients with bi-lobar liver metastases and limited functional liver remnants, portal vein embolization can be used with CRC surgery to assure tumor regression and hepatic hypertrophy (FLR). The two-stage hepatectomy would also enable the total removal of bi-lobar liver metastases and FLR regulation. To get around the drawback of liver resection in CRC patients with a small FLR and numerous liver metastases, associating liver partition and portal vein ligation for phased hepatectomy (ALPPS) was created. According to reports, there was no discernible difference between ALPPS and two-stage hepatectomy in terms of postoperative morbidities and fatalities, although ALPPS had improved survival outcomes in randomized controlled trials [25,26].

Different strategies would be taken into consideration for individuals with synchronous liver metastases depending on their general health, the likelihood of curative resection, and extra-hepatic metastasis. There have been recommendations for simultaneous resection, liver-first strategy, and bowel first approach. Although a simultaneous liver and colon resection has advantages over a liver-first/bowel-first approach in terms of avoiding two surgeries, expediting the start of chemotherapy, and lowering the risk of cancer dissemination, postoperative complications and increased surgical stress are still a concern [27–29].

Surgical treatment for lung metastases and peritoneal metastases is developing in addition to liver metastases. Surgery can be beneficial for pulmonary metastasis, a metastatic lesion that is similar to liver metastasis in terms of how well it responds to treatment [30,31]. A five-year OS rate of more than 50% was observed after pulmonary metastasectomy in a systematic analysis of surgical removal of pulmonary metastases in CRC patients [31]. Now, pulmonary oligo-metastasis and solitary lesions are frequently treated with video-assisted thoracoscopic surgery. In a recent meta-analysis, there was no discernible difference in the rates of OS and recurrence-free survival between open thoracotomy and video-assisted thoracoscopic surgery for pulmonary metastasectomy [32]. Additionally, SBRT is beginning to show promise in the management of lung metastases. The examination of a sizable multi-center database revealed that OS was enhanced by SBRT for oligo-metastatic CRC. Retrospective analysis of 381 oligo-

metastatic CRC lesions in 235 CRC patients revealed that those who underwent SBRT had two-year OS rates of 76.1% and five-year OS rates of 35.9% [21,33]. The advancement of non-surgical local therapy benefits the active management of lung metastases as well.

It is known that peritoneal metastasis occurs in about 5%–15% of CRC patients, and the metastasis of CRC is known to have the worst prognosis [16]. Surgery has a very small part in the management of peritoneal metastases; the primary therapy is palliative chemotherapy. However, the role of surgery has been consistently examined in patients with limited peritoneal metastases, and efforts to increase the survival rate have persisted through active treatment with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) [16,34–36] (Fig. 2). In some patients with peritoneal metastases, CRS/HIPEC may enhance oncological outcomes, according to long-term randomized controlled trials and meta-analyses [35,36]. Effectiveness of HIPEC has been questioned, though, with the advent of systemic chemotherapy [37], and it is thought that this is due to resistance to the anticancer medications that are currently being employed. As a result, progress in treating metastatic CRC, particularly in raising the survival rate, has stalled. Instead, doctors are still choosing anticancer drugs that are sensitive to the disease and using precision medicine when it is necessary. It appears to be a solution for the treatment of peritoneal metastasis [38]. In order to effectively treat metastatic CRC in the future, new medications will need to be created and used, with treatment decisions based on more precise genetic data. In addition, the role of sophisticated multidisciplinary treatment involving professionals will be critical for improving oncological outcomes in order to increase the potential of curing as well as controlling the disease by performing surgical treatment and other local treatments at the right moment.

## Paradigm Shift of Rectal Cancer Treatment

Neoadjuvant chemoradiotherapy (nCRT) altered the idea of surgical excision in the treatment

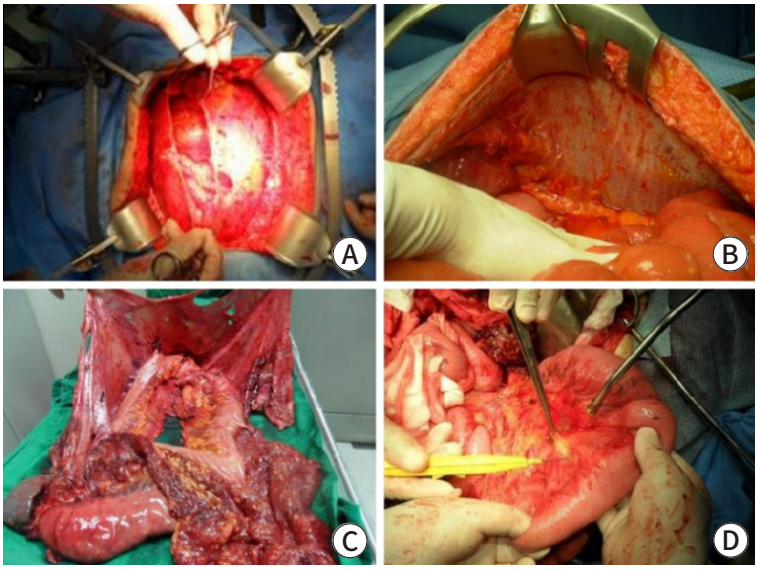


**Fig. 2.** Cytoreductive surgery for patients with peritoneal carcinomatosis from colorectal cancer. Peritoectomy process at (A) pelvic cavity, (B) left upper quadrant, (C) intestinal organs, (D) and small bowel mesentery. Adapted from Kim and Kim 2021 [16] with CC-BY-NC.


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of rectal cancer. Surgery has always been and continues to be regarded as the most crucial and necessary step for cure of CRC [39]. Although it is known that there is no change in the OS or recurrence-free survival rates when compared to postoperative radiation therapy or surgical resection alone, radiation therapy prior to rectal cancer surgery boosts the full resection rate of rectal cancer and lowers the local recurrence rate [40]. Despite this drawback, finding total or nearly complete rectal cancer regression to nCRT allowed even individuals with early-stage advanced rectal cancer to use an organ-preserving method. Although radical resection of rectal cancer has improved functional outcomes and greater sphincter preservation due to technical advancements [41,42], organ preservation strategies have grown in popularity due to its obvious functional benefits when compared to oncologic outcomes [43–45]. When the results of representative trials, which showed good oncologic outcomes following organ preservation [44,45], were compared to the outcomes of radical resection for patients who respond well to nCRT, interest in organ preservation of rectal cancer has sharply increased. Many initiatives have been made in an effort to increase the number of patients who fully respond to nCRT. The greatest barrier to incorporating organ preservation techniques into actual clinical practice, meanwhile, continues to be the poor accuracy of response evaluation to nCRT. It also has to do with the diagnosis of local regrowth, a rare variation of local recurrence in rectal cancer treated with organ preservation techniques. However, the salvage percentage for these patients was observed to vary [46,47]. Local regrowth occurred in 20%–30% of patients who undergo organ preservation [44–46]. In this context, we must be careful not to reduce the likelihood of a cure by improperly implementing an organ preservation strategy.

In the era of advanced rectal cancer treatment, trials to enhance distant metastasis control are ongoing, along with enhancing quality of life by including comprehensive neoadjuvant treatment (TNT) [48,49]. TNT, however, has not yet demonstrated any advantages in terms of controlling distant metastases, although showing a rise in clinical near-complete responders. After nCRT, distant metastasis is still a significant oncologic issue, therefore we need to wait and critically examine long-term results [50]. The emphasis on striking a balance between quality of life and oncologic outcomes for the treatment of rectal cancer will continue.

## Conclusion

A significant cancer subtype that continues to endanger public health is CRC. Although the screening program is now run well, there is ongoing concern about how to increase compliance and practically apply non-invasive tests. The screening program must be revised to reflect epidemiologic shift as the prevalence of young-age CRC grew and, on the other hand, elderly CRC patients increased due to an increase in life expectancy. Physicians and patients are more interested in finding ways to balance quality of life and oncologic outcomes, and surveillance is more crucial to find cancer as early as feasible in order to preserve function without impairing oncologic results.

Active treatment for metastatic CRC has been carried out to break the CRC survival plateau. The role of surgical treatment has increased for metastatic CRC along with systemic treatment and targeted treatment based on genomic features of individuals. On the other hand, one of the most significant changes in the period of surgical therapy of CRC is the judicious deferral of surgical treatment, including nCRT/TNT.

The overall trend in CRC treatment is toward precision medicine, which protects the patient's quality of life while also ensuring the best oncological treatment outcomes by taking into

account the patient's unique traits, way of life, and genetic characteristics. As a result, the trend in treatment showed development at both ends: for rectal cancer, which responds well to neoadjuvant therapy, efforts are rising in the direction of organ preservation, and for metastatic CRC, which had previously undergone rather harsh treatment. It will be able to offer a new development direction for CRC treatment when the financial support to move from the current standard, which concentrated on standard treatment to enhance the overall treatment outcome, to precision treatment and the improvement of the system come together.

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### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### ORCID iD

Chan Wook Kim: https://orcid.org/0000-0002-2382-0939

### Author Contribution

The article is prepared by a single author.

### Ethics Approval and Consent to Participate

Not applicable.

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Review Article

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# Is It a Refractory Disease?- Fecal Incontinence; beyond Medication

**Chungyeop Lee**[1], **Jong Lyul Lee**[2]

[1]Department of Surgery, Pohang Naval Hospital, Pohang, Korea
[2]Department of Colon and Rectal Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

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**Corresponding author**
Jong Lyul Lee
Department of Colon and Rectal Surgery, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: 82-2-3010-1732
Fax: 82-2-3010-6710
E-mail: iamleejong@amc.seoul.kr

**Key Words**
Fecal incontinence; Treatment outcome; Implantable neurostimulators; Surgery; Stem cell transplantation

Fecal incontinence (FI) is recurrent uncontrolled passage of fecal material in patients. The life expectancy of humans has increased. Elderly patients have a significant rate of FI. Therefore, the number of patients with FI will increase. For diagnosis of FI, the digital rectal exam, ultrasonography, and anal manometry are used. In addition, the severity of FI can be assessed using the FI score system by examining symptoms. Recent applications include three-dimensional ultrasonography and other novel approaches. The treatments for FI include biofeedback therapy, anal implant, artificial sphincter, nerve modulation, SECCA, stem cell therapy, and surgical intervention. Biofeedback therapy is a noninvasive procedure. Anal implant, stem cell therapy, and SECCA are all minimally invasive treatments. And more methods constitute intrusive treatment. None of these therapies has been conclusively demonstrated to be superior. Depending on the severity of the symptoms, a non-invasive approach or an intrusive treatment is most frequently employed. In this review, I will discuss the diagnosis and treatment options for FI.

## Introduction

Socially and psychologically, fecal incontinence (FI) is a tragedy. Normal bowel continence is a complicated process including the anal sphincters, pelvic floor, stool volume, rectal compliance, and neurologic function. It's possible for FI to occur if even one of these things goes wrong [1].

Due to the humiliating nature of FI symptoms, many are reluctant to disclose their illnesses to doctors. Because individuals underreported their symptoms, the true prevalence of FI was unclear. Consequently, the prevalence of FI has fluctuated widely between 2% and 20% [2,3]. FI prevalence varies with age. The prevalence of FI rose with age, from 2.91% in individuals aged 20% to 29% to 16.16% in those aged 70 and older [2]. Extremely high incidence of FI are found among nursing home residents. The prevalence of FI is considerably higher than 50% among nursing home residents [3,4]. Currently, breakthroughs in sphincter-preserving surgery for rectal cancer result in incontinence, which is a symptom of the low anterior resection syndrome [5,6]. Consequently, the old population is anticipated to grow. Consequently, the prevalence of FI is anticipated to increase. The treatment of FI ranges from non-invasive strategies, such as lifestyle modifications, medical pills, sphincter augmentation with injections, and biofeedback therapy (BFT), to invasive sacral nerve stimulation (SNS) and surgical interventions [7–9].

Given that the number of patients with FI is likely to rise, it is crucial to identify the treatments now in development and to establish treatment indications. In this review, we therefore considered BFT and surgical procedures for FI.

## Definition and Etiology of Fecal Incontinence

Rome IV diagnostic criteria described FI as "recurrent uncontrolled flow of feces in an individual with at least 4 years of developmental age." [10]. With the release of Rome IV diagnostic criteria in 2016, the definition of FI was modified. Rome III separated structural and neurogenic factors for functional FI. However, Rome IV defines FI as the involuntary passage of solid or liquid stool, regardless of the underlying reason. This indicates that there are several, overlapping causes of FI, and that patients with purely psychosocial or bowel habit disorders are uncommon. Additionally, there was no effective treatment advice based on the differentiation between causes of FI. The second modification to the diagnostic criteria for FI concerns the definition of event frequency. FI is defined as the development of symptoms at least six months prior with two to four episodes of FI over four weeks. In contrast, Rome III required only one FI event within the previous three months [11]. According to several researchers, this restricted modification negatively impacts the quality of life for some patients. This stringent frequency threshold resulted in a lower prevalence of FI compared to prior estimations. These excluded patients have a diminished life quality [12]. Therefore, additional research is necessary to provide a precise definition of FI in Rome V. Damages to the continence process, including the anal sphincter, bowel habits, rectal compliances, pelvic floor muscles, and rectal sensibility, might cause FI. Multiple variables cause FI in 80% of individuals [13]. Several studies have identified FI risk factors (Table 1) [13–15]. Age and gastrointestinal (GI) diseases that cause stool alterations are risk factors for FI. Aging impacts the etiology of FI, resulting in a decrease in pelvic floor muscle mass and an increase in co-morbidities that compromise the mechanism of continence. In addition, sphincters may be altered by fibrosis and thickening as a result of decreased resting tone, with the external anal sphincter's thinning resulting in a decrease in anal pressure. Moreover, diminished rectal sensitivity, rectal compliance, and rectal capacity impede anal sensory, motor, and rectal reservoir function in the aged [16]. Inflammatory bowel disease and irritable bowel syndrome characterized mostly by diarrhea are risk factors for FI. However, any GI condition that causes frequent bowel movements or a change in bowel habits can lead to FI [17]. And the structural causes of FI are obstetric injuries [18], anorectal surgery [19,20],

**Table 1.** Risk factors of fecal incontinence

| Category | Factors |
|---|---|
| Patient | Aging, obesity, smoking, post-menopause, nursing home residency |
| Structural comorbidities | Obstetric injuries, anorectal surgeries, rectal propapse, rectocele, trauma, sphincter sparing bowel resection |
| Medical comorbidities | Irritable bowel syndrome, inflammatory bowel disease, radiation proctitis, malabsorption, hypersecretory tumors, fecal impaction, diarrhea, diabetes mellitus, urinary incontinence, multiple sclerosis, scleroderma, history of prostate cancer, cholecystectomy |
| Neurologic comorbidities | Pudendal neuropathy, dementia, stroke, spina bifida, spinal cord inury, spinal surgery |
| Congenital comorbidities | Imperforate anus, cloacal defect |


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rectal prolapse [21], and anal intercourse [22]. Puborectal or anal sphincter dysfunction may result in FI. These injuries are possible during spontaneous vaginal birth or forceps-assisted surgical delivery. Ischemia, laceration, and compression of anal muscles caused by spontaneous labor and delivery contribute to incontinence [23]. Even in the absence of complications, up to 35% of first-time vaginal deliveries may result in hidden sphincter injury. Risk factors for FI included forceps-assisted surgical delivery, occipitoposterior presentation of the infant, and protracted labor [16]. Patients who underwent anorectal procedures such as hemorrhoidectomy, sphincterotomy, and fistula surgery were frequently discovered to have FI [24]. Rectal prolapse results in incontinence as a result of rectal mucosa transporting feces via the anus. And chronic rectal prolapse causes anal sphincter dilatation and dysfunction [21].

## Diagnosis

As with any disorder, FI requires a more thorough medical history. Patients are hesitant to discuss their incontinence problems regularly due to their feelings of embarrassment. The history of a patient's symptoms must be taken with care, thoroughness, and sensitivity [25]. Clinicians should question thoroughly about the patient's underlying condition, medications, and surgical history. In addition to obstetric and anorectal surgery, which are directly associated, it is vital to examine the patient's surgical history, including procedures that appear unrelated, such as cholecystectomy and spinal surgery. Additionally, it is vital to consider drugs for diarrhea and constipation. Changes in bowel, feces, and gas patterns must also be evaluated. Bowel diaries and the Bristol stool form scale can help describe the severity of FI symptoms [26].

Scoring FI systems have been utilized for objective evaluation and evaluation of therapy outcomes. The Wexner Cleveland Clinic Score [27] and the St. Mark's Incontinence Score [28] in conjunction with the FI Quality of Life (FIQL) scale [29] accepted by the American Society of Colon and Rectal Surgeons (Table 2). CCF is the most widely used historical scale. The CCF comprises of five questions, and the sum of each score allows for the diagnosis of FI. The FI Quality of Life scale analyzes performance across four broad categories. Lifestyle, coping/behavior, depression/self-perception, and shame are these categories [29]. St. Mark's score is determined by four criteria: solid stool incontinence, liquid stool incontinence, gas, and lifestyle changes [28]. There are various scales that can be used to assess the severity of FI symptoms. All of these measures have been employed to diagnose FI, despite the fact that only one has been identified. The physical examination involves a perineal skin inspection for scars from trauma, childbirth, past surgery, fistula, or hemorrhoids, as well as a digital rectal exam. The perineal body of female patients was palpated to see if it has been thinning. The Valsalva technique is a strong attempt to exhale against a closed airway, typically performed by closing the mouth and pinching the nose while exhaling. This action is beneficial for distinguishing rectal prolapse. Examining the perianal sensation to pinprick and the ano-cutaneous "wink" reflex will provide a straightforward assessment of neurologic function. A digital rectal examination can detect a fistula or hemorrhoid tumor or lesion. With the doctor's finger inserted into the patient's anus, the patient is instructed to squeeze the sphincter, which provides a general assessment of both resting tone and voluntary squeeze. Colonic exams such as colonoscopy and anoscopy are also helpful to diagnose FI [30].

Ultrasound imaging of the anorectum is the most sensitive method for evaluating the anal complex for the existence of any defect or lesion [30]. Endoanal ultrasound imaging permits the categorization of lesions according to their whole or partial thickness and degree of disruption. A

**Table 2.** Fecal incontinence assessment score

| **Wexner cleveland clinic score** | | | | | |
|---|---|---|---|---|---|
| **Type of incontinence** | **Frequency of symptoms** | | | | |
| | **Never** | **Rarely** | **Sometimes** | **Usually** | **Always** |
| Solid | 0 | 1 | 2 | 3 | 4 |
| Liquid | 0 | 1 | 2 | 3 | 4 |
| Gas | 0 | 1 | 2 | 3 | 4 |
| Pad usage | 0 | 1 | 2 | 3 | 4 |
| Impact on life style | 0 | 1 | 2 | 3 | 4 |
| Score of 0=perfect continence; 20=complete incontinence<br>Never, 0; rarely, <1/ month; sometimes, >1/ month; usually, >1/ week, <1/ day; always, >1/ day | | | | | |
| **St. Mark's incontinence score** | | | | | |
| | **Never** | **Rarely** | **Sometimes** | **Weekly** | **Daily** |
| Incontinence for solidd stool | 0 | 1 | 2 | 3 | 4 |
| Incontinence for liquid stool | 0 | 1 | 2 | 3 | 4 |
| Incontinence for gas | 0 | 1 | 2 | 3 | 4 |
| Alteration in lifestyle | 0 | 1 | 2 | 3 | 4 |
| | | | | No | Yes |
| Need to wear a pad or plug | | | | 0 | 2 |
| Taking constipating medicines | | | | 0 | 2 |
| Lack of ability to defer defecation for 15 minutes | | | | 0 | 4 |
| Score of 0=perfect continence; 24=totally incontinence<br>never, 0; rarely, 1/ month; sometimes, >1/ month but <1 a week; weekly, ≥1/ week but <1 a day; daily, ≥1/ day | | | | | |
| **Fecal incontinence quality of life (FIQL) scale composition** | | | | | |
| Questions: scale 1-lifestyle<br>I cannot do many of things I want to do.<br>I am afraid to go out.<br>It is important to plan my schedule around my bowel pattern.<br>I cut down on how much I eat before I go out.<br>It is difficult for me to get out and do things like going to a movie or to church.<br>I avoid traveling by plane or train.<br>I avoid traveling.<br>I avoid visiting friends.<br>I avoid going out to eat.<br>I avoid staying overnight away from home. | | | | | |
| Scale 2. coping/behavior<br>I have sex less often than I would like to.<br>The possibility of bowel accidents is always on my mind.<br>I feel I have no control over my bowels.<br>Whenever I go someplace new, I specifically locate where the bathrooms are.<br>I worry about not being able to get to the toilet in time.<br>I worry about bowel accidents.<br>I try to prevent bowel accidents by staying very near a bathroom.<br>I can't hold my bowel movement long enough to get to the bathroom.<br>Whenever I am away from home, I try to stay near a restroom as much as possible. | | | | | |
| Question: scale 3-depression/self perception<br>In general, would you say your health is excellent, very good, good, fair, and poor.<br>I am afraid to have sex.<br>I feel different from other people.<br>I enjoy life less.<br>I feel like I am not a healthy person.<br>I feel depressed.<br>During past month, have you felt so sad, discouraged, hopeless, or had so many problems that you wondered if anything was worthwhile. | | | | | |
| Question: scale 4-embarrassment<br>I leak stool without even knowing it.<br>I worry about others smelling stool on me.<br>I feel ashamed. | | | | | |


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common application of anal ultrasonography prior to anus surgery is to identify the location and extent of anal sphincter problems. Ultrasonography of the 3D pelvic floor revealed anal sphincter damage and levator ani muscle avulsion in all groups. In addition, defecography and pelvic MRI are tests that can detect rectoceles and internal rectal prolapse, as well as see pelvic floor muscle activity during defecation (Fig. 1) [31,32].

Anorectal manometry evaluates the resting and squeezed anal sphincter function of patients [25]. Manometry measures muscular strength and reservoir function, which includes anorectal sensation, volume tolerance, and rectal compliance [33]. In the high-pressure region of the rectum, the recto-anal inhibitory reflex is evaluated via fast balloon inflation and deflation. A diminished recto-anal inhibitory reflex is indicative of a neurological disorder. Pudendal nerve terminal motor latency is used to diagnose pudendal neuropathy or systemic diseases such as diabetes and chemotherapy. Electrical impulses are administered to the pudendal nerve after an electrode is affixed to the examiner's finger and directed toward the ischial spine. The response time at the external anal sphincter level is measured. Normal reaction time is 2.0±0.2

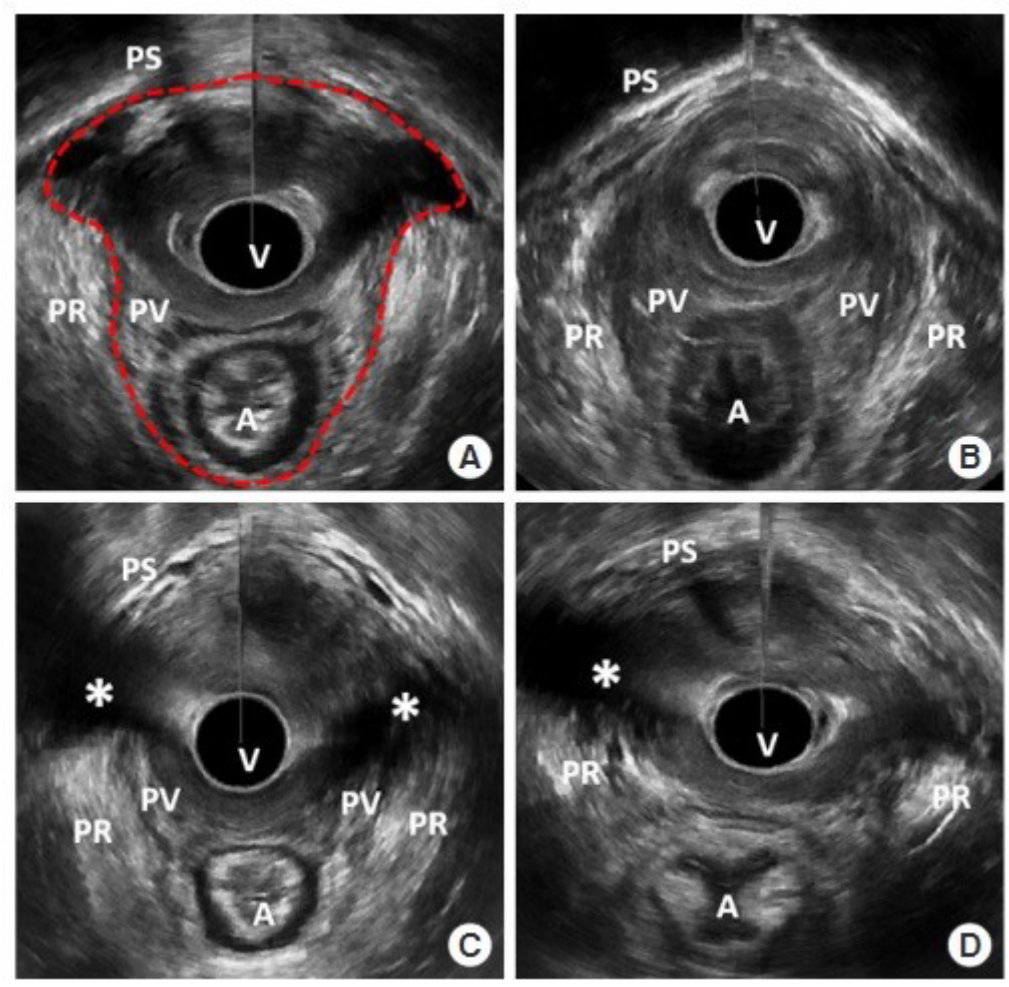


**Fig. 1.** 3D-pelvic floor ultrasonography. (A) Minimal levator hiatus (MLH), (B) mild levator ani deficiency (LAD) score, (C) severe LAD score, (D) levator ani muscle avulsion. Red dot-ted line, MLH area; asterisk, avulsion site. A, anus; PR, puborectalis muscle; PS, pubic symphysis; PV, pubovisceralis muscle; V, vaginal [31]. Adapted from Jeong et al. [31] with CC-BY-NC.


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milliseconds.

Electromyography employs a concentric needle electrode to record the electrical activity produced by the anal sphincter muscle fibers. Encircling the anal canal, continuous recordings of the motor units are taken. This test is used to map the external sphincter and neuromuscular function.

## Treatment

FI treatment can be categorized into non-surgical and surgical approaches. We stated non-medical treatment methods that excluded drug treatment.

**1. Biofeedback therapy**

BFT involves the use of electronic devices to monitor physiologic activities, followed by the transmission of a visual or auditory signal to the patient (Fig. 2). It makes patients sensitive to rectal distension and reinforces correct sphincter contraction. Anorectal manometry or electromyography are utilized to perform the BFT. BFT consists of rectal sensitivity training, pelvic floor muscle strength training, and coordination training involving the insertion of an air or water-filled balloon into the rectum of patients. Patients feel the distension of the balloon and are instructed to squeeze their pelvic floor muscles to determine the sensation of rectal filling and prevent leakage [34].

In 2012, a Cochran review of 21 studies involving a total of 1,525 patients did not find evidence that pelvic floor muscle exercise and BFT were superior to other treatments. However, it was discovered that BFT was more effective than pelvic floor muscle exercises alone, such as Kegel, for patients whose conservative treatments had failed [35]. In a recent randomized controlled trial, patients with FI responded similarly to oral placebo plus education only, oral placebo plus anorectal manometry-assisted biofeedback, loperamide plus education only, and loperamide plus anorectal manometry-assisted biofeedback [36]. BFT is a noninvasive, first-line treatment option for highly motivated patients whose medical treatments have failed [37].

**Fig. 2.** Biofeedback therapy. An electrical device capable of monitoring the physiological activity of the anus is attached to the patient. The patient looks at the monitor and practices contraction and relaxation of the anus.


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### 2. Neuromodulation

SNS is a treatment for patients whose conservative treatment has failed. SNS has been used as a treatment for FI for twenty years, and it is believed to improve FI. It stimulates sacral nerves and associated muscles by applying a low-voltage electrical current through the sacral foramen via an implanted electrode. The surgical placement of a tined lead with electrodes through the S3 sacral foramen is required. The lead is attached to the pulse generator's battery and placed beneath the lumbar region of the patient's skin (Fig. 3). Thus, SNS is commonly referred to as a minimally invasive treatment for FI [38]. Recently, SNS devices that are rechargeable and MRI-safe have emerged. The estimated battery lifespan of rechargeable devices was 15 years, whereas the estimated battery lifespan of charge-free devices was 5 to 7 years. In addition, these new devices offer advantages to patients who require an MRI [39]. The benefit of SNS is that there is no incision around the anus. This prevents scarring and infection near the anus. Numerous studies have been conducted on SNS.

The benefit of SNS is that there is no incision around the anus. This prevents scarring and infection near the anus. According to some reports, SNS is effective at enhancing FI. In multiple cross-over studies, the incidence of FI was reduced relative to medical therapy [40].

Percutaneous stimulation of the tibial nerve is an additional nerve modulation treatment for FI. The tibial nerve and sacral nerve share nerve fibers. According to some studies, percutaneous tibial nerve stimulation yielded comparable results to SNS [41].

### 3. Anal implant

Anal plugs are used to prevent stool leakage by occluding the anus. The high failure rate of anal plugs limits their use as a treatment. However, it is believed to be beneficial for immobile patients or those residing in nursing homes with diminished anal-rectal sensation. The Renew Insert anal plug is designed for self-insertion and natural expulsion with defecation (Fig. 4). Among 91 patients treated with the Renew insert, 73 (80%) completed all 12 weeks of treatment ("completers"), while 85 (93%) completed at least 1 week of treatment (modified intention-to-treat cohort). 77% of the 73 participants who completed the study experienced a 50% reduction in incontinence frequency. 51% of patients experienced complications, but 98% of these were minor, including anorectal urgency, irritation, GI discomfort, gas, and hemorrhoids. Additionally, 78% of participants were pleased with the device [42].

A vaginal bowel control system (Eclipse System) was designed to offer women with FI a low-risk, reversible treatment (Fig. 5). The system consisted of a silicone-coated base, an inflatable

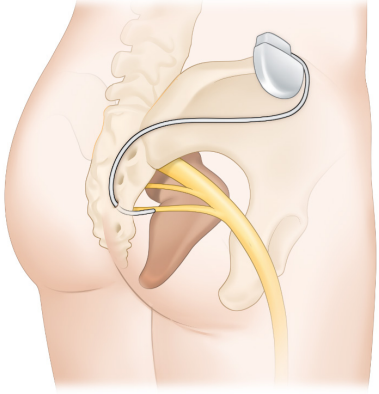

**Fig. 3.** Sacral nerve stimulation. An electrical device is inserted in subcutaneous of patient's lumbar region. This device controls the anus by providing electrical stimulation to the sacral nerve and its associated muscles.


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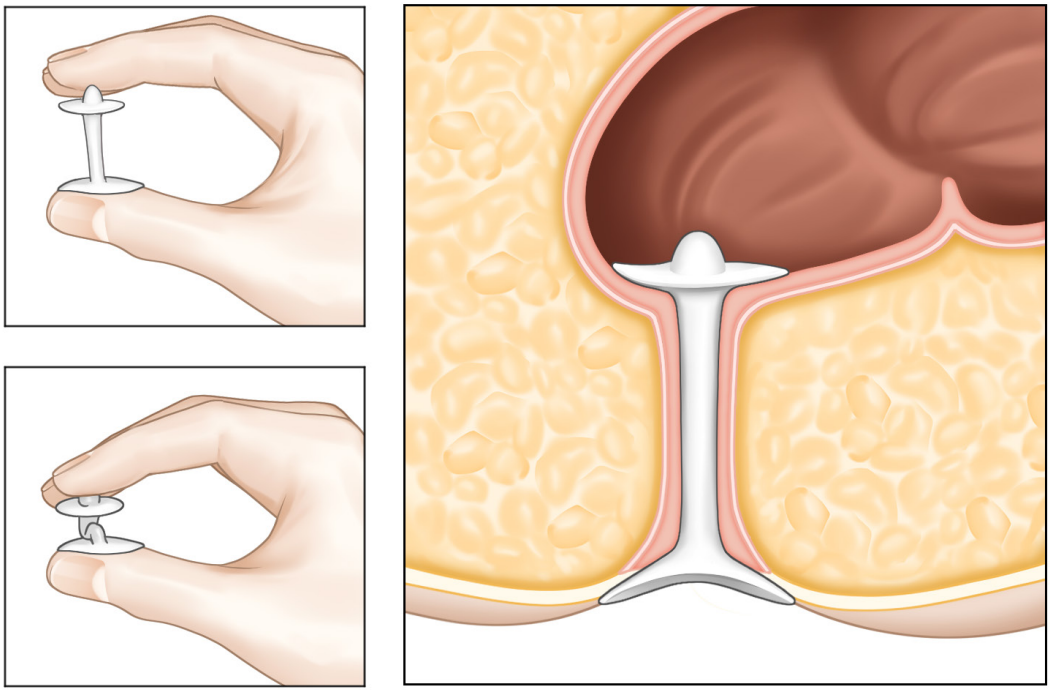

**Fig. 4.** Anal plug. This device is designed for self-insertion and natural expulsion with defecation.

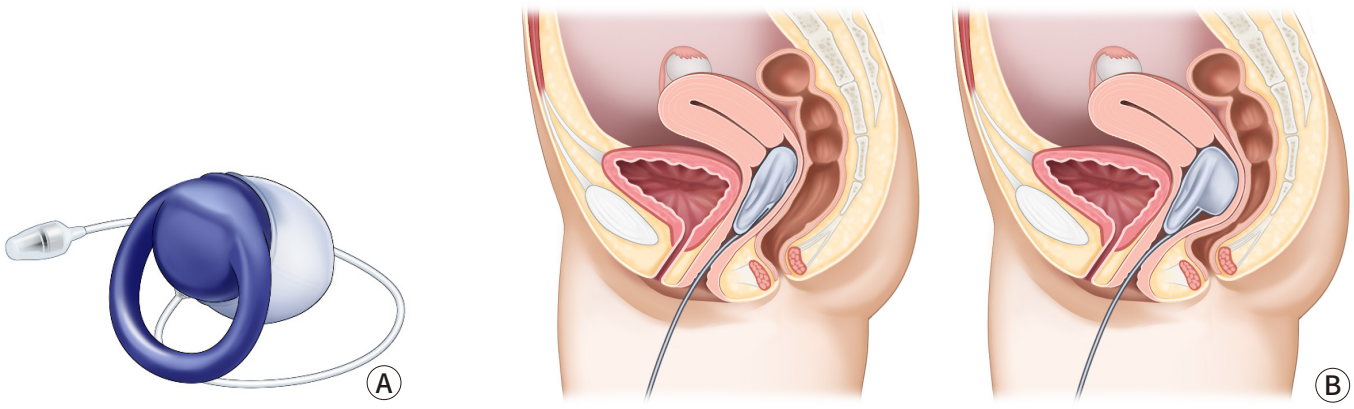


**Fig. 5.** Vaginal bowel control system. (A) Vaginal bowel control system. (B) It is a balloon-shaped structure that is inserted into the vagina. By applying pressure by hand, the balloon inflates and pressure is applied to the rectum to control the stool.

balloon, and a hand-held pressure control pump. This device is inserted vaginally. When the balloon is inflated, the vaginal wall is compressed to prevent stool leakage.

Perianal injectables increase the resting anal sphincter tone by acting as a bulking agent. Its primary use is for the treatment of minor FI caused by dysfunction of the internal anal sphincter. Bulking materials injected into the submucosa or inter-sphincteric space increase tissue volume in the high-pressure zone, resulting in a tighter anus at rest, and can target defective areas of the internal anal sphincter to create anal canal continuity, if present [34]. The most research has been conducted on non-animal stabilized hyaluronic acid/dextranomer for the treatment of FI resistant to conservative therapy. The procedures were performed while the patient was in the

lithotomy, left-lateral, or prone position. Typically, 1 mL of agent is injected through an endoscope into the deep submucosa at four sites (typically 3, 6, 9, and 12 o'clock). Active inflammatory bowel disease, previous anorectal radiation, full-thickness rectal prolapse, and anorectal malformations are contraindications. Post-injection complications consisted primarily of transient bleeding, pain, and discomfort that resolved on their own [43]. Due to concerns regarding the bulking agent's absorption and migration, additional long-term data are still required [34].

### 4. SECCA procedure

In 1999, the SECCA® procedure, which involves the application of temperature-controlled radiofrequency energy to the anal canal, was first used in Mexico to treat FI.

As a result of the thermal energy delivered, there is an immediate contraction of collagen fibers, which is followed by permanent shortening via remodeling, resulting in a tightening of the anal sphincter muscle. In the SECCA® procedure, radiofrequency is delivered to the anal sphincter while monitoring temperature and tissue impedance and cooling the probes at the surface to prevent mucosal damage. If the tissue temperature rises above 85°C at the electrode tip or 42°C at the anoderm surface, the current is automatically cut off (Fig. 6).

Patients who failed conventional treatments such food modification, medication, and biofeedback and do not have a clearly visible sphincter dysfunction would be indication for SECCA® procedure. Typically, the Secca® operation is carried out as an outpatient while being sedated intravenously and given local anesthesia. T The patient is in the prone jackknife or lithotomy posture. Electrodes are positioned at the level of the dentate line and the device is introduced into the anal canal. The radiofrequency is then transmitted to one quadrant for 90 seconds. The procedure is then repeated for each of the four quadrants at a depth of 5 mm. At the site of insertion, complications include bleeding and ulceration. Occasionally, stitches or surgical therapy may be necessary [44].

### 5. Artificial sphincter

Typically, the synthetic sphincter was utilized to treat urine incontinence. The instrument has been adapted for use around the anus (Fig. 7). To attach an artificial anus to the patient's body, a transverse perineal incision is typically made to create a subcutaneous tunnel around the anus. The prosthetic sphincter cuff is positioned around the anus. The pump is inserted via a pfannensteil incision that extends to the labia or scrotum. The reservoir is located in the Retzius space. The gadget provides continence by maintaining a full cuff in a resting condition. When a patient needs to defecate, fluid is pumped from the cuff to the reservoir. And the cuff will passively

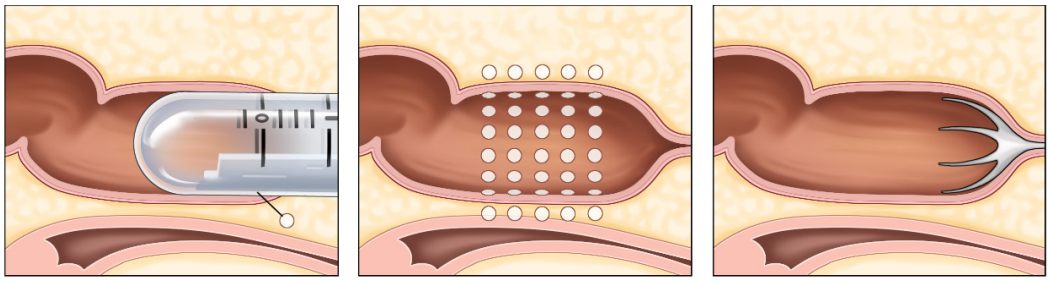

**Fig. 6.** SECCA procedure. A device that uses temperature-controlled radiofrequency energy is inserted into the anus of the patient. This device stimulates the patient's anus, causing the anal sphincter to tighten.


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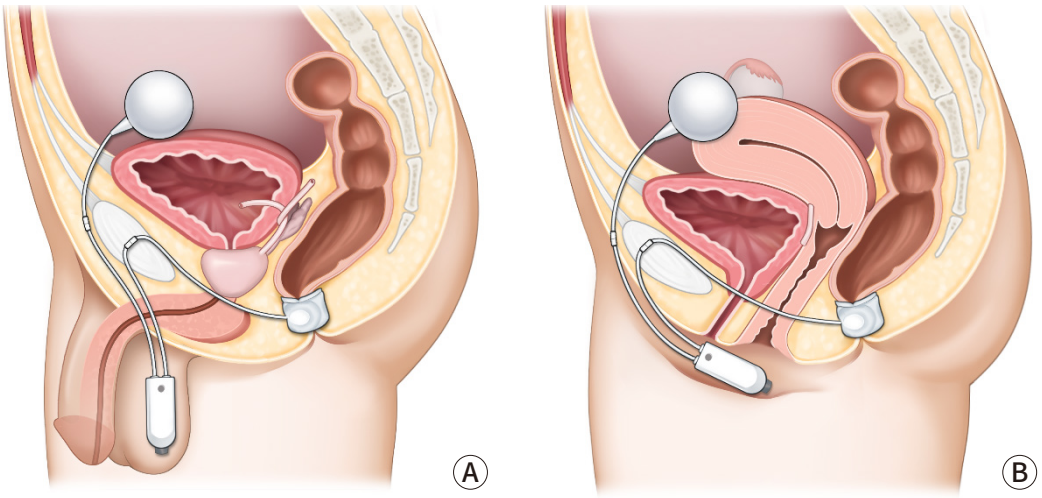


**Fig. 7.** Artificial sphincter. A cuff-shaped structure is wrapped around the anus and inserted (A) male, (B) female. Continence is maintained normally. Patient needs to press the pump located in the testicles or perineum for defecation. Then, cuff is closed naturally after defecation.

refill. This procedure must require a sufficient quantity of perineal soft tissue. Because the device is not covered by thin soft tissue, erosion can occur. It is also necessary to instruct patients to activate the device independently. Magnetic anal sphincter is a new artificial anal sphincter option. A single perineal incision is used in the procedure. The perineal body was dissected to a depth of 5 cm. The left and right fossa ischiorectalis were then tunneled, with the tip of the coccyx as a landmark. After the tunneling was completed, the sizing tool was used to determine the proper sized device. Fluoroscopy was used to confirm the correct placement and contact of the beads. For the treatment of severe FI patients, magnetic anal sphincter has shown consistent results [45].

Postoperative complications were discovered in a multicenter study [46]. There were 384 device-related complications in 99 of the 112 patients who received artificial sphincter treatment. 246 events did not necessitate intervention. However, 73 revisional operations were performed on 51 (46%) of the patients. 28 (25%) patients developed infections that necessitated surgical revision, and 41 (37%) patients had their devices completely removed.

### 6. Stem cell therapy

In 2008, stem cell therapies were validated. In clinical and experimental contexts involving hematological, cardiovascular, neurological, digestive, traumatic, endocrine, renal, and metabolic disorders, stem cell therapy has been shown to be safe and to have encouraging effects. Hematopoietic stem cells, mesenchymal stem cells, and adipose-derived stem cells are utilized most frequently. It has also been demonstrated that stem cell therapy promotes the healing of acute and subacute anal sphincter injuries. On bioengineered scaffolds, the formation of an innervated anal sphincter was accomplished by combining stem cells with normal cells. According to some reports, stem cell therapy is a successful treatment for FI; nevertheless, additional research in both animal models and clinical settings is required to determine its efficacy. Nonetheless, stem cell therapy is one of the potential treatments for FI [47].

### 7. Surgical option

Surgical therapy is also beneficial for treating FI symptoms. Because surgery is an intrusive

treatment, many practitioners should evaluate the co-morbidities, socioeconomic circumstances, and activity levels of their patients [48].

Sphincteroplasty aims to restore sphincter architecture and function. Although anal sphincteroplasty gives temporary symptom relief, it rarely results in permanent continence recovery. Surgical consequences consist of wound dehiscence, nerve injury, and infection, and older patients have poorer outcomes. The most severe side effect of sphincteroplasty is rectovaginal fistula. For the treatment of obstetric FI, sphincteroplasty has favorable short- to medium-term outcomes in terms of continence and quality of life [7,49].

The transposition of the gracilics muscle is an another method that can be used during surgery (Fig. 8). Patients who did not respond to conventional medical treatment for FI may be candidates for this technique. However, there is a considerable risk of problems occurring over the course of this surgery. Sexual dysfunction and soreness in the area of the operation site are also common negative outcomes associated with this procedure [1].

Transposition of the antropyloric valve has recently emerged as a therapy for FI. Beginning the process with a midline laparotomy incision. The colonic hepatic flexure was mobilized, and the duodenum was kocherized. The gastro epiploic branches and larger stomach branch curvature were ligated. The left gastroepiploic pedicle was then utilized to mobilize the antropyloric valve. The pelvic dissection was followed by rectum mobilization and incision. The portion of the antropyloric valve was sutured to the proximal rectal end. Invagination of the graft into the distal rectum. The end of the duodenum was sutured using perianal skin. Transposition of the antropyloric valve perineally is a unique procedure for individuals with significantly compromised anorectal function. Complications of gastrojejunostomy, such as dumping syndrome and alkaline reflux syndrome, were common with this treatment [50]. In patients who did not respond to the aforementioned treatment and had a severely diminished quality of life, the creation of an ostomy would be considered.

## Conclusion

With the advent of medicine, patients' lifespans have been lengthened. Consequently,

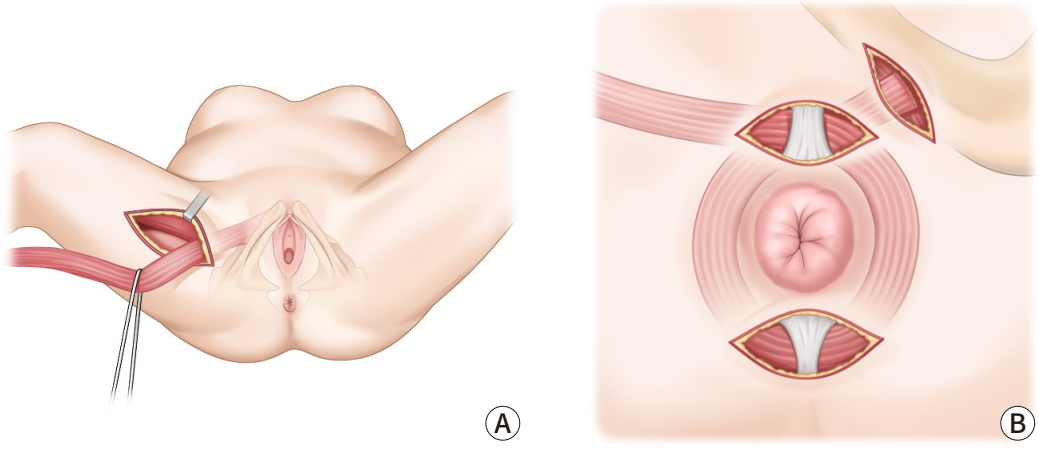


**Fig. 8.** Transposition of gracilis muscle. (A) This procedure is mobilization of the gracilis muscle, (B) transposition of the muscle around the anus and fixation to the contralateral ischial tuberosity.


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**Table 3.** Recommendations from professional society guideline of surgical treatment for fecal incontinence (FI)

| Treatment | American college of Gastroenterology (ACG) | American Society of Colon and Rectal Surgeons (ASCRS) |
|---|---|---|
| Anal sphincter repair | Do not respond to conservative therapy, have anatomic sphincter defect | Have defect of external anal sphincter |
| Redo anal sphincter repair | Not addressed | After failed overlapping sphincteroplasty should be avoided unless other treatments are not possible |
| Anatomic defect correction (prolapse, fistula, etc.) | Not addressed | Fistula, hemorrhoid, fistula or cloaca should be corrected for treatment of fecal incontinence. |
| Other surgeries | Dynamic graciloplasty may allow patient with FI to avoid colostomy | Insufficient to support the use of the magnetic sphincter |
| Colostomy | Last resort procedure | Have failed to other therapies |

numerous studies on diseases with a high prevalence among the elderly have been done. Incontinence of feces is a prevalent condition in the older population. Patients' quality of life is negatively impacted by this disease, thus it is evidently a disease that requires control. It has not been demonstrated which treatment option for FI is the most effective (Table 3). Nevertheless, the majority of therapy techniques often progress from medicinal treatment to a more intrusive strategy. In addition, when applied clinically to a patient, multiple treatments are administered concurrently, as opposed to a single treatment. Examples include SNS, stem cell therapy, and BFT. It indicates that there is no recognized way for treating FI, but that these various treatment strategies have a small impact on the improvement of patients' symptoms. It is believed that research on a definitive therapy for FI will be required in the foreseeable future. This is important in order to be prepared for an increase in the number of patients.

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### ORCID iD

Chungyeop Lee: https://orcid.org/0000-0003-4119-4035
Jong Lyul Lee: https://orcid.org/0000-0002-5878-8000

### Author Contribution

Conceptualization: Lee C, Lee JL
Formal Analysis: Lee C
Investigation: Lee C, Lee JL
Methodology: Lee C
Project Administration: Lee C, Lee JL
Writing – Original Draft: Lee C
Writing – Review & Editing: Lee C, Lee JL

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Not applicable.

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Review Article

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# Robot-Assisted Colorectal Surgery

**Young Il Kim**

Division of Colon and Rectal Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

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**Corresponding author**
Young Il Kim
Division of Colon and Rectal Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul 05505, Korea
Tel: 82-2-3010-1206
E-mail: illie@amc.seoul.kr

**Key Words**
Robot surgical procedures; Colonic neoplasms; Rectal neoplasms; Colorectal disease

Minimally invasive surgery for colorectal disease has now become the standard treatment in Republic of Korea. However, there are limitations to the laparoscopic approach, such as an unstable camera support, a limited range of motion, and poor ergonomics. Recent advances in technology have led to the introduction of robotic surgical systems in colorectal surgery to overcome these shortcomings. Robot-assisted colorectal surgery has clear advantages in many aspects. Surgery involving the rectum benefits the most among colorectal diseases owing to technical difficulties in rectum dissection. The concept of robotic surgery is not different from laparoscopic surgery in that it is a minimally invasive surgery, and abundant research demonstrates comparable results from both modalities for postoperative complications, oncological outcomes, and functional outcomes. However, the cost of robot-assisted surgery limits surgeons to performing robotic surgeries in only selected cases. Improvements regarding cost-effectiveness and more convincing studies that support benefits of robotic surgery are needed to popularize robot-assisted colorectal surgery.

## Introduction

Since the introduction of laparoscopic colorectal surgery in the early 1990s, minimally invasive surgery (MIS) for colorectal disease has now become the standard treatment in Republic of Korea (Korea). While the MIS approach was applied for less than 50% of colorectal cancer patients in 2008, it increased to nearly 80% in 2018 [1]. Important randomized controlled trials (RCTs) have presented evidence that laparoscopic surgery is feasible oncologically and technically [2–4]. MIS provides a faster recovery, less postoperative pain, and a reduced risk of surgical site infection compared to open surgery with comparable survival outcomes [5–7]. However, there are limitations to the laparoscopic approach, such as an unstable camera support, a limited range of motion owing to the rigid straight surgical equipment, and poor ergonomics. Constant efforts are ongoing to overcome these problems, and recent advances in technology have led to the introduction of robotic surgical systems in colorectal surgery.

The concept of modern robots first appeared in 1921 where the word "robot" was used in the play R.U.R.: Rossum's Universal Robots by a Czech novelist Karel Capek. Robot means forced labor in the Czech language [8]. This nomenclature seems well defined in that one of the key advantages of robotic surgery is to aid surgeons during physically demanding procedures. Robotic assistance provides an immersive 3-dimensional view that the operator can control without any additional human assistance, while manipulating articulated surgical instruments for a much more versatile movement. The first robot-assisted surgery performed for colorectal disease was in 2001 with the

Da Vinci telerobotic surgical system. The feasibility of robotic colorectal surgery has been validated by many studies since then and it is now practiced worldwide for various colorectal diseases; malignancies, benign lesions and inflammatory bowel diseases (IBD). This article reviews the clinical impacts of applying robotic surgical systems to treating colorectal diseases.

## Current Evidence for Robotic Surgery in Colorectal Diseases

Specific features of robot-assisted surgery led to variations in the extent of application of the robotic system according to the target organ. Even though the colon and rectum are both a continuation of the large bowel, each organ has a distinct anatomy and thus benefits from robot-assisted surgery differently. Also, the diverse spectrum of colorectal diseases (malignant, benign, IBD, etc.) presents dissimilar practices and indications for adapting robotic surgery.

### 1. Rectal cancer

The most widely appreciated site for the application of robotic systems is the rectum. This is due to the anatomical characteristics of the rectum. The rectum is located in a confined compartment constituted by the sacral promontory posteriorly, genitourinary organs anteriorly, and pelvic floor muscles laterally. The bony structure of the pelvis forms a narrow canal, and this feature is particularly prominent in male patients. Operating in such environment is challenging and surgeons often experience limitations of their rigid laparoscopic instruments. Manipulating the rectum in such a narrow pelvis for traction, especially with a bulky tumor, is time consuming and causes surgeons to become exhausted. There are several studies that demonstrated a longer operation time, a worse quality of total mesorectal excision, and a higher rate of postoperative morbidities in patients with a narrow pelvis or a bulky tumor when operated on laparoscopically [9–12].

Robot-assisted surgery provides a comfortable environment for surgeons. The fully wristed robot instruments and stable 3-dimensional camera vision that can be controlled by the operator enables a much more versatile movement in narrow spaces [13]. The difficulty of the pelvic anatomy does not result in an overtly prolonged operation time, and Baek et al. reported a shorter operation time even in patients with a narrow pelvis when using a robotic system [14]. This advantage of robotic surgery for rectal cancer also leads to better preservation of urinary and sexual functions. Identifying pelvic autonomic nerves and not damaging the nerves is extremely important during total mesorectal excision for rectal cancer [15]. The nerves are at risk of transection or thermal injury during the ligation of the inferior mesenteric artery, dissection of the mesorectum at the level of the sacral promontory, and dissection of the antero-lateral planes of the rectoprostatic/rectovaginal (Denonvilliers') fascia. Although a laparoscopic camera provides a more magnified vision compared to open surgery, the robotic system is equipped with an immersive 3-dimensional camera, which allows for identification and direct observation of these important structures in greater detail. Previous studies have shown higher rates of preserved physiological functions after robot-assisted rectal surgery compared to laparoscopic surgery [16].

All of these benefits of robotic systems would not be acceptable without oncological safety. A series of RCTs from various centers worldwide, along with numerous retrospective studies over the past 20 years of clinical practice, have presented unified results of comparable survival outcomes of robot-assisted rectal cancer surgery with laparoscopic surgery (Table 1) [17–21]. Confidence from accumulated experience has led to the adaption of robotic surgery to even more complicated and advanced cases of rectal cancer [22–26].


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**Table 1.** Studies validating robot-assisted surgery for rectal cancer

| Study [Ref.] | Design | Diagnosis | Operation | Study arms | Sample size | Conclusion |
|---|---|---|---|---|---|---|
| Baik et al., 2009 [17] | Prospective | Rectal cancer | Low anterior resection | Robot | 56 | Lower conversion rate and serious complication rate in robot group. |
| | | | | Laparoscope | 57 | |
| Patriti et al., 2009 [18] | Case-matched | Rectal cancer | All rectal resection (LAR, ISR, APR) | Robot | 29 | Lower conversion rate in robot group, comparable OS and DFS. |
| | | | | Laparoscope | 37 | |
| Jayne et al., 2017 [19] | RCT | Rectal cancer | All rectal resection (AR, LAR, APR) | Robot | 236 | Comparable conversion rate, CRM, and sexual/urinary functions. |
| | | | | Laparoscope | 230 | |
| Kim et al., 2018 [20] | RCT | Rectal cancer | All rectal resection (LAR, APR, Hartmann) | Robot | 66 | Comparable TME quality, postoperative morbidity, bowel function recovery, QoL. |
| | | | | Laparoscope | 73 | |
| Kim et al., 2017 [21] | Retrospective, PPM | Rectal cancer | All rectal resection (AR, LAR, ISR, APR) | Robot | 224 | Favorable 5-year OS, CSS, DFS in the robot group. |
| | | | | Laparoscope | 224 | |

LAR, low anterior resection; ISR, intersphincteric resection; APR, abdominoperineal resection; OS, overall survival; DFS, disease-free survival; RCT, randomized controlled trial; AR, anterior resection; CRM, circumferential resection margin; TME, total mesorectal excision; QoL, quality of life; PPM, propensity score matching; CSS, cancer-specific survival.

### 2. Colon cancer

Surgery for colon cancer is not fundamentally different from rectal cancer in that the principle concept is to excise the mesocolon along with the draining vessels and lymphatics from the primary tumor, defined as complete mesocolic excision. This surgical objective is equivalent to TME for rectal cancer and is known to be essential for an optimal survival outcome [27,28]. However, the anatomical distinction between the colon and rectum makes surgery on the colon less challenging; nevertheless, it requires additional caution during dissection. The colon is not confined within a limited compartment, and the surgical field is much broader and more open. Basically, the whole intraperitoneal space can be used to manipulate the instruments. Therefore, the advantages of robotic surgery may not be as prominent during colon resection.

This is supported by a RCT from Park et al., which compared robotic-assisted colectomy with traditional laparoscopic-assisted colectomy in right-sided colon cancer [29]. The length of hospital-stay, postoperative morbidity, and the number of harvested lymph nodes were comparable between the two groups, but the operation time was significantly longer in the robot-assisted colectomy group (195 min versus 130 min, $P<0.001$). The overall medical cost was also significantly higher in the robot-assisted surgery group and there were no benefits in the long-term survival outcomes [30]. Choi et al. concluded that there were no clinical benefits of robot surgery in right-sided colon cancer that outweighs the high costs [1]. However, to date, there are not enough studies with a large sample size and statistical power to strongly contraindicate robot-assisted colectomy.

Recent technological advances in robotic systems have led to the development of single-platform robot systems since 2018 (da Vinci SP) (Fig. 1). The operator can perform reduced port surgeries more comfortably with fully wristed robotic instruments through a single-port compared to the conventional single-incision laparoscopic surgery. Single-incision laparoscopic surgery is known to be beneficial in terms of cosmetic aspects but it is usually only used for

**Fig. 1.** Da Vinci robot surgical systems, (A) X system, (B) Xi system, and (C) SP system. Constant improvement of the technology has expanded the use of robot-assisted surgery in colorectal diseases.

highly selected patients due to technical difficulties [31]. The utility of a robotic system for single-port surgery may become a safer and more practical approach for surgeons to perform colon cancer resection [32–34].

### 3. Ventral rectopexy

The perineal or a transabdominal approach are both available treatment modalities for pelvic organ prolapses. In particular, abdominal ventral mesh rectopexy is an effective approach for treating rectal prolapse and MIS has shown benefits of a low complication rate and recurrence rate, with improved symptoms of fecal incontinence and obstructed defecation syndrome [35–37]. The key procedures of ventral mesh rectopexy are similar to rectum resection in that the dissection of the rectum down to the rectovaginal or rectoprostatic septum is essential. Therefore, patients indicated for ventral mesh rectopexy can also benefit from robot-assisted surgery, similar to patients with rectal cancer. Theoretically, suturing the mesh to the anterior wall of the lower rectum can be performed readily with the fully wristed robotic instruments.

A RCT comparing robot-assisted ventral mesh rectopexy (RVMR) to laparoscopic ventral mesh rectopexy demonstrated no difference in operation time or postoperative complications. The RVMR group showed a trend of less residual rectocele postoperatively in terms of amount and size [38]. However, there are mixed results regarding the operation time in retrospective studies and RVMR should be applied to selected patients depending on the cost-effectiveness and surgeon compatibility [39,40].

### 4. Inflammatory bowel disease

Extensive studies still need to be conducted to prove the feasibility of robotic surgery in IBD patients. A retrospective study analyzed the perioperative outcomes of 108 patients with Crohn's disease who received robotic-assisted ileocolic resection and compared the results to open cases. The robot-assisted cases had a significantly shorter hospital stay by 2 days ($P<0.0001$) with a lower 30-day complication rate (24% versus 38%, $P=0.039$), but they required a mean of 60 min additional operation time ($P<0.0001$) [41].

Two case-matched comparison studies of robotic versus laparoscopic proctectomy for IBD patients presented similar complication rates, short-term functional results, conversion rate, and length of stay for both groups, but the robotic group had a longer operative time [42,43]. Robot-

assisted surgery can have advantages in pelvic nerve preservation during proctectomy, but further research is warranted as surgeons adapt to robotic surgery for IBDs [44].

## Cost-Effectiveness of Robot-Assisted Surgery

The biggest obstacle to the nationwide adaption of robot-assisted colorectal surgery in Korea is the cost benefit ratio. Since the first approval of robot-assisted surgery in the year 2005 by the Ministry of Food and Drug Safety of Korea, robot surgery has been classified as non-reimbursable. All citizens of Korea are obligated to obtain national health insurance and essential medical services are generally covered by this national health insurance system. While robot-assisted surgery has been praised for its minimally invasive approach and shortened hospital stay, its cost-effectiveness has been considered unclear for coverage by the national health insurance system. This results in a roughly 2- to 4-fold higher operative cost for patients receiving robot-assisted surgery compared to laparoscopic surgery in Korea [45,46]. The national insurance policy differs in each country but robotic surgery is universally accepted to be more expensive compared to laparoscopic surgery (Table 2) [19,30,45–48]. This is the core issue why robot-assisted surgery, while presenting comparable postoperative outcomes and survival outcomes to laparoscopic surgery, still cannot be the standard treatment for colorectal diseases.

## Conclusion

Robot-assisted colorectal surgery has clear advantages in many aspects. Surgery involving the rectum benefits the most among colorectal diseases owing to technical difficulties in rectum dissection. The fundamental concept of robotic surgery is not that different from laparoscopic surgery in that it is a minimally invasive approach, and abundant research demonstrates comparable results from both modalities for postoperative complications, oncological outcomes, and functional outcomes.

However, the cost of robot-assisted surgery limits surgeons to performing robotic surgeries in only selected cases. Currently, few patients meet the indications to justify the high costs of

**Table 2.** Studies analyzing cost of robot-assisted surgery for colorectal disease

| Study (Ref.) | Design | Diagnosis | Operation | Study arms | Costs | P-value |
|---|---|---|---|---|---|---|
| Baek et al., 2012 [45] | Retrospective | Rectal cancer | All rectal rection (AR, LAR, ISR, APR, TPC) | Robot | $14,647 | 0.001 |
| | | | | Laparoscope | $9,978 | |
| Park et al., 2015 [46] | Prospective | Rectal cancer | LAR | Robot | $12,742 | <0.001 |
| | | | | Laparoscope | $10,101 | |
| Jayne et al., 2017 [19] | RCT | Rectal cancer | All rectal resection (AR, LAR, APR) | Robot | $13,668 | 0.02 |
| | | | | Laparoscope | $12 556 | |
| Morelli et al., 2016 [48] | Retrospective | Rectal cancer | All rectal resection (AR, LAR, ISR, APR) | Robot | Euro 12,283 | <0.001 |
| | | | | Laparoscope | Euro 7,619 | |
| Park et al., 2019 [30] | RCT | Colon cancer | Right colectomy | Robot | $12,235 | 0.013 |
| | | | | Laparoscope | $10,320 | |

AR, anterior resection; LAR, low anterior resection; ISR, intersphincteric resection; APR, abdominoperineal resection; TPC, total proctocolectomy; RCT, randomized controlled trial.


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robot-assisted surgery. Further advances in robotic surgical systems may improve the cost-effectiveness of robotic surgery and influence national insurance policies to provide a more comprehensive indication criterion for applying robot-assisted surgery in colorectal diseases.

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### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### ORCID iD

Young Il Kim : https://orcid.org/0000-0002-0212-9196

### Author Contribution

The article is prepared by a single author.

### Ethics Approval and Consent to Participate

Not applicable.

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Review Article

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# Treatment of Hemorrhoid in Unusual Condition-Pregnancy

**Hyo Seon Ryu**

Division of Colon and Rectal Surgery, Department of Surgery, Korea University College of Medicine, Seoul, Korea

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**Corresponding author**
Hyo Seon Ryu
Division of Colon and Rectal Surgery, Department of Surgery, Korea University College of Medicine, 73, Goryeodae-ro, Sungbuk-gu, Seoul 02841, Korea
Tel: 82-2-920-5978
Fax: 82-2-928-1631
E-mail: hsryu@kumc.or.kr

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Hemorrhoids are varicose veins of the rectum that are located in or near the anal canal and are covered by mucosa. They can occur at any age, are generally symptomless, and affect both sexes equally. Hemorrhoids are a common complaint among younger women and are more likely to occur during pregnancy and the menstrual cycle. In this article, we discuss the many approaches in the treatment of hemorrhoids. Laxatives, stool softeners, and fiber supplements are all considered safe for use by pregnant women. Moderate use of laxatives is also acceptable. Since there is a lack of sufficient evidence to support the safety and efficiency of topical medicines or oral phlebotomies during pregnancy, these treatments must to be utilized with an increased degree of extreme caution. In the case that considerable bleeding occurs, anal packing may be a straight forward and helpful operation to implement. A hemorhoidectomy is the treatment option for hemorrhoids that have become strangulated, badly thrombosed, or have bleeding that cannot be controlled.

## Introduction

One of the most common disorders that can affect the anorectum is hemorrhoidal disease. Anal bleeding, the sense of a prolapsing lesion, anal pain, anal irritation, and anal soiling are not symptoms that are unique to hemorrhoidal disease; however, these symptoms can occasionally be helpful in distinguishing hemorrhoidal disease from other disorders [1,2]. In actual clinical practice, classification of hemorrhoids was done based on the extent of internal hemorrhoidal tissue prolapse, and treatment was outlined in accordance with classical classification [3]. According to some findings, classification systems that take into account many symptoms at once are more practical [4,5]. The treatment for hemorrhoid was determined according to the severity of the symptoms, which might range from conservative management to intervention or surgical treatment [6–9]. Nevertheless, the therapy of hemorrhoidal disease in unusual conditions is considerably more challenging.

## Incidence or Pathogenesis of Hemorrhoidal Disaease in Pregnancy

Hemorrhoidal disease is often symptomatic and bothersome for pregnant women. It affects 25–35 percent of pregnant women [10], primarily presents in the third trimester, and can be

internal or external. There is a rise in blood volume (between 40% and 50% of the volume before pregnancy). During pregnancy, there is an increase in cardiac output and utero-placental blood flow, as well as an increase in the inflow and intravenous pressure in the pelvic veins [11,12]. T These mechanisms result in increased blood flow in collateral circulation veins (vulvar, rectal, and lumbar), which increases the likelihood of developing hemorrhoids. The pelvic veins are compressed during pregnancy due to the enlarged uterus [13]. In the first trimester of pregnancy, an increase in venous pressure mixed with hormonal changes causes venous relaxation. Several mediators were associated with these alterations. Estrogens are responsible for mesenchymal release, but progesterone has a myolytic action across the body. These effects on the vein system result in a tissue vascular dislocation (estrogen) and a decrease in venous tone (progesterone) [13,14].

As a result of altered venous drainage through the hemorrhoid plexus, some circumstances (such as constipation and prolonged exertion) may contribute to the development of hemorrhoids by increasing intra-abdominal pressure [15]. Some dietary and lifestyle factors, including as a diet low in fiber, spicy foods, and alcohol consumption, may contribute to the development of hemorrhoids and the exacerbation of symptoms [16].

The most common manifestation of hemorrhoidal pathology is painless rectal bleeding during feces, with or without anal tissue protrusion. Anal pain may be experienced by patients with complex hemorrhoids, such as external hemorrhoids with thrombosis or internal imprisoned hemorrhoids. On clinical examination, a nodule at the level of the anal margin may be identified. It is uncommon for patients with simple hemorrhoids to experience anal pain. Anal pain with hemorrhoids is more likely to be caused by an anal fissure or an anal abscess [17].

## Conservative Treatment

The purpose of hemorrhoid treatment in pregnant women is to control the symptoms, which typically disappear on their own during the postpartum period, and to protect the perineal region, which is susceptible to stress during vaginal delivery. Except in cases of acute thrombosis, a conservative approach is always suggested. If possible, surgical procedures should be delayed until a few weeks after delivery. It would be advantageous to avoid potential complications associated with hemorrhoidectomy [18,19].

The consumption of fiber and fluids positively affects costipation, which is one of the elements that contribute to the development of uterine fibroids during pregnancy. Constipation is a risk factor for long-term pelvic organ prolapse when combined with changes in anal sphincter pressure [20,21]. It is important to consume fresh fruits and vegetables on a regular basis [22]. In a study of 40 pregnant women in their third trimester, those who consumed 10 grams of fiber in the form of biscuits or wheat bran had significantly greater digestive motility than the control group [23].

Moderate physical activity increases intestinal motility and promotes anorectal coordination, and should be included among the prenatal hygiene interventions.The usage of Psyllium in the treatment of constipation has been linked to enhanced intestinal transit and intestinal motility, as well as the generation of soft, highly-lubricated stool [24].

Osmotic laxatives contain ions or molecules that are not reabsorbable and that hold water in the intestinal lumen. Polyethylene glycol and lactulose are the most widely utilized. According to the meta-analysis, polyethylene glycol is more efficient than lactulose in terms of stool frequency and consistency, with fewer adverse effects; osmotic laxatives should be considered

the first choice [25]. In addition, the favorable safety and tolerability profile enables their use in unique circumstances, such as pregnancy. The safety of stimulant laxatives during pregnancy is not currently recommended because there are insufficient evidences of their safety profiles. Sitz-baths diminish the tone of the internal sphincter, alleviate venous congestion, edema, and inflammation, and provide excellent symptomatic control for inflamed hemorrhoids [26]. A study of two groups of patients with acute anal pain due to hemorrhagic disease or anal fissure (24 patients in total, 12 for each group) who had used cold water [group 1, 10.8°C (range 5–13)] and hot water [group 2, 38.5°C (range 20–40)] did not reveal any differences in the clinical course of the disease, despite a reduction in painful symptoms with the use of hot water [27]. Because ice has a local anesthetic effect, applying it directly to an injury can make it feel less painful [28]. The analgesic effect of cold was achieved by decreasing cellular metabolism and sensory nerve transmission, which led to sphincter relaxation. Additionally, local vasoconstriction helped diminish edema and swelling of the tissue, which contributed to the analgesic effect of cold.

## Medical Treatment

The goal of the medical treatment for hemorrhoids that occur during pregnancy is to alleviate the symptoms, however the therapeutic options are restricted. Anti-inflammatory medications are frequently taken in order to acquire a rapid regression of the symptoms; nevertheless, the usage of these medications is associated with the risk of developing problems. Corticosteroids and non-steroidal anti-inflammatory medications are the most often used anti-inflammatory drugs, however they cannot be used during or after nursing. There are insufficient scientific studies to demonstrate the safety and efficacy of steroidal anti-inflammatory medicines, whether they are administered orally, topically, or with suppositories [10]. Long-term topical steroid usage is connected with the development of allergic reactions and sensitization. Multiple investigations have indicated that the teratogenic effect of oral corticosteroids is dose-dependent, and four case-control studies have demonstrated an association between corticosteroids use and the development of cleft palate [29].

Inhaled corticosteroids were observed to be connected with a modest increase in the risk of spontaneous abortion during pregnancy. On the other hand, oral corticosteroids were not related to an increase in the risk of congenital abnormalities [30]. Because breastfeeding makes it unsafe to use nonsteroidal anti-inflammatory drugs, it was recommended that pregnant women with thrombotic hemorrhoids and significant edema before and after delivery use corticosteroids at a dose of 40 mg per day for three to five days. Although betamethasone is the most often used corticosteroid in clinical practice, dexamethasone exhibited similar efficacy [31]. However, the prenatal exposure to dexamethasone was observed to increase the chance of neurological changes when compared to betamethasone and placebo [32].

Paracetamol, also known as acetaminophen and N-acetyl-p-aminophenol, can be recommended to alleviate uncomfortable sensations at the typical dose; nevertheless, recent research has indicated its relation with fetal development problems [33]. It is not recommended to use codeine while breastfeeding and is only safe to take during the first and second trimesters of pregnancy for a limited amount of time. Treatment with tramadol is only permitted in the second trimester of pregnancy [34]. The application of topical anesthetics such as benzocaine, dibucaine, and pramoxine after each defecation can alleviate anal itching and discomfort, with possible sensitization following prolonged use [22].

For the treatment of hemorrhagic diseases, phlebotonic drugs are commonly prescribed.

Phlebotonics function as antioxidants, exert a protective effect against pro-inflammatory mediators, and enhance venous tone and lymph drainage. Floavonoid has been shown to be effective in the treatment of hemorrhoids illness in pregnant women, and it has been shown to decrease symptoms such as bleeding, itching, and recurrence of hemorrhoid [35]. Micronized pure flavonoic fraction has demonstrated efficacy in lowering pain and bleeding in patients with acute hemorrhoidal episodes, in addition to tolerability [36]. Rutosides belong to the family of flavonoids, which are plant-derived natural compounds. These are recommended drugs for treating chronic venous insufficiency. Although their mechanism of action is not well understood, the phlebotonic effect (the action of boosting venous tone) may be associated with an increase in lymphatic drainage (drawing of linfatic fluids), an improvement in venous tone, and a decrease in capillary hyper permeability (the passage of substances through the membrane of the smallest vessels). In patients with pregnancy-related grade I–III hemorrhoids, rutoside, a flavonoic glycoside, shown considerable improvement in pain alleviating, in comparison to placebo [37]. The symptoms of nausea, dizziness, gastrointestinal pain, vomiting, dry mouth, constipation, headache, and fatigue were the ones that were reported as occurring the most frequently in patients who experienced adverse reactions. Compared to placebo, there were no significant differences in adverse reactions, fetal death, early delivery, or congenital abnormalities. Nonetheless, several researches discovered a link between Rutoside and congenital abnormality and advised against its use during the first trimester of pregnancy [38,39]. There were no adverse effects recorded in terms of issues with prenatal development, birth weight, or postnatal nutrition in connection with the usage of 500 mg of Daflon [22]. It was recommended that micronized diamines (Daflon) be administered at a dose of 1–2 g/day for short periods only, and not for prolonged use [34]. Lacroix et al. [40] reported the first epidemiological data about suspected veinotonic side effects in pregnant women.They discovered no higher risk of unfavorable pregnancy outcomes in women exposed to veinotonics compared to those who were not exposed.According to a double-blind, randomized, controlled trial, weakened calcium, a phlebotonic medication with anti-haemodynamic action, is helpful in treating the acute phase of hemorrhoids, with a marked reduction in inflammation [41]. Dobesilated calcium (calcium 2,5-dihydroxybenzenesulfonate) inhibits, dose-dependently, the production of PGF1a, PGF2a, PGE2, and TXB2 [42]. Calcium Dobesilate impacts blood pressure and, as a result, reduces the need for medication and hospitalization in cases of mild to moderate midtrimester hypertension, according to a pilot research [43]. There have not been enough research done to determine the safety profile or the teratogenicity of the weakened calcium when it is consumed during pregnancy.

## Interventional and Surgical Treatment

The treatment of hemorroids during pregnancy should be conservative, consisting of improving eating habits and using suppositories or ointments as necessary. Sclerotherapy, which involves injecting sclerosing chemicals at the level of the hemorrhagic plexus, is a controversial operation that can be performed during pregnancy. In the majority of instances, hemorrhoids disappear on their own within two months of delivery, along with the regression of risk factors that contributed to their development [44,45]. In the event of severe bleeding and pain that does not respond to any of the available analgesics, invasive procedures can be considered medically necessary during pregnancy. Thrombosis of the caudal hemorrhoid cushion is what causes hemorrhoids to protrude along the anal border and the anal canal. This condition is known as hemorrhoids thrombosis. Pain that comes on suddenly and swelling at the level of the

anal edge are both symptoms of hemorrhoid thrombosis. The diagnosis can be easily confirmed by an examination of the perianal region. Surgery is typically not indicated for patients who have inadequate symptoms in their condition. The aim of the treatment is to lessen the patient's level of discomfort by way of a systemic anti-inflammatory approach utilizing non-steroidal anti-inflammatory medicines. Ibuprofen and Diclofenac can be taken throughout pregnancy up until the 30th week of the pregnancy. It was previously thought that paracetamol could be taken throughout the entirety of a woman's pregnancy; however, growing evidence from both experimental and epidemiological research suggests that prenatal exposure to paracetamol may alter fetal development, which may in turn increase the risk of certain neurodevelopmental, reproductive, and urogenital disorders. Caution is therefore required when using this medication during pregnancy [33]. Anesthetic ointments, such as Procain, Bupivacin, Lidovain, and Mepivacain, as well as local cooling, may be used in conjunction with the systemic treatment. With this conservative treatment, the pain should go away in a few days, and although the nodule will remain, it should go away on its own in two to four weeks [46]. Necrosis of the vascular wall and skin can, in extremely rare instances, be linked with spontaneous resolution of the thrombus, which in turn leads to relief of the symptoms. In urgent circumstances, due to the severe pain and the presence of a large thrombus, local anesthesia is used for surgical treatment, which involves the complete excision of the whole thrombosed hemorrhoid. Some have reported that metronidazole would be effective in the management of post-hemorrhoidectomy pain. a thrombus is a collection of blood cells that can block blood flow through a blood vessel [47]. Because there is a risk of the thrombus forming again, surgical procedures such as incision and drainage are not advised [48,49].

## Conclusion

The most common kind of anorectal disease that occurs during pregnancy is hemorrhoids, particularly in the third trimester [50]. At the beginning of treatment for hemorrhoids that occur during pregnancy, a conservative approach is utilized. The most significant risk factor, which is also present in the general population, is refractory constipation, which is often accompanied by the possibility of traumatic vaginal birth. In order to limit the incidence of symptomatic hemorrhoids, it is crucial to avoid constipation during pregnancy, particularly after childbirth. Short-term relief of symptoms may be achieved through the use of local interventions such as sitz baths, ice, or ointments containing anesthetics, phlebotonics, or glucocorticoids, either alone or in combination. Surgery for an incurable sickness ought to be put off until the fetus is no longer in danger, or even better, until after the baby has been born. Excision is necessary as soon as possible for external hemorrhoids that have developed acute strangulation thrombosis.

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No potential conflict of interest relevant to this article was reported.

**ORCID iD**
Hyo Seon Ryu : https://orcid.org/0000-0003-2606-9973

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# Low Anterior Resection Syndrome: Pathophysiology, Risk Factors, and Current Management

**Seung Mi Yeo**[1], **Gyung Mo Son**[2]

[1]Department of Rehabilitation Medicine, Pusan National University Yangsan Hospital, Pusan University School of Medicine, Yangsan, Korea
[2]Department of Surgery, Pusan National University Yangsan Hospital, Pusan University School of Medicine, Yangsan, Korea

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**Corresponding author**
Seung Mi Yeo
Department of Rehabilitation Medicine, Pusan National University Yangsan Hospital, Pusan University College of Medicine, 20 Geumo-ro, Mulgeum-eup, Yangsan 50612, Korea
Tel: 82-55-360-4104
E-mail: seungmi7@gmail.com

**Key Words**
Low anterior resection syndrome; Fecal incontinence; Rectal neoplasms; Rehabilitation

Low anterior resection syndrome (LARS) is a condition of anorectal dysfunction that occurs frequently following anal sphincter-preserving surgery for rectal cancer and can reduce the quality of life. In this review, we summarize the main symptoms and pathophysiology of this syndrome and discuss the treatment approaches. Early evaluation and initiation of appropriate treatment postoperatively are crucial. The most frequently used tool to evaluate the severity of LARS is the LARS score, and an anorectal manometer is used for objective evaluation. LARS is believed to be caused by multiple factors, and some of its causes include direct structural damage to the anal sphincter, damage to the innervation, loss of rectoanal inhibitory reflex, and decreased rectal volume and compliance. Diet modifications, medications, pelvic floor muscle training and biofeedback are the primary treatments, and rectal irrigation can be added as a secondary treatment. If LARS symptoms persist even after 1 to 2 years and significantly reduce the quality of life, antegrade irrigation, sacral nerve stimulation or definitive stoma may be considered. High-quality evidence-based studies on LARS treatment are lacking, and randomized controlled trials aimed at developing severity-based treatment algorithms are needed.

## Introduction

The annual incidence of colorectal cancer (CRC) in Korea is 44.5 cases per 100,000 persons, which is one of the highest in the world [1]. According to a recent review article, the incidence of early onset cancer per 100,000 people aged 20–49 years was 12.9, which was the highest of 42 countries that were investigated [2]. In addition to stage 0-I CRC, locally advanced stage II-III CRC is also resected en bloc together with surrounding organs or structures; therefore, surgical treatment is the most important treatment for CRC [3]. Multidisciplinary approaches to the treatment of rectal cancer and improved surgical techniques, including laparoscopic [4] and robotic total mesorectal excision [5], have improved the rate of local recurrence and postoperative complications [6] following rectal resection. Owing to the development of surgical techniques and multimodal treatment in rectal cancer, sphincter preservation surgery is preferred over abdominoperineal resection which requires a permanent colostomy [7]. Up to 80% of patients with rectal cancer have undergone sphincter preservation surgery [8] and up to 90% of them have impaired anorectal function, which is called low anterior resection (LAR) syndrome (LARS) [9]. This review describes the definition, epidemiology, risk factors, and evaluation tools of LARS and

introduces treatments with an emphasis on rehabilitation to improve LARS.

## Definitions of Low Anterior Resection Syndrome (LARS)

LARS is defined as "a combination of symptoms, such as increased frequency and urgency of bowel movements, fecal incontinence, sense of incomplete emptying, and fragmentation after rectal resection, which reduces the quality of life [10]." Patients with LARS can be divided into two overlapping groups: those with urgency and fecal incontinence primarily, and those with evacuatory dysfunction. Recently, an international consensus Delphi process was conducted for patients who received LAR to refine the definition of LARS. This study has defined eight symptoms and eight consequences considered the highest priority in LARS, and are summarized in Table 1. To meet the definition of LARS, a patient receiving LAR should experience at least one of these symptoms that result in at least one of these consequence [11].

## Epidemiology and Evaluation Tools of Low Anterior Resection Syndrome (LARS)

Since LARS is a syndrome that includes various symptoms, varying prevalence rates have been reported depending on the evaluation tools used. Prevalence surveys using the LARS questionnaire [12] have been conducted in recent years. The reported prevalence of major LARS, the most severe anorectal dysfunction, ranges from 17.8% to 56.0% [13–15]. According to the most recent meta-analysis, the prevalence of major LARS was reported to be 44% [15] and 41% [14], and the combined rate of minor and major LARS was reported to be 65% [14].

Tools for evaluating LARS include the LARS score [12], Wexner score [16], Kirwan classification [17], Fecal incontinence severity index [18] and anal examination scoring system (PASS) [19]. Of them, the LARS score is a simple and valid scoring system, and it is a questionnaire that reflects

**Table 1.** International consensus definition of LARS. LARS is defined as having at least one of eight symptoms and at least one of eight consequences after anterior resection

| Symptoms | Consequences |
|---|---|
| Variable, unpredictable bowel function | Toilet dependence |
| Altered stool consistency | Preoccupation with bowel function |
| Increased stool frequency<br>- Compared with preoperative state | Dissatisfaction with bowels |
| Repeated painful stools<br>- Pain on urge, pain on and/or after passing a bowel movement | Strategies and compromises |
| Emptying difficulties<br>- Inability to completely empty the bowel after defecation, returning to the toilet multiple times | Mental and emotional wellbeing |
| Urgency<br>- Need to rush to the toilet to defecate, inability to delay passing a bowel movement | Social and daily activities |
| Incontinence<br>- Unintended passage of a large volume of fecal material | Relationships and intimacy |
| Soiling<br>- Involuntary passage of a small amount of material onto clothing or a sanitary item | Roles, commitments and responsibilities |

LARS, low anterior resection syndrome.


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incontinence, frequent bowel movements, bowel emptying difficulties, and urges that occur following LAR. It has been translated into Korean [20], validated, and used in several studies.
For objective evaluation, most studies have assessed the anorectal function using manometry. The parameters assessed using anorectal manometry include resting pressure, squeeze pressure, rectoanal inhibitory reflex (RAIR), rectal sensitivity (first sensation volume, urge to defecate volume, and discomfort volume), and compliance [21].

## Pathophysiology of Low Anterior Resection Syndrome (LARS)

Although the exact pathophysiology of LARS is not fully understood, it is believed that the symptoms result from multiple causes and mechanisms [10].

**1. Structural damage to the internal anal sphincter**

The internal anal sphincter (IAS) is an involuntary muscle that plays an important role in maintaining resting continence. The internal sphincter is contracted by the parasympathetic nerves of S2-4. The internal sphincter is often resected during intersphincteric resection. It has been reported that direct structural damage occurs during this procedure with a resultant lowering of the resting pressure of the IAS. It is also known that the lower the pressure, the more major LARS that occurs. Additionally, the direct damage depends on the device used for anastomosis, such as a stapler, which results in the lowering of the mean resting pressure of the IAS. Structural damage to the IAS is evaluated using endosonography [22].

**2. Damage to the nerve supply**

IAS function can also be impaired by damage to the autonomic nervous system. The risk of damage to the sympathetic/parasympathetic nerves entering the rectal wall is high during total mesorectal excision [23]. It is known that anal canal sensitivity is reduced secondary to a loss of the sensory branch of the pudendal nerve, which is responsible for sensations of the rectum, along with other nerves of the autonomic nervous system, which result in significant effects on postoperative incontinence [24].

**3. Loss of the rectoanal inhibitory reflex (RAIR)**

RAIR refers to temporary IAS relaxation due to rectal distention. This reflex makes it possible to distinguish between liquids, solids, and gases. Although the role of RAIR in incontinence is not well known, previous studies have revealed many cases of RAIR loss following LAR [25]. Previous studies have demonstrated that the frequency of soiling is higher in patients in whom RAIR does not recover and that RAIR loss is a predictor of bowel dysfunction 1 year after LAR [26].

**4. Decreased rectal volume and compliance**

Rectal volume and compliance of the rectum serve as reservoirs for feces and gases between evacuations. Surgical treatment reduces the maximal rectal volume by removing varying lengths of the rectum [27], and radiotherapy reduces rectal compliance [28]. Reduced volume and compliance correlate with urgency, frequency, and urge incontinence [29]. Additionally, the volume required to initiate the urge to defecate is lowered in patients with LAR and further reduced in patients with a short remnant rectum [30] and those who undergone irradiation [28]. For this reason, surgeons have developed techniques to increase the neorectal volume by constructing a remnant rectum. Side-to-end anastomosis, colonic J-pouch, and

transverse coloplasty are known to significantly reduce bowel frequency for up to 24 months postoperatively.

**5. Altered colonic motility**

LAR involves ligation of the inferior mesenteric artery and sympathetic denervation of the left colon. Studies conducted in rats to investigate the changes in colonic motility following denervation confirmed that colonic migrating contractions increased in the distal colon early after denervation, which is the basis for multiple evacuations after LAR [31,32]. A previous study evaluated the colonic motility following meals in patients with and without an increase in stool frequency following LAR and in healthy controls [33]. The results demonstrated that colonic contractions proximal to the anastomosis site were increased in patients who underwent LAR than those in healthy controls; additionally, colonic contractions occurred earlier in patients with increased stool frequency who underwent LAR than those in patients with normal stool frequency who underwent LAR. In a study that evaluated the colonic transit time using single-photon emission CT/CT scintigraphy, patients with major LARS had significantly faster colonic transit time than those without LARS [34]. In cases of a longer denervated neorectum due to proximal inferior mesenteric artery dissection, propagated contractions disappeared more often and spastic minor contractions were higher in the neorectum [35], which correlated with the urgency of defecation and multiple evacuations [36].

## Risk Factors of Low Anterior Resection Syndrome (LARS)

In recently published papers and systematic reviews, low tumor height and thus low anastomotic height, and radiotherapy were the highest risk factors for LARS [14,15,37]. Furthermore, some studies have identified anastomotic leak [38] and diverting stoma as additional risk factors for LARS. The formation of a neorectal pouch was more common with no functional advantage. Additionally, radiotherapy (OR, 2.89, 95% CI, 2.06–4.05), low tumor height (OR, 2.13, 95% CI, 1.49–3.04), anastomotic leak (OR, 1.98, 95% CI, 1.34–2.93), and diverting stoma (OR, 1.89, 95% CI, 1.58–2.27) were associated with an increased risk of major LARS [15].

## Management of Low Anterior Resection Syndrome (LARS)

A multimodal approach, rather than a single treatment, could represent the best management option for patients with LARS. Diet modifications, medications, pelvic floor muscle training (PFMT) and biofeedback are the primary treatments, and rectal irrigation can be added as a secondary treatment. If LARS symptoms persist even after 1 to 2 years and significantly reduce the quality of life, antegrade irrigation, sacral nerve stimulation (SNS) or definitive stoma may be considered. The treatment algorithm proposed by the author is shown in Fig. 1.

**1. Self-care strategies including diet and practice management**

Self-care strategies and dietary modifications are the easiest and earliest interventions for patients with LARS. Although the evidence is rare, these strategies include the advantage of being simple and that they can be controlled by the patient. It was reported that 96% of patients with rectal cancer who underwent LAR changed their diet postoperatively [39]. It is important to avoid foods that stimulate the bowels and loosen stools, such as alcohol, caffeine, and spicy foods. Although studies on LARS are lacking, it is known that a high intake of soluble

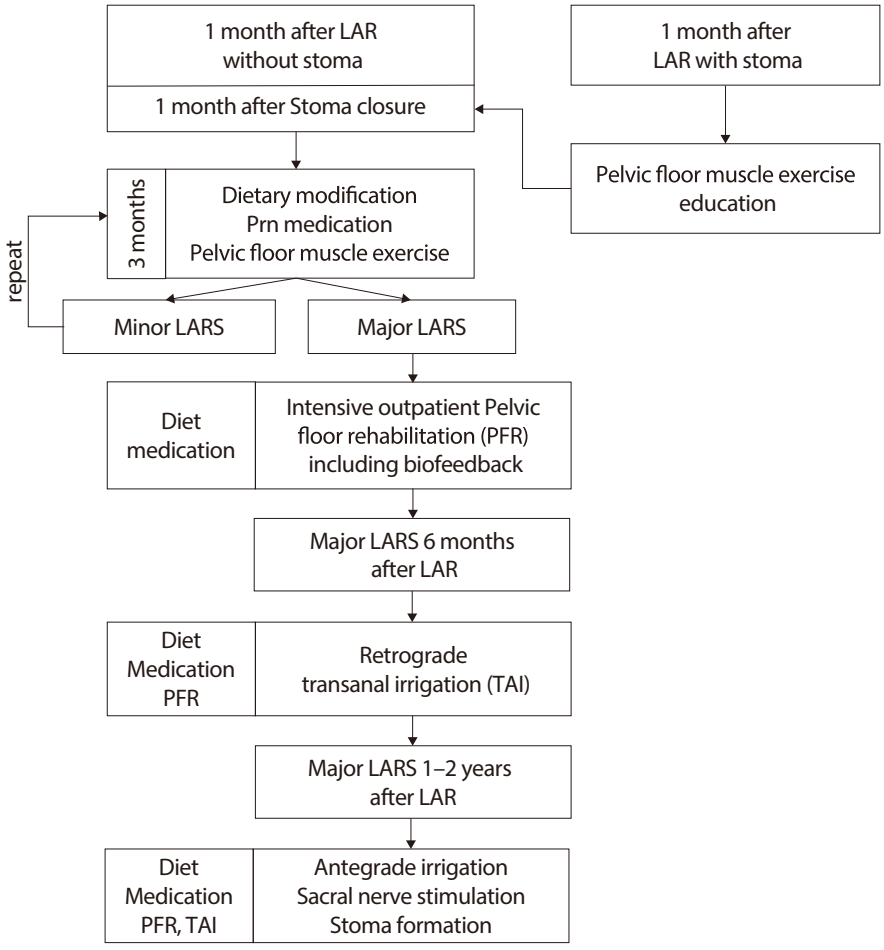


**Fig. 1.** Proposed treatment algorithm for low anterior resection syndrome. LARS, low anterior resection syndrome; PFR, pelvic floor rehabilitation.

dietary fibers (oats, peas, beans, apples, citrus fruits, carrots, barley, and psyllium) in the general population is associated with a decreased riskof fecal incontinence [40]; therefore, post-LAR, patients are recommended to consume these foods.

Probiotics have also been evaluated based on the hypothesis that LARS is caused by changes in the colonic mucosal physiology and the bacterial environment; however, no significant difference was found in comparison with placebo.

### 2. Medications

Medications are the first-line treatment for LARS, which can be attempted when symptoms cannot be controlled with self-care strategies, diet, or exercise. Loperamide, a mu-opioid receptor agonist, is the most commonly prescribed drug along with sitz baths or topical ointments and is the most effective therapy for increased bowel frequency and incontinence [41]. Loperamide is believed to decrease colonic motility and increase the tone of the IAS. Additionally, 5-HT3 antagonists (mosetron or alosetron) are known to treat intestinal hypermobility. Recently, a randomized controlled trial that included 100 patients with LARS who were treated with ramosetron in Korea reported that it significantly reduced the proportion of major LARS and improved the quality of life in comparison with the control group [42].

### 3. Pelvic floor rehabilitation

Pelvic floor rehabilitation consists of PFMT, biofeedback, rectal balloon retraining, and electrical stimulation aimed at improving pelvic floor muscle strength and coordination and rectal sensations. PFMT includes external anal sphincter strength training and isometric contraction exercises that strengthen the pelvic floor muscles. It can be administered along with biofeedback or electrical stimulation but can also be used as monotherapy. PFMT is thought to improve LARS by enhancing structural support, timing, and strength of autonomatic contractions [43]. The important thing to note during exercise is not to hold breath, not to contract the gluteal or abdominal muscles, and to have the same contraction and relaxation time. The anorectal angle, the angle between the anal canal and the rectum that is maintained by the puborectalis, is important for maintaining continence. Repetitive voluntary contractions during PFMT and external anal sphincter are believed to help improve incontinence by reducing the anorectal angle during the resting state.

Biofeedback training is a therapy that uses electronic equipment to inform the user of internal physiological events in the form of visual or auditory signals. Biofeedback consists of rectal sensitivity, strength, and coordination training [44]. Sensory training involves the use of a rectal balloon that gradually inflates until the patient reports the first sense of filling. Repeated reinflation is performed to teach the patient to feel inflation at progressively lower volumes. This allows the patient to detect the need to pass stools at a lower threshold of filling. Strength training is a process in which the patient contracts and relaxes the anal sphincter to reach a target signal based on hearing or watching feedback. It is also possible to receive feedback by attaching reference electrodes to the abdominal or gluteal muscles such that no force is applied to the muscles other than that from the pelvic floor muscles. Coordination training is a process in which the patient contracts the abdominal muscles and relaxes the pelvic floor muscles while evacuating the balloon from the rectum [45].

### 4. Transanal irrigation

Transanal retrograde irrigation is a method of mechanical colon flushing using a pump or an irrigation bag. A cone-shaped end attached to the distal tip is inserted into the anal canal, and 500–1000 cc of water with a temperature similar to the body temperature is injected. It is usually administered daily, and the amount and frequency of water injected may vary between patients. The patient is instructed to evacuate the rectum until urgency is felt. If it is difficult to maintain a cone-shaped end, irrigation can be performed by inserting a balloon catheter into the rectum. Rectal irrigation does not result in true continence; rather, it produces pseudocontinence between washouts. However, it is known to be safe and improve patients' quality of life by preventing nocturnal soiling, improving fecal incontinence, and regularizing of defecation. Since patients irrigate large volumes by themselves, education regarding the correct method is essential. The treatment algorithm used in one study suggested that rectal irrigation could be performed 30 days after LAR [46], but the algorithm in another paper suggested that it should be performed after 6 months [37]. A recent study evaluated prophylactic rectal irrigation early after stoma closure in high-risk patients with LARS and reported that early rectal irrigation was safe and improved LARS [47].

### 5. Antegrade irrigation

Antegrade irrigation refers to daily irrigation using an external catheter after performing percutaneous endoscopic colostomy (PEC). The largest case series report of antegrade

irrigation in rectal cancer was a study involving 25 patients, of which 4 (16%) had catheters removed, meaning that the procedure was ineffect in 16%. LARS score significantly decreased from 33 to 4 after PEC procedure and antegrade irrigation, and rate of major LARS decreased significantly from 73% to 9%. However, PEC shoulder be chosen carefully as there are some complications such as local pain, sweating, granulation at the PEC entry, leakage, and wound infection [48].

### 6. Sacral stimulation and tibial nerve stimulation

Given the evidence that SNS affects not only the anus and rectum but also the upper gastrointestinal tract and colon, the effects of SNS on anorectal function appear to originate at the pelvic afferent or central level. Recently, a systematic review article on studies that used SNS to improve LARS was published [49]. Before permanent SNS implantation, a temporary electrode was inserted through the S3 foramen to confirm the effectiveness of SNS, and percutaneous nerve evaluation (PNE) was performed. Permanent SNS was implanted when PNE confirmed improvement in fecal incontinence. A total of 94 patients underwent PNE and 79.8% of them underwent permanent SNS implantation. Although each study was different, stimulation was used with a pulse width of 210 μs and a frequency of 14 pulses/s; the amplitude was controlled by determining the degree to which the patient felt perineal and anal sphincter contractions. Although the studies included in the systematic review were not randomized controlled trials and the sample size was small, it is a meaningful result that the degree of fecal incontinence and LARS score improved significantly with implantation, especially because the patients who received SNS had chronic LARS. The use of SNS can be a treatment option in patients with refractory LARS.

Tibial nerve stimulation (TNS) is a novel, cost-effective and less invasive form of indirect neuromodulation of sacral nerve function. The tibial nerve is a mixture of sensory and motor nerves originating from the L4 to S3 spinal nerve roots, overlapping with the from S2 to S4 spinal nerve roots, from which nerves to the pelvic floor muscle and sphincter originate. TNS is thought to improve the resing and stress pressure of the sphincter and enhance rectal sensitivity by triggering multiple nerve pathways at the medulla and brain levels. TNS can modulate higher perception of afferent information and is thought to modulate colonic motility by triggering local somato-visceral reflexes [50]. A small electrode is inserted close to the posterior tibial nerve at ankle level and stimulated for 30 minutes, once a week, for a total of 16 to 20 times. Stimulation was used with a pulse width of 200 μs and a frequency of 20 pulses/s; the amplitude was ranged from 0.5 to 9.0 mA. Two of the three randomized controlled trials had no significant effect, and in one study, only the TNS group had a positive result that improvement of LARS and fecal incontinence scores were maintained up to 12 months [50].

## Conclusion

With an increasing number of patients receiving neoadjuvant concurrent chemoradiotherapy and sphincter-preserving surgery for rectal cancer, the number of patients with a reduced quality of life due to LARS is increasing. After appropriate evaluations, it is important to provide treatment according to the postoperative duration and severity of LARS. Further studies are required to improve the level of evidence.


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### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### ORCID iD

Seung Mi Yeo: https://orcid.org/0000-0002-9633-6179
Gyung Mo Son: https://orcid.org/0000-0002-8861-6293

### Author Contribution

Conceptualization: Yeo SM, Son GM
Formal Analysis: Yeo SM
Investigation: Yeo SM
Methodology: Yeo SM
Project Administration: Yeo SM
Writing – Original Draft: Yeo SM
Writing – Review & Editing: Yeo SM, Son GM

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Review Article

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# Metabolic Syndrome in Children and Adolescents

**Yoojin Lindsey Chung**[1], **Young-Jun Rhie**[2]

[1]Department of Pediatrics, Myoungji Hospital, Goyang, Korea
[2]Department of Pediatrics, Korea University Ansan Hospital, Ansan, Korea

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**Corresponding author**
Young-Jun Rhie
Department of Pediatrics, Korea University Ansan Hospital, 123, Jeokgeum-ro, Danwon-gu, Ansan 15355, Korea
Tel: 82-31-412-4846
Fax: 82-31-405-8591
E-mail: human21@korea.ac.kr

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Metabolic syndrome; Cardiovascular disease; Obesity; Insulin resistance; Pediatrics

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities that include hypertension, altered glucose metabolism, dyslipidemia, and abdominal obesity and is strongly associated with an increased risk for diabetes and cardiovascular disease onset in obese adults and children. A progressively greater number of children and adolescents are being affected by this syndrome due to the constant increase in the prevalence of obesity. Like obesity, childhood MetS highly tracks to adulthood. The pathogenesis of MetS includes the interaction between obesity, insulin resistance, and inflammation. Early diagnosis and intervention are important in order to conduct lifestyle modification. In this article, we review the definition and pathophysiology of MetS, the importance of screening, and prevention and treatment options for MetS in childhood.

## Introduction

Metabolic syndrome (MetS) is characterized by a cluster of cardiovascular risk factors (hypertension, altered glucose metabolism, dyslipidemia, and abdominal obesity) that occur in obese adults and children [1]. MetS risk is rising in children and adolescents as childhood obesity continues to rise [2,3]. In order to better manage MetS in childhood, we must understand its pathophysiology, risk factors, and management methods.

MetS affects >30% of the adult population >30 years of age in South Korea [4]. According to the Korea National Health and Nutrition Examination Survey, its prevalence has been increasing gradually in young adults since 1998 [5]. Controversy exists regarding the various definitions of the syndrome and its ability to predict future adverse cardiometabolic events in a manner surpassing other well-described risk factors. Despite this, there can be little controversy regarding the current national and worldwide epidemic of obesity, and the links between risk factors in youth and subsequent adult cardiovascular disease (CVD) [6]. Also, the rise in the prevalence of pediatric obesity is one of the most alarming public health issues facing the world, including Korea, today [7].

MetS is associated with many clinical conditions besides CVD and type 2 diabetes (T2DM), including chronic low-grade inflammation, oxidative stress, hyperuricemia, hypertension, dyslipidemia, hyperandrogenism and polycystic ovarian syndrome (PCOS), hepatic steatosis and non-alcoholic fatty liver disease (NAFLD), impaired glucose tolerance, obstructive sleep apnea, hypogonadism, vascular dementia and Alzheimer' disease, and certain forms of cancer [8,9].

Despite the risks and associated conditions, several factors contribute to the controversy

surrounding pediatric MetS. First of all, it is difficult to define MetS in pediatric populations. MetS in adults is predictive of CVD and T2DM; however, several definitions of MetS have been proposed for children and adolescents, and there is no clear consensus on which one should be applied [10,11]. Moreover, regardless of the definition used, there is no uniform way to treat MetS other than weight management.

Our purpose in this review article is to provide an overview of MetS in the pediatric population, focusing on its definition, pathophysiology, screening, prevention, and treatment.

## Definition of Metabolic Syndrome in Childhood

MetS among adults has been defined clinically by at least five health organizations, including the World Health Organization (WHO); the U.S. National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III; the American Association of Clinical Endocrinologists/American College of Endocrinology; the International Diabetes Federation (IDF); and the American Heart Association (AHA) in conjunction with the National Heart, Lung, and Blood Institute (NHLBI) of the U.S. National Institutes of Health. In 2001, the NCEP developed the first risk criteria definition for atherosclerosis and cardiovascular disease based on the "any three of five" risk criteria. NCEP ATP III defines five risks: (I) hyperglycemia, (II) hypertriglyceridemia, (III) low high-density lipoprotein cholesterol (HDL-C) level, (IV) hypertension, and (V) an increase in waist circumference. In 2005, the AHA/NHLBI modified this definition of MetS by reducing glucose cut points, and the IDF introduced its "worldwide" definition of MetS, placing greater emphasis on abdominal obesity by making it a necessary criterion for MetS diagnosis. Although the AHA/NHLBI and IDF definitions have many similarities, there are important differences between them with respect to cut points of the various component risks. However, most commonly used definitions agree that the following components are relevant: central obesity, impaired glucose tolerance, dyslipidemia, and hypertension.

Among children and adolescents, MetS definitions differ even more than among adults. MetS was first studied among adolescents in a pediatric population; however, the prevalence varied by more than 2-fold in the same database. In 2007, the IDF assembled an international group of experts to develop a consensus definition. Specifically, the IDF recommended pediatric MetS should only be applied to children ≥10 years of age with three or more of following risk factors: high waist circumference, high blood pressure, IR, and dyslipidemia [10]. Among those 10–15 years of age, those in the >90$^{th}$ percentile for waist circumference or with a systolic blood pressure>130 mmHg or diastolic blood pressure>85 mmHg, triglycerides>150 mg/dL, or HDL-C<40 mg/dL would be defined as having MetS. For adolescents>15 years of age, the adult criteria should be used for diagnosis (Table 1).

In its scientific statement published two years later, the AHA stressed the importance of identifying pediatric cardiometabolic risks and noted that only some of them could be identified by the current MetS criteria. The AHA did not include a definition of MetS for pediatric populations and noted that adapting adult definitions to pediatric populations had limitations. To date, there is no clear consensus on whether MetS should be defined in pediatric populations and, if defined, which definition should be used. However, this definition also stated that children <10 years of age should not be diagnosed with MetS. This was explained by the absence of age-specific reference values for MetS components for this age group [10]. In 2014, Ahrens et al. proposed a quantitative MetS score using age- and gender-specific anthropometric and metabolic parameters in children 2–11 years of age [11]. To help physicians identify children at

**Table 1.** Pediatric definition of MetS (IDF definition)

| Variables | IDF definition age<10 years | IDF definition ages 10–16 years |
|---|---|---|
| Defining criteria | Cannot be diagnosed in the age group | Central obesity with at least 2 out of 4 criteria |
| Central obesity | | WC≥90$^{th}$ percentile or adult cutoff if lower |
| Hypertension | | SBP≥130 mmHg or DBP ≥85 mmHg or treatment with anti-hypertensive medication |
| Hypertriglyceridemia | | TG≥150 mg/dL |
| Low HDL | | HDL<40 mg/dL |
| Impaired glucose | | FPG≥100 mg/dL or known T2DM |

IDF, International Diabetes Federation; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; HDL, high-density lipoprotein; FPG, fasting plasma glucose; T2DM, type 2 diabetes mellitus.

risk, the scoring system recommends strict monitoring of children in the ≥90$^{th}$ percentile of body mass index (BMI), and for those in the ≥95$^{th}$ percentile, urgent intervention is recommended [11].

MetS' utility in pediatrics is contested beyond its definition. The presence of MetS predicts the presence of CVD and diabetes in adulthood. As compared to patients without MetS risk factors, Malik et al. found that a person with MetS and diabetes had an increased hazard ratio for coronary heart disease mortality by 1.75 times [12]. However, there has been some concern that the syndrome is ineffective in adolescents, given that there is some instability in the definition of the syndrome as adolescent's transition from adolescence to adulthood.

Most children defined as having MetS at childhood fail to meet diagnostic criteria three to six years later during follow-up. Even though the prevalence of MetS has increased at the population level, within-person variation in the presence or absence of MetS has been large in observational longitudinal studies. Many studies have shown that 50% of MetS-positive subjects become MetS-negative over time, either during short-term follow-up (~3 weeks) or long-term (9 years) [13]. There was no correlation between this instability and a change in weight [13]. As a result, MetS remains highly unstable throughout childhood. In a child, the criteria can be met at one point in time and not at another, and it is unclear whether this represents an improvement or a deterioration in health.

Given the absence of a consensus on the definition of MetS, the unstable nature of MetS, and the lack of clarity about the predictive value of MetS for future health in pediatric populations, pediatricians are rightly confused about MetS. Thus, rather than focusing on defining MetS in youth, the American Academy of Pediatrics (AAP) recommends that pediatricians focus on the concept of cardiovascular risk factor clustering and associated risk factor screening. This concept is especially important because the Bogalusa Heart Study demonstrated that increased clustering of atherosclerotic CVD risk factors was associated with increased severity of atherosclerotic lesions [14]. In addition, the AAP recommends pediatricians avoid using cut points based on MetS definitions. MetS identifies multiple components that cluster together and are associated with insulin resistance and adipose tissue pathology. Disparities in these thresholds are a major reason for discrepancy between definitions. In addition, there is a continuum of risk associated with many risk factors. A continuous variable may be more reliable in predicting the future risk of young adults from early adolescence [15]. Risk factor screening and the identification of youth with MetS risk factor abnormalities allow providers to allocate scarce resources to children who are at a higher cardiometabolic risk, specifically those

with multiple components. The screening and associated treatment of MetS is an important component of preventive pediatric care.

## Pathogenesis of Metabolic Syndrome

Despite the lack of clarity about MetS pathogenesis, recent research suggests that obesity, insulin resistance, and inflammation play a key role in the development of MetS.

### 1. Insulin resistance

Insulin resistance is the opposite of insulin sensitivity and is defined as a decreased response to insulin-mediated cellular actions. The phrase "insulin resistance," as generally applied, refers to whole-body reduced glucose uptake in response to physiologic insulin levels and its consequent effects on glucose and insulin metabolism. However, it is now clear that not all insulin-responsive tissues are equally sensitive to insulin. Generalized insulin resistance would result in global metabolic dysfunction, such as leprechaunism or Rabson–Mendenhall syndrome. Thus, the insulin resistance in obesity inevitably affects different tissues quantitatively.

#### *1) Hepatic insulin resistance*

In addition to being a primary target of insulin action, the liver plays a critical role in substrate metabolism. After insulin is released from β-cells following a glucose loading, it travels directly to the liver via the portal vein, where it binds to insulin receptors and elicits two key actions at the level of gene transcription. First, insulin stimulates the phosphorylation of FoxO1, preventing it from entering cell nuclei and decreasing the expression of genes required for gluconeogenesis, which are principally phosphoenolpyruvate carboxykinase and glucose 6-phosphatase [16]. This process leads to decreased hepatic glucose production. A second effect of insulin is that it activates the transcription factor sterol regulatory element–binding protein (SREBP)-1c. This increases the transcription of genes required for fatty acid and TG biosynthesis, particularly adenosine triphosphate citrate lyase, acetyl-coenzyme A carboxylase, and fatty acid synthase, which together promote the process of de novo lipogenesis (DNL). TGs synthesized by DNL are then packaged with apoliprotein B into very-low-density lipoproteins (VLDLs), which are then exported to the periphery to be stored. The use of VLDLs is then enabled by the reciprocal activation of lipoprotein lipase on the surface of endothelial cells within the adipose tissue or the muscle tissue [17]. For reasons that remain unclear, in insulin-resistant individuals, hepatic insulin resistance is usually selective or dissociated; that is, they have impaired insulin-mediated glucose homeostasis (mediated by the FoxO1 pathway) but enhanced insulin-mediated hepatic DNL (mediated by the SREBP-1c pathway) [18]. The increase in free fatty acid (FFA) flux within the liver, either by DNL or FFA delivery via the portal vein, impairs hepatic insulin action, which, in turn, leads to increases in hepatic glucose output, the synthesis of pro-inflammatory cytokines; excess TG; low HDL-C secretion by the liver; and an elevated number of relatively cholesterol-depleted, small, dense LDL particles. As a result of these intrahepatic accumulations of FFA and lipids, liver insulin sensitivity is also negatively affected [19].

#### *2) Adipose tissue insulin resistance*

The expanded adipose tissue mass attributable to obesity often increases lipolysis and FFA turnover. Normally, insulin inhibits adipose tissue lipolysis; however, in the insulin-resistant state, the process is accelerated, increasing the release of FFA into the circulation. Furthermore,

visceral adipocytes are more sensitive to catecholamine-stimulated lipolysis than subcutaneous adipocytes, which increases the FFA flux [20]. Adipose tissue also receives macrophage infiltration, which leads to the hypertrophy of adipocytes and the release of cytokines [21]. These circulating cytokines also affect insulin action in liver and muscle tissues.

*3) Muscle insulin resistance*

The increased plasma FFA levels from insulin-resistant livers disrupt the glucose-fatty acid or Randle cycle, facilitating hyperglycemia by impairing insulin-mediated glucose transport to skeletal muscle [22]. The ectopic deposition in skeletal muscle of fat as intramyocellular lipid may also play a direct role in the pathogenesis of insulin resistance and MetS via lipid metabolite-induced activation of protein PKCε with subsequent impairment of insulin signaling [23]. In childhood, ethnicity and puberty are the two most important biological factors influencing insulin resistance.

**2. Lipid partitioning**

The phrase "lipid partitioning" refers to the distribution of body fat in various organs and compartments. The majority of excess fat is stored in its conventional subcutaneous depot, yet other potential storage sites exist as well, such as the intraabdominal (visceral) fat compartment and insulin-responsive tissues like muscle and the liver. Although still under debate, a potential etiology of MetS involves a pattern of lipid partitioning (i.e., the specific depots in which excess fat is stored). This pattern of lipid storage determines the secretion profile of adipocytokines and its effect on circulating levels of inflammatory cytokines and FFA flux. Through their combined effects, these factors impact insulin-mediated pathways in target organs (such as muscle and the liver) and vascular system by influencing endothelial function.

**3. Adipocytokines**

*1) Leptin*

Adipocytes secrete several proteins that act as regulators of glucose and lipid metabolism. Because they share structural similarities with cytokines, these proteins are collectively termed adipocytokines. The level of circulating leptin serves as an adiposity sensor to prevent starvation and correlates with the degree of obesity in the body. Leptin probably has a permissive role in high-energy metabolic processes such as puberty, ovulation, and pregnancy, but its role in states of energy excess is less known. In obesity, the development of leptin resistance may lead to abnormal partitioning of surplus lipids within adipocytes [24].

*2) Adiponectin*

Adiponectin is distinctive in obesity because, in contrast to the other adipocytokines, its level is decreased in obese people. The adiponectin gene is found on chromosome 3q27, which has previously been associated with the emergence of T2DM and MetS. Numerous single-nucleotide polymorphisms in the adiponectin gene have been linked to the emergence of T2DM in people all over the world, indicating that adiponectin is crucial for the regulation of glucose and lipid metabolism [25]. Two adiponectin receptors, ADIPOR1 and ADIPOR2, have been identified. ADIPOR1 is expressed in numerous tissues, including muscle, while ADIPOR2 is mostly restricted expression in the liver. Both ADIPOR1 and ADIPOR2 are receptors for the globular head of adiponectin and operate as start-up molecules for signal transduction pathways that result in

elevated peroxisome proliferator–activated receptor (PPAR)-α and adenosine monophosphate kinase activity, which encourages the absorption of glucose and the oxidation of fatty acids. Additionally, it has been demonstrated that adiponectin has strong anti-atherogenic properties because it accumulates in the subendothelial region of damaged vascular walls and inhibits the development of adhesion molecules and the attraction of macrophages [26].

Studies in obese children and adolescents have revealed that adiponectin levels are inversely associated to the degree of obesity, insulin resistance, visceral adiposity, IHCL, and IMCL, while weight loss increases adiponectin concentrations.

*3) Inflammatory cytokines*

It is becoming increasingly clear that obesity contributes to chronic inflammation in a subclinical manner [27]. Thus, adipose tissue functions not only as an energy reservoir but also as an active secretory organ, releasing peptides into the circulation, such as inflammatory cytokines. As obesity progresses, the balance between these peptides is altered, and large adipocytes and macrophages embedded within them produce more inflammation-inducing cytokines (i.e., tumor necrosis factor–α and interleukin-6) and fewer anti-inflammatory peptides such as adiponectin. One hypothesis posits that, as adipocytes store energy, the perilipin borders of the fat vacuoles break down, leading to the adipocyte's dismiss. Cell death then recruits macrophages in the adipose tissue, especially the visceral compartment, which also secrete inflammatory cytokines in the process of clearing debris, initiating a pro-inflammatory cascade that anticipates and possibly drives the development of systemic insulin resistance, diabetes, and endothelial dysfunction [28]. Elevated levels of CRP also correlate with other components of MetS in obese children [29]. Thus, inflammation may be one of the links between obesity and insulin resistance, and it may also promote endothelial dysfunction and early atherogenesis.

Most of the aforementioned molecules have been associated with elements of MetS and its characteristic pattern of lipid partitioning. Specifically, low adiponectin levels have been associated with insulin resistance, low-grade inflammation, and increased intramuscular fat [30]. Moreover, component analyses of plasma leptin concentrations and the variables that are considered relevant to MetS revealed that plasma leptin concentrations were clustered with insulin resistance and hyperinsulinemia [31].

## Screening

Clinicians should recognize children who are obese and overweight and at risk for T2DM and CVD. It is important to screen these children for behavioral and medical risks, including persistent obesity, as well as its associated co-morbidities [32]. A significant risk factor for childhood obesity that needs to be considered during the screening evaluation is the presence of obese parents [32]. The history and physical examination are the first steps in the comorbidity screening process. Clinicians should request information about the signs and symptoms for associated comorbidities that may be present, such as PCOS, liver disease, and obstructive sleep apnea, which can be confirmed as a comorbidity with polysomnography [32]. Serum alanine aminotransferase and aspartate aminotransferase levels are respectably effective screening tests for fatty liver disease. When values are double the upper limit of normal, a pediatric hepatologist should be consulted [32]. Bi-annual liver disease screening is recommended starting at the age of 10 years for children with obesity or those who are overweight with other risk factors [33]. Screening for T2DM is recommended in overweight (≥

85th percentile) or obese (≥95th percentile) children and adolescents with ≥1 of the following risk factors: (I) Family history of T2DM in first- or second-degree relatives; (II) at risk race or ethnicity (Native American, African American, Latino, Asian American, and Pacific Islander); (III) signs of insulin resistance or associated conditions, such as acanthosis nigricans, hypertension, dyslipidemia, PCOS, or a history of being born small for gestational age; and (IV) maternal history of diabetes or gestational diabetes during the child's gestation [34]. The ADA recommends starting screening at the age of 10 years or at the onset of puberty, whichever arrives earlier, and be repeated every three years [34]. Generally, fasting plasma glucose, 2-hour plasma glucose measured during the 75-gram oral glucose tolerance test, and the glycated hemoglobin test are equally appropriate for diagnostic screening [34]. Starting at age 3 years, blood pressure should be obtained annually at all regular health check-ups, and results should be compared to reference ranges from tables issued by the NHLBI [35]. Finally, children should be routinely screened for dyslipidemia with universal lipid screening between 9–11 years of age with a non-fasting, non-HDL lipid profile. Screening children 2–8 years of age with fasting lipid profiles is recommended for obese children since obesity is considered a moderate- to high-risk factor [35]. The NHLBI recommends repeating lipid profiling in overweight adolescents at 12–16 years of age. The level of abnormality, the presence of additional known risk factors, and the presence of high-risk diseases should determine whether to pursue dietary or medicinal intervention [35].

## Prevention and Treatment of Metabolic Syndrome

### 1. Prevention

Pediatric obesity prevention involves promoting healthy diet and increasing physical activity as the primary prevention strategies in order to avoid MetS in children. Lifestyle modifications to achieve a healthy diet include increasing consumption of vegetables and fruits; increasing fiber intake while reducing dietary fat; and avoiding carbonated beverages, refined carbohydrates, high-fructose corn syrup, high sodium, and processed foods [36]. Fruit juice should be replaced with whole fruits for additional nutritional value. Physical activity is also recommended 3–5 days per week with ≥20 min of vigorous short bursts to improve metabolic measures in children and adolescents, which may prevent obesity [36]. A meta-analysis conducted by Kamath et al. found that lifestyle modification had a positive effect on reducing sedentary behavior in long-term trials and reduced unhealthy dietary habits. In comparison to adolescents, those adjustments were more successful with children [37]. Adopting healthy sleep habits, limiting non-academic screen time, involving the entire family and community in prevention efforts, and using school-based programs and community engagement for the prevention of pediatric obesity are additional lifestyle changes that can lower the risk of developing obesity [36].

### 2. Treatment

In general, childhood MetS is treated through weight reduction by lifestyle modifications, including dietary intervention, increased physical activity, and the management of various disease-specific factors. Pharmacological treatments and bariatric surgery are other alternatives for managing obesity.

*1) Lifestyle modifications and behavioral treatment*

For the first step to change, clinicians should assess patients and families. In this way, family and patient interventions will be more easily incorporated. When compared to programs

focused solely on the child, those that involved the entire family in lifestyle change were found to have favorable outcomes for lowering BMI [37]. Comprehensive weight reduction programs, including nutritional, physical activity, education, and behavioral therapy, have been linked to improvements in a number of metabolic parameters, including blood pressure and lipid profile indices in obese children and adolescents [38]. Obese children and adolescents should be screened for mental health, including eating disorders, depression, and other mood disorders. Support and referral to available behavioral health resources for those disorders are essential.

(1) Dietary intervention

Basic dietary recommendations are mostly based on low-fat diets and, recently, low-carbohydrate diets are gaining popularity [39]. Recent Endocrine Society guidelines recommended avoiding beverages sweetened with sugar, elimination of fructose-rich corn syrup, and decreased consumption of processed foods high in salt and saturated dietary fat in children over 2 years of age and adolescents. Furthermore, consumption of dietary fibers, vegetables, and whole fruits other than fruit juice or carbonated drinks is encouraged. Additionally advocated for nutritional intervention are education about portion control, improved product labeling, and the consumption of frequent meals to prevent snacking [36]. In addition, because eating fast and the risk of developing T2DM are highly associated, slow eating should be taught as an important eating habit [40]. According to a systematic review of 107 trials, low-carbohydrate diets had weight reduction outcomes proportional to those of low-fat diets and had no particularly negative impact on blood pressure, insulin, fasting serum glucose, or cholesterol levels [39].

(2) Physical activity

The second-most important behavioral intervention is physical activity. The AAP and the European Society for Pediatric Endocrinology advise engaging in physical activity regardless of weight status, aiming for at least 30 minutes of daily moderate to vigorous activity, and keeping non-academic screen time to no more than one to two hours per day [36,41]. It is recognized that inactivity can decrease insulin sensitivity in skeletal muscle, which can be reversed by increasing physical activity. Physical activity is also helpful in improving the lipid profile by lowering LDL and triglyceride concentrations and increasing the HDL concentration [42]. Regular physical activity increases cardiorespiratory fitness by reducing blood pressure, arterial stiffness, and abdominal fat [43]. Most children, including children with obesity, do not achieve these recommendations. Exercise physiologists and physical therapists can help these children by developing individual exercise plans, especially when movement is limited by gross motor delay or musculoskeletal pain [44].

*2) Pharmacological therapies*

As previously stated, lifestyle modification therapy is the primary form of treatment for MetS. When patients are unable to achieve their weight loss objectives with lifestyle modification therapy alone, pharmacotherapy is the next logical treatment option to consider (Table 2) [45-49]. The indication for pharmacotherapy to treat pediatric obesity includes an age of ≥10 years and a BMI in the ≥95$^{th}$ percentile with weight-related co-morbidities or a BMI that is ≥120% of the 95$^{th}$ percentile, regardless of comorbidities, without an appropriate response to lifestyle modification [36]. Intense lifestyle modification programs should be considered along with pharmacotherapy [32].

Options for pharmacotherapy to treat pediatric obesity are limited. Orlistat, a lipase inhibitor

**Table 2.** Medications for weight loss in the pediatric population

| Drug name | Mechanism of action | FDA indication | Off-label drug use | Side effects |
|---|---|---|---|---|
| Orlistat [45] | Pancreatic and gastric lipase inhibitor | Obesity≥12 years of age | Not indicated | Flatulence, oily spotty stools, diarrhea, vitamin/mineral deficiency |
| Exenatide [46] | GLP-1 agonist | T2DM in adults | <18 years of age for obesity (polygenic with the presence of diabetes, hypothalamic, syndromic) | Bloating, diarrhea, flatulence |
| Liraglutide [47,48] | GLP-1 agonist | 3.0 mg of liraglutide approved for obesity in adolescents (12–17 years) with a reduced-calorie diet and increased physical activity | Not indicated | Bloating, nausea/vomiting, abdominal pain, the elevation of pancreatic amylase and lipase |
| Metformin [49] | Activation of protein kinase pathway | ≥10 years of age, T2DM | PCOS, insulin resistance, prediabetes, metabolic syndrome, anti-psychotic medication–induced weight gain, stress eating/emotional eating | Bloating, diarrhea, flatulence, contraindicated with risk of lactic acidosis |

T2DM, type 2 diabetes mellitus.

that blocks the absorption of fats from the human diet, is the only medicine recognized by the American Food and Drug Administration (FDA) for long-term use in the treatment of pediatric obesity (≥12 years of age). However, due to its modest efficacy (2.61-kg weight loss after one year of treatment), its therapeutic application is somewhat limited, and many adolescents may find its side effects unpleasant (flatulence; oily, spotty stools; and diarrhea) [45].

Glucagon-like peptide-1 receptor (GLP-1) agonists include exenatide and liraglutide. Exenatide has FDA approval for adult T2DM, and a liraglutide 3.0-mg injection has FDA approval for adult obesity. Recently, a liraglutide 3.0-mg injection received FDA approval for the treatment of obesity in adolescents (aged 12–17 years) with a body weight>60 kg and an initial BMI≥30 kg/m$^2$ combined with a reduced-calorie diet and increased physical activity. GLP-1 agonist–associated weight reduction appears to be related to decreased gastric emptying and increased satiety and appetite suppression. Recently, a randomized controlled trial of adolescent obesity with a 56-week liraglutide treatment period reported that the use of a liraglutide 3.0-mg injection combined with lifestyle modification led to significant reduction in BMI z-score [46]. In patients with syndromic and hypothalamic obesity with hyperphagia, GLP-1 agonist therapy has the potential for weight reduction and weight stabilization [47,48].

Metformin, a biguanide primarily used for glycemic control, has been used off-label to achieve weight loss in children. Meformin is FDA-approved for children≥10 years of age for T2DM. Currently, in a systematic review of randomized controlled trials on children and adolescents, Masarwa et al. [49] assessed the effectiveness of metformin. Researchers discovered that metformin reduced BMI z-score modestly in obese subjects and had the greatest effect on children and adolescents with NAFLD. Several studies reported improvements in fasting plasma glucose and insulin resistance, but not in lipid levels. As compared to a placebo, metformin was associated with double the number of gastrointestinal adverse effects [49]. By this finding, the question of whether metformin is an appropriate adjuvant therapy to lifestyle change for the treatment of pediatric obesity is raised.

*3) Surgical therapies*

As a standard course of treatment, surgical intervention for childhood and adolescent obesity is still not approved. In children and adolescents, research on the effects of surgery on growth and development is limited. Thus, it should only be considered when growth and puberty are complete. Also, surgical treatment for children and adolescents in growing process should be limited to strict standards. Before considering surgical treatment, evaluation for previous treatment, such as multidisciplinary treatment and pharmacotherapy, should be conducted. Furthermore, adolescents and their families should have psychological stability and competence, availability for appropriate follow-up care, and a demonstrated ability to comply with healthy dietary and activity routines. It is also very important that the patient has a reliable caretaker who can provide physical and psychosocial support through the entire process. Recently, metabolic and bariatric surgery (MBS) has been shown to be an effective treatment for severe obesity in adolescences, and studies have reported significant improvements in co-morbidities associated with obesity [50]. According to the most recent recommendations issued by the American Society for Metabolic and Bariatric Surgical Pediatric Committee, MBS could be considered for children ≥10 years of age with a BMI that is ≥120% of the 95$^{th}$ percentile who also have a weight-related co-morbidity, such as T2DM, hypertension, NAFLD, and/or obstructive sleep apnea, or those with a BMI that is ≥140% of the 95$^{th}$ percentile regardless of co-morbidities [50]. According to the recommendations, treatment should be provided to adolescents who have previously attempted to reduce weight, have a low Tanner stage, and have immature bone growth [50]. Lack of evidence, however, suggests that MBS may have a negative impact on a child's pubertal status as determined by Tanner staging, linear development, or height. The impact of MBS on children's pubertal development should therefore be the subject of additional research. MBS has the potential to result in both macro- and micronutrient deficit, therefore lifetime supplemental protein, iron, calcium, and vitamins are necessary to prevent deficiencies [50]. Gastroesophageal reflux, which has been recorded in >12%–30% of patients requiring long-term usage of proton pump inhibitors, is another side effect of MBS [51]. Patients undergoing any of these surgical procedures are at risk of anastomosis site leaking, hernia, stricture, and wound infection; however, children are less likely than adults to experience these consequences [51].

## Conclusion

It is known that early diagnosis and successful treatment of MetS are key to reducing the risk of cardiometabolic disease. Although sometimes the diagnosis is delayed because MetS is overlooked by families, early identification and management are crucial and help to attenuate the disease progression. Screening children and adolescents for overweightness and obesity by considering up-to-date reference values, age- and sex-related percentiles, and comorbidities using good clinical judgment is highly recommended. According to the 2017 Korean National Growth Charts (KNGC2017), BMI for age≥85$^{th}$ percentile and <95$^{th}$ percentile is defined as overweight and BMI for age≥95$^{th}$ percentile is defined as indicative of obesity [52]. To provide specialized care, it is crucial to assemble a knowledgeable multidisciplinary team, which has to be composed of a pediatrician, mental health professional, nutritionist, nurses, and other referral specialists for complications [35]. The health system must, however, confront with the question of how to support such a multidisciplinary team financially.

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### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### ORCID iD

Yoojin Lindsey Chung: https://orcid.org/0000-0002-7447-6250
Young-Jun Rhie: http://orcid.org/0000-0002-1250-6469

### Author Contribution

Conceptualization: Chung YL, Rhie YJ
Formal Analysis: Chung YL
Investigation: Chung YL
Project Administration: Chung YL
Writing – Original Draft: Chung LY, Rhie YJ
Writing – Review & Editing: Chung LY, Rhie YJ

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Not applicable.

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# Comparative Analysis of Health Patterns and Gaps due to Environmental Influences in South Korea and North Korea, 2000–2017

**Yoorim Bang[1,*], Jongmin Oh[2,*], Eun Mee Kim[3], Ji Hyen Lee[4], Minah Kang[5], Miju Kim[6], Seok Hyang Kim[6], Jae Jin Han[7], Hae Soon Kim[4], Oran Kwon[8,9], Hunjoo Ha[10], Harris Hyun-soo Kim[11], Hye Won Chung[12], Eunshil Kim[13], Young Ju Kim[12], Yuri Kim[8], Younhee Kang[14], Eunhee Ha[2,9,15]**

[1]Institute for Development and Human Security, Ewha Womans University, Seoul, Korea
[2]Department of Environmental Medicine, College of Medicine, Ewha Womans University, Seoul, Korea
[3]Graduate School of International Studies, Ewha Womans University, Seoul, Korea
[4]Department of Pediatrics, College of Medicine, Ewha Womans University, Seoul, Korea
[5]Department of Public Administration, Ewha Womans University, Seoul, Korea
[6]Department of North Korean Studies, Ewha Womans University, Seoul, Korea
[7]Department of Thoracic and Cardiovascular Surgery, College of Medicine, Ewha Womans University, Seoul, Korea
[8]Department of Nutrition Science and Food Management, Ewha Womans University, Seoul, Korea
[9]Graduate Program in System Health Science and Engineering, College of Medicine, Ewha Womans University, Seoul, Korea
[10]Graduate School of Pharmaceutical Sciences, College of Pharmacy, Ewha Womans University, Seoul, Korea
[11]Department of Sociology, Ewha Womans University, Seoul, Korea
[12]Department of Obstetrics and Gynecology, College of Medicine, Ewha Womans University, Seoul, Korea
[13]Department of Women's Studies, Ewha Womans University, Seoul, Korea
[14]College of Nursing, Ewha Womans University, Seoul, Korea
[15]Institute of Ewha-SCL for Environmental Health (IESEH), College of Medicine, Ewha Womans University, Seoul, Korea

*These authors contributed equally to this work.

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**Corresponding author**
Eunhee Ha
Department of Environmental Medicine, College of Medicine, Graduate Program in System Health Science and Engineering, Ewha Womans University, 260 Gonghang-daero, Gangseo-gu, Seoul 07804, Korea
Tel: 82-2-6986-6234
Fax: 82-2-6986-7022
E-mail: eunheeha@ewha.ac.kr

**Key Words**
Child health; Environmental health; Environmental exposure; Environmental pollution; Environment and public health

**Objectives:** To conduct a comparative study of children's health in South Korea versus North Korea focusing on air pollution.

**Methods:** We used annual mortality rate, prevalence, and environmental indicators data from the World Bank and World Health Organizations (WHO). Trend analysis of the two Koreas was conducted to evaluate changes in health status over time. Spearman's correlation analysis was used to find out the correlation between environmental indicators and children's health status.

**Results:** We found a distinct gap in children's health status between the two Koreas. While North Korea reported a higher death rate of children than South Korea, both showed a decreasing trend with the gap narrowing from 2000 to 2017. The prevalence of overweight and obesity increased and that of thinness decreased in both Koreas. Except $PM_{2.5}$ exposure, South Korea reported higher figures in most indicators of air pollutant emissions (South Korea, mean (SD)=28.3 (2.0); North Korea, mean (SD)=36.5 (2.8), P-value=0.002).

**Conclusion:** This study empirically discovered the gaps and patterns of children's health between South Korea and North Korea. North Korean children experienced more severe health outcomes than children in South Korea. These findings imply that epigenetic modification caused by environmental stressors affect children's health in the two Koreas despite similar genetic characteristics. Considering the gaps in children's health between the two Koreas, more attention and resources need to be directed towards North Korea because the necessary commodities and services to improve children's health are lacking in North Korea.

## Introduction

Children's health is an important theme in public health since its impact covers the life-course from childhood to adulthood. Children have a unique vulnerability to health-related issues and harmful exposures compared to adults [1,2]. Since young children go through rapid growth and development, their metabolism is immature and more vulnerable to environmental stressors [2]. Environmental exposures affect children's health and create a larger burden of diseases, including respiratory diseases (e.g., acute lower respiratory infection [ALRI], pneumonia, and asthma) [1,3,4]. Environmental exposure is known as an important determinant of health in both developed and developing countries, although the patterns of exposure vary [3]. Existing literature discusses the effect of environmental exposure on children's health, which causes a larger burden of diseases [4]. Previous epidemiological studies have reported the association between air pollution exposure and mortality in children under 5 years [5–8]. Health risks caused by air pollution have a great impact in low- and middle-income countries [3,9]. People in wealthier nations may be healthier since economic prosperity allows them to spend more on personal health, leading to better health outcomes [10]. However, economic development has led to a higher level of environmental pollution which damages people's health [11]. We thus argue that environmental exposure is an important determinant of health.

Another body of literature emphasizes the importance of epigenetic modifications caused by environmental stressors such as air pollutants, particulate matter, and metal exposure, thereby affecting children's health [12–14]. Epigenetic change considers genetics as a factor but puts greater emphasis on environmental circumstances that modify one's health [14]. A comparative study of the Republic of Korea (hereafter referred to as South Korea) and the Democratic People's Republic of Korea (hereafter referred to as North Korea) presents a unique opportunity to compare the effects of a shared genetic background versus epigenetic modifications caused by environmental stressors [12,13].

There are few empirical studies on North Korean children's health, despite the ample media reports of widespread malnutrition and infectious diseases. South Korea and North Korea have been isolated from each other due to the politics of the Korean War and the Cold War dynamics on the Korean Peninsula. Such separation from each other while sharing the same ethnicity and early history provides a rich ground for comparative research. However, there are few comparative studies on children's health in these two countries. There are two pertinent points of comparison in this research. First is the impact of the "North Korean Famine (1995–1998)" or "the Arduous March," which has resulted in children's widespread malnutrition and stunting. South Korea did not suffer from famine or malnutrition during the same period. A second point is the remarkably different environmental circumstances due to the different pace and level of economic development.

South Korea and North Korea have been divided since 1945 and their division has solidified after the Korean War in 1950–1953 [15]. Over 7 decades, they have experienced different political regimes and socio-economic development. We assume that the health status of children is conspicuously different between South Korea and North Korea due to socioeconomic, cultural, and environmental factors. Based on this assumption, we hypothesize that harmful environmental circumstances exacerbate the gap in children's health in the two Koreas. Thus, this study aims to analyze the differences in children's health status and the correlation between the environment and children's health in South Korea and North Korea to answer three research questions: (1) How different is the general status of children's health between South Korea and

North Korea, and how has the gap changed over time? (2) What are the disease patterns of children in the two Koreas? and (3) How much do the environmental factors affect children's health in South Korea and North Korea? The comparative analysis will provide interesting findings since many variables have been held constant due to the division. The comparative analysis will help identify the patterns of, and gaps in, children's health in South Korea and North Korea from the perspective of environmental influences on disease patterns across countries of varying levels of economic development.

A comparative study of children's health in South Korea versus North Korea is important for three reasons. First, it can provide a rich comparative analysis of the effect of the environment on children's health with many important health factors held constant. Second, this study will help delineate how a developed, as opposed to a developing, country's environmental factors change as a result of economic progress. Finally, it can contribute as a preparatory study to the understanding of children's health status of the two Koreas to prevent and minimize social disturbances that can be caused by reunification.

## Method

### 1. Data source

We used estimated data for North Korea since the country does not provide official statistics on environmental and health measurements. We utilized data provided by international organizations (for details of data source, see the appendix [Table S1]). The collected (ecological) data are from 2000 to 2017 and included two strands of indicators: (1) environmental indicators and (2) children's health status (mortality rate, prevalence). The collected data were published by the World Bank and the World Health Organization (WHO) [16,17]. Environmental indicators include fine particulate matter ($PM_{2.5}$) exposure and air pollutant emissions, including gas emissions and fossil fuels. In the supplementary material, we provide annual population characteristics and medical and nutritional status collected from the United Nations Children's Fund (UNICEF), Energy Information Administration (EIA), World Bank, Organisation for Economic Co-operation and Development (OECD), and Korea Statistical Information Service. We categorized the indicators of children's health status into four categories: reproductive health, respiratory disease, chronic disease, and nutritional disease.

### 2. Air pollution indicators

The annual mean $PM_{2.5}$ concentration estimates were derived from the Global Burden of Disease study [18–20]. These data are estimates of the population-weighted average exposure and a general air quality indication to inform cross-country comparisons of health risks. The population estimation data are based on the Gridded Population of the World by NASA Socioeconomic Data and Applications Center (version 4). The detailed description of the exposure estimates is based on previous studies of global estimates of air pollution and environmental risks [18–20]. The emission data include carbon dioxide ($CO_2$), nitrous oxide ($N_2O$), methane, and fossil fuel information.

### 3. Outcome indicators

Children's health indicators consist of two types: (1) annual children's mortality rate (infant, stillbirth, neonatal, under-five, ALRI), congenital anomalies, prematurity, birth asphyxia, diarrheal disease, meningitis/encephalitis, sepsis and other infections) and (2) prevalence (anemia,

overweight, obesity, thinness). Infant mortality, stillbirth, and neonatal mortality were calculated as deaths per 1,000 live births (0–4 years old). Mortality of under–five, ALRI, congenital anomalies, prematurity, birth asphyxia, diarrheal disease, meningitis/encephalitis, sepsis and other infections was calculated as deaths per 1,000 children (0–4 years old). We used data on the prevalence of anemia in children under 5 years of age and that of overweight, obesity, and thinness in children 5–9 years of age. Here, overweight is defined as the Body Mass Index (BMI) exceeding +1 SD above the median, obesity as the BMI exceeding +2 SD above the median, and thinness means as a BMI is below median -2 SD.

### 4. Statistical analysis

We performed two analyses to examine how South Korea and North Korea are differently situated after the "North Korean Famine" in terms of air pollution and health status. First, we compared descriptive statistics for South Korea and North Korea. Second, we performed trend analysis to observe how children's health status in South Korea and North Korea has changed over time.

As the children's health indicator data were estimated annually, we focused on observing the changes per year. Overall, we considered three methods for trend analysis of children's health status: (1) Sen's slope, (2) Mann-Kendall trend test, and (3) linear regression. The first two methods are used to analyze the trends for non-parametric data. If the beta coefficient is greater than zero ($\beta > 0$), the data are considered to show a positive trend. When there are many missing values, the Mann-Kendall trend test can be used as a way to adjust missing data. This method validates significance by using Kendall's correlation coefficient.

We analyzed the correlation coefficient between environmental indicators and children's health status. Since our data spans from 2000 to 2017, the number of pair samples for health status is 18. As the sample number is too small to assume a specific distribution, we utilized Spearman's correlation based on the non-parametric method.

### 5. Sensitivity analysis

The sources of data in this study are international organizations. Since the data we use are secondary, a direct comparison between the two Koreas is limited. Thus, we cross-checked our results with the data reported by the OECD and the South Korean government (Statistics Korea) for sensitivity analysis [21,22]. This study also extracted North Korean data from the South Korean database (Statistics Korea).

## Results

Over a total span of 18 years (2000–2017), we found a distinct gap between South Korea and North Korea in two domains: (1) children's health status (mortality rate, prevalence) and (2) environmental indicators. Differences were observed despite similar demographic trends from 2000 to 2018 – growing population, increase in life expectancy, decrease in total fertility rate, and aging (Table 1).

The time-plots show the trends in children's annual mortality and prevalence in South Korea and North Korea, respectively (Figs. 1, 2). The results of the trend analysis are presented in the appendix (Table S2). Child mortality rates in South Korea and North Korea are decreasing, except for prematurity. While North Korea reported a higher death rate of children than South Korea, the gaps in children's mortality and their health status in both Koreas narrowed from 2000 to 2017

**Table 1.** Demographic characteristics of South Korea and North Korea

| Year | Population (1,000 people) | | Life expectancy (yr) | | | | | | Total fertility rate (births per 1,000 women) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | South Korea | North Korea | South Korea | | | North Korea | | | South Korea | North Korea |
| | | | Total | Male | Female | Total | Male | Female | | |
| 2000 | 47,008 | 22,702 | 76.0 | 72.3 | 79.7 | 65.3 | 61.2 | 69.0 | 1.48 | 1.99 |
| 2001 | 47,370 | 22,902 | 76.5 | 72.9 | 80.1 | 66.1 | 62.1 | 69.7 | 1.31 | 1.99 |
| 2002 | 47,645 | 23,088 | 76.8 | 73.4 | 80.3 | 66.9 | 63.0 | 70.4 | 1.18 | 1.99 |
| 2003 | 47,892 | 23,254 | 77.3 | 73.8 | 80.8 | 67.6 | 63.8 | 71.0 | 1.19 | 1.99 |
| 2004 | 48,083 | 23,411 | 77.8 | 74.3 | 81.2 | 68.1 | 64.3 | 71.5 | 1.16 | 1.98 |
| 2005 | 48,185 | 23,561 | 78.2 | 74.9 | 81.6 | 68.4 | 64.7 | 71.7 | 1.09 | 1.98 |
| 2006 | 48,438 | 23,707 | 78.8 | 75.4 | 82.1 | 68.5 | 64.8 | 71.8 | 1.13 | 1.97 |
| 2007 | 48,684 | 23,849 | 79.2 | 75.9 | 82.5 | 68.7 | 65.0 | 72.0 | 1.26 | 1.96 |
| 2008 | 49,055 | 23,934 | 79.6 | 76.2 | 83.0 | 68.9 | 65.3 | 72.2 | 1.19 | 1.95 |
| 2009 | 49,308 | 24,062 | 80.0 | 76.7 | 83.4 | 69.2 | 65.6 | 72.5 | 1.15 | 1.94 |
| 2010 | 49,554 | 24,187 | 80.2 | 76.8 | 83.6 | 69.6 | 66.0 | 72.9 | 1.23 | 1.94 |
| 2011 | 49,937 | 24,308 | 80.6 | 77.3 | 84.0 | 70.0 | 66.4 | 73.3 | 1.24 | 1.93 |
| 2012 | 50,200 | 24,427 | 80.9 | 77.6 | 84.2 | 70.5 | 66.8 | 73.8 | 1.30 | 1.93 |
| 2013 | 50,429 | 24,545 | 81.4 | 78.1 | 84.6 | 70.9 | 67.2 | 74.2 | 1.18 | 1.93 |
| 2014 | 50,747 | 24,662 | 81.8 | 78.6 | 85.0 | 71.2 | 67.6 | 74.5 | 1.21 | 1.93 |
| 2015 | 51,015 | 24,779 | 82.1 | 79.0 | 85.2 | 71.5 | 67.8 | 74.9 | 1.24 | 1.92 |
| 2016 | 51,218 | 24,897 | 82.4 | 79.3 | 85.4 | 71.7 | 68.1 | 75.1 | 1.17 | 1.92 |
| 2017 | 51,362 | 25,014 | 82.7 | 79.7 | 85.7 | 71.9 | 68.3 | 75.3 | 1.05 | 1.91 |
| Average (SD) | 49,229.4 (1,394.1) | 23,960.5 (702.7) | 79.6 (2.1) | 76.2 (2.3) | 82.9 (2.0) | 69.2 (1.9) | 65.4 (2.1) | 72.5 (1.9) | 1.2 (0.1) | 2.0 (0.0) |
| Sen's slope (95% CI) | 260.3 (253, 272.9) | 125.3 (120.0, 134.7) | 0.4 (0.4, 0.4) | 0.4 (0.4, 0.4) | 0.4 (0.3, 0.4) | 0.3 (0.3, 0.4) | 0.4 (0.3, 0.4) | 0.3 (0.3, 0.4) | 0.00 (−0.02, 0.01) | 0.00 (−0.01, −0.00) |
| Mann-Kendall statistics | 5.8 (P–value <0.001) | 5.8 (P–value <0.001) | 5.8 (P–value <0.001) | 5.8 (P–value <0.001) | 5.8 (P–value <0.001) | 5.8 (P–value <0.001) | 5.8 (P–value <0.001) | 5.8 (P–value <0.001) | −0.8 (P–value: 0.425) | −5.3 (P–value: <0.001) |
| β (Slope) (95% CI)* | 260.6 (252.5, 268.7) | 131.2 (125.9, 136.5) | 0.4 (0.4, 0.4) | 0.4 (0.4, 0.4) | 0.4 (0.3, 0.4) | 0.4 (0.3, 0.4) | 0.4 (0.3, 0.4) | 0.3 (0.3, 0.4) | 0.01 (−0.02, 0.00) | 0.00 (−0.01, 0.00) |

*The slope coefficient for simple linear regression.

(Fig. 1). In particular, North Korean children recorded a sharp decline in mortality rate indicators, especially after 2005.

The prevalence of overweight and obesity has increased and that of thinness decreased in both Koreas (Fig. 2). While South Korean children showed an increasing prevalence of anemia, North Korean children decreased and then increased again in North Korean children after 2009. For North Korean children under the age of 5 years who had anemia, a U–shaped pattern was observed since it decreased in the early 2000s and then increased after 2008 (Fig. 2).

We discovered differences in environmental indicators between the two Koreas. Except for $PM_{2.5}$ exposure, South Korea recorded much higher figures than North Korea in most indicators of air pollutant emissions such as $CO_2$, $N_2O$, and methane emissions (Table 2 and Fig. S1). An interesting finding is that $PM_{2.5}$ concentration estimates were higher in North Korea than in

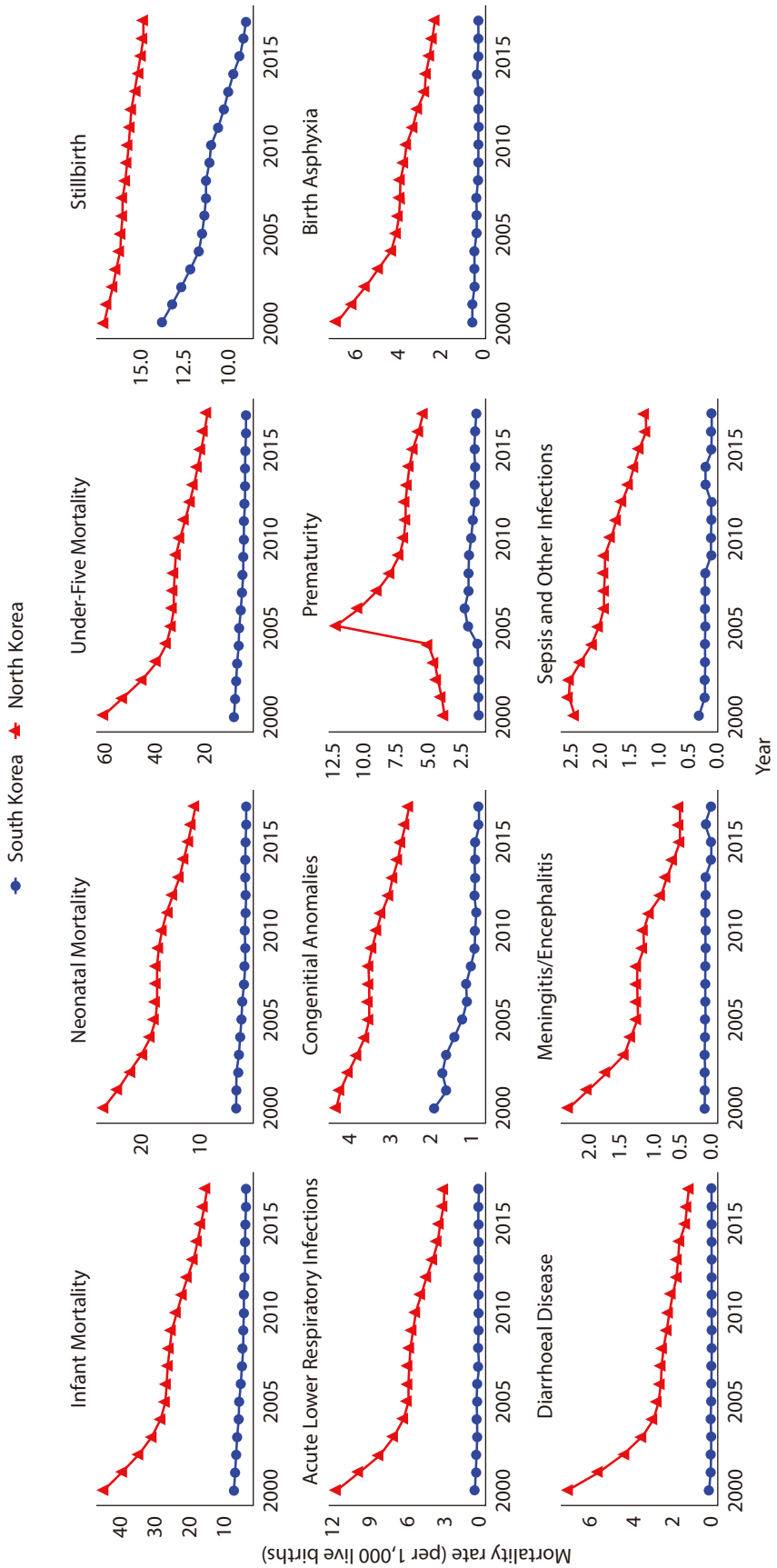


**Fig. 1.** Trends in children's health (mortality) in South Korea and North Korea. The red line stands for children's health status (mortality, per 1,000 live births) in North Korea and the blue line for South Korea.


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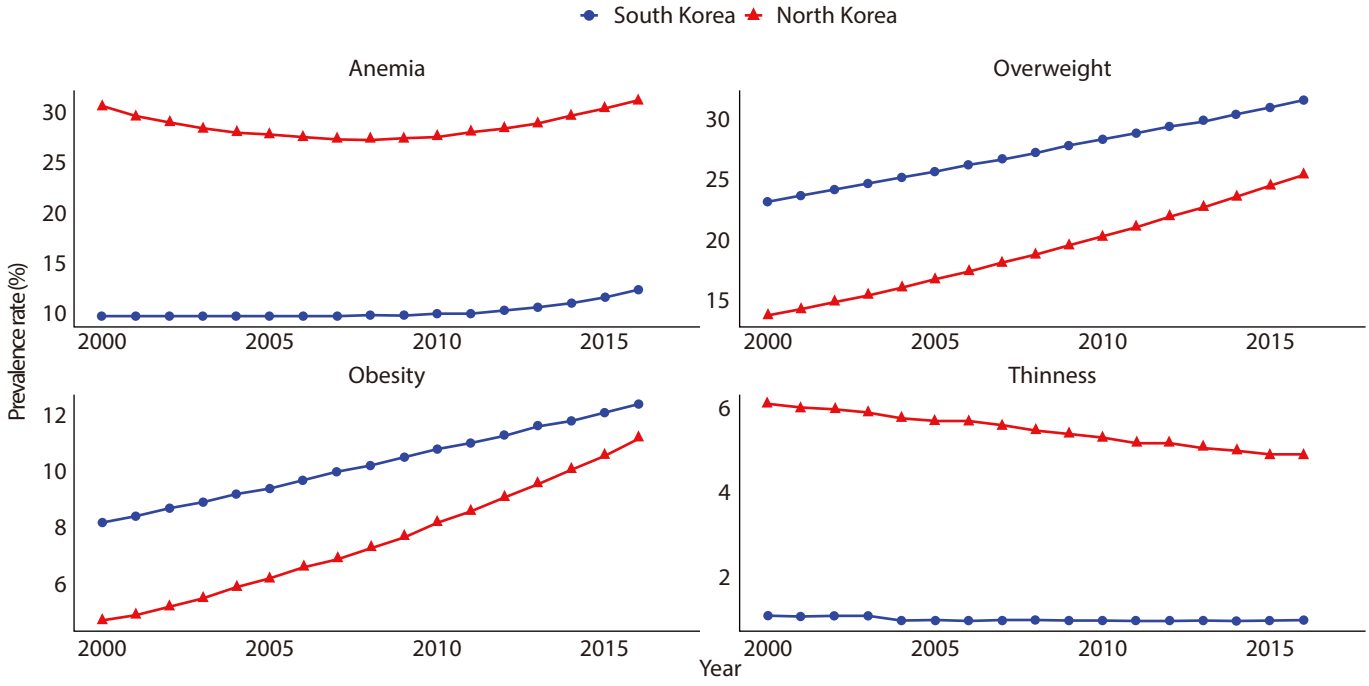


**Fig. 2.** Trends in children's health (prevalence) in South Korea and North Korea. The red line stands for children's health status (prevalence, %) in North Korea and the blue line for South Korea.

South Korea. North Korea is faced with the danger of high $PM_{2.5}$ concentration which is known to increase the risk of children's ALRI.

Given the differences in environmental indicators between South Korea and North Korea, we examined the association between the environment and children's health. $PM_{2.5}$ showed a positive relationship with infant and child mortality indicators and a negative relationship with the prevalence of anemia, overweight, and obesity in the two Koreas (Fig. 3). In the Poisson regression model, North Korea's $PM_{2.5}$ exposure concentrations were related to infant mortality (% increase: 9.07, 95% confidence interval [CI]: 3.06, 15.44), neonatal mortality (% increase: 7.50, 95% CI: 0.52, 14.97), and under-five mortality (% increase: 8.67, 95% CI: 3.44, 14.17). Meanwhile, the correlation of $CO_2$, $N_2O$, and fossil fuel emissions with health effects varied between the two Koreas. It is positive in North Korea, while South Korea has a negative or no correlation.

## Discussion

There is a large gap in children's health status between South Korea and North Korea. Children living in North Korea experienced more severe health outcomes than those in South Korea. The death rate of prematurity, congenital anomalies, and birth asphyxia is higher in North Korea, which indicates that newborns in North Korea are more susceptible to these diseases than their South Korean counterparts. This trend has continued albeit with a decreasing rate over time. The time-plot of infant mortality rate during the North Korean famine is provided in the supplementary appendix (Figs. S2 and S3).

While South Korea recorded higher figures in air pollutant emissions such as $CO_2$, $N_2O$, and methane than North Korea, $PM_{2.5}$ concentration estimates are higher in North Korea (Table 2). Although both Koreas are affected by air pollution, including fine particulate matters and dust


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**Table 2.** Comparison of environmental indicators in South Korea and North Korea

| | South Korea | | | North Korea | | | P–value |
|---|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD | |
| Environmental indicator | | | | | | | |
| $PM_{2.5}$ (μg/m³) | 10 | 28.3 | 2 | 10 | 36.5 | 2.8 | 0.002 |
| $CO_2$ emissions (metric tons per capita) | 17 | 10.6 | 1 | 17 | 2.3 | 0.9 | <0.001 |
| $N_2O$ emissions (thousand metric tons of $CO_2$ equivalent) | 13 | 14,338.0 | 1,996.8 | 13 | 3,286.2 | 74.8 | <0.001 |
| Methane emissions (kt of $CO_2$ equivalent) | 13 | 31,680.5 | 703.4 | 13 | 18,390.4 | 671.1 | <0.001 |
| Fossil fuel (% of total) | 16 | 82.4 | 1.2 | 15 | 79.5 | 13.1 | 0.421 |

P-value by Wilcoxon's sign rank test.

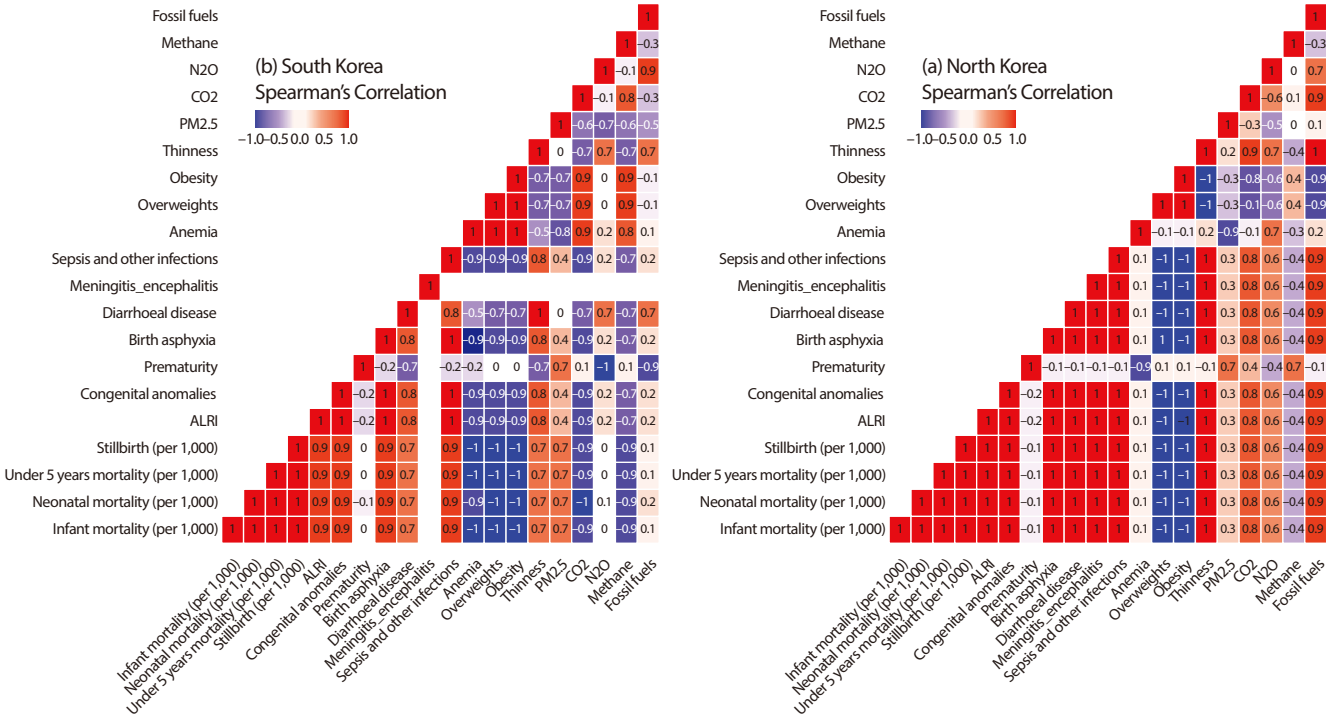


**Fig. 3.** Correlation between air pollution exposure and children's health in South Korea and North Korea.

flying from China, North Korea showed a higher rate of $PM_{2.5}$ concentration estimates than South Korea. We speculate that North Korea's use of cooking and heating fuel with low combustion rate and low thermal efficiency, as well as low-quality coal, has resulted in a higher exposure to $PM_{2.5}$ (Fig. S4). North Korea's use of ineffective domestic fuel is likely to release particulate matter and increase the level of $PM_{2.5}$ concentration over that in South Korea [23]. Fossil fuels, particularly coal and heavy oil, in thermal power plants, industrial boilers, kilns, motor cars, and households are the major pollutants in the largest city of North Korea (Pyongyang) and in nearby industrial districts [24].


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We also found a gap in prevalence indicators between the two Koreas. The prevalence of anemia, overweight, obesity, and thinness is lagged for estimation, and North Korean children are faced with a greater danger of anemia and thinness while those in South Korea experience a higher prevalence of overweight and obesity. More interestingly, the prevalence of overweight and obesity is increasing and that of thinness is decreasing in both Koreas. This trend in prevalence indicators is probably caused by nutritional factors rather than air pollution. The previous study on North Korean refugee children residing in South Korea showed that the gap in growth (height and weight) and obesity rates between South Korean and North Korean children was narrowed after consuming sufficient food [25]. The nutritional status of South Korean and North Korean is provided in the appendix (Table S3 and Fig. S5). It implies that poor nutritional intake in North Korea has led to the children's malnutrition causing anemia and thinness, while the higher prevalence of overweight and obesity in South Korea is most likely caused by a Westernized dietary pattern, which contains high amounts of saturated fatty acids and energy-dense foods that are poor in micronutrients.

The differences in environmental indicators such as air pollutant emissions between South Korea and North Korea created gaps in the children's health status. The higher emissions of environmental pollutants, including $PM_{2.5}$, serve as a trigger for increasing the incidence of respiratory diseases (ALRI, pneumonia, and asthma) [4]. This relationship was supported by another study showing that long-term exposure to ambient fine particulate matter ($PM_{2.5}$) is inversely associated with lung function in children, adolescents, and young adults [26]. In addition to air pollutants, lead is more noxious to children than adults [27]. In particular, anemia is observed in young children who have lead poisoning [27]. Iron deficiency anemia is a risk factor for lead toxicity, as it not only promotes pica behavior but also increases the absorption of lead from the gastrointestinal tract [28]. Lead exposure and nutritional deficiencies, which are prevalent in North Korea, put children in danger of growth retardation and behavioral challenges. For instance, the active use of inefficient cooking and heating fuel such as a tire close to the furnace increases the level of lead exposure among North Korean children. North Korean children have a higher risk of respiratory infections caused by indoor air pollution from low-quality fuels.

Further, this study found an interesting pattern in diseases between South Korea and North Korea. The two Koreas have been isolated from each other since 1945, sharing the same ethnicity and similar genetic characteristics (Fig. S6). The different environmental circumstances for over 7 decades since the division have led to very different disease characteristics. North Korean children suffer from infectious diseases such as parasite infection, tuberculosis, lower respiratory tract infections, acute infectious diarrhea, malaria, meningitis, and sepsis. Infectious diseases are prevalent in North Korea due to poor conditions – pollution of drinking water (Figs. S7 and S8), weak management of vaccination, and unavailability of antibiotics. In contrast, pediatric allergic, autoimmune, and metabolic diseases are prevalent among South Korean children. The so-called "hygiene hypothesis" explains this by assuming that microbes such as bacteria stimulate the immune response and the too-clean environmental and hygienic conditions decrease immunity so that people can be more susceptible to allergies and autoimmune diseases [29,30]. As immune polarization caused by different environmental stressors exists in South Korea and North Korea, the disease patterns are different [14,31,32]. The disease pattern of North Korean children is similar to that of developing countries, whereas the disease pattern of South Korean children is similar to that of developed countries, as illustrated in the appendix based on the mortality rate and prevalence of each disease (Figs. S9–S12).

This study offers two key contributions. First, the study examines the gap in children's health


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between South Korea and North Korea, explores the association between the environment and children's health, and finds the disease patterns of South Korea and North Korea to be similar to the differences found between developed and developing countries. While there have been few studies comparing the children's health status between South Korea and North Korea, this study empirically highlighted the differences and patterns of children's health, which helps to fill the lacunae in the children's health studies. Second, this study is meaningful in that it compared children's health status and environmental circumstances between South Korea and North Korea after the two were forcibly divided in 1945 and further distanced by a war between the two in 1950¬–1953. The two countries in the Korean Peninsula provide an interesting test-bed for a rich comparative analysis as a social experiment to examine how South Korea and North Korea have evolved for over 7 decades since the division in terms of the environment and children's health.

Our findings should be interpreted, however, in light of data limitations. First, official data on North Korean health, environment, or nutrition are not available. Therefore, we used data collected from multiple international organizations including the World Bank and WHO. Second, we cannot determine a direct relationship between air pollution exposure and health effects in South Korea and North Korea due to data constraints. To overcome this, we conducted comparative and trend analyses. The differences in mortality and morbidity of children in the two Koreas might be caused by socioeconomic and cultural factors, as well as environmental factors. Thus, it would be necessary to secure national data for precise research to improve North Korean children's health. Therefore, more reliable data sources representing a larger sample or that enable longitudinal studies such as cohort studies are needed. Third, it is difficult to access prevalence indicators since their availability is limited compared to mortality indicators. Lastly, the dataset does not consider regional disparities within North Korea. It would be important to identify regional differences to help reduce the health status gaps among different regions.

Considering the patterns and gaps in children's health between South Korea and North Korea, more attention and resources need to be directed towards North Korea. The current health status of North Korean children needs intensive international development cooperation because the necessary commodities and services to improve the health of children are lacking in North Korea (Fig. S13). Although the governments of South Korea and North Korea have not had a Summit since 2018, there is hope that future official summits between South Korea and North Korea, and with other countries including the US could open doors for cooperation and unification. Should North Korea become open to international development cooperation, South Korea can play an important role in assisting North Korea although its assistance cannot be counted toward foreign aid as the two do not recognize each other as separate countries. Nevertheless, South Korea's shared ethnicity, language, culture, and geographical proximity would be very useful to assist the international efforts for development cooperation in North Korea.

These findings imply that epigenetic modification resulting from environmental stressors has had an impact on children's health in South Korea and North Korea despite sharing similar genetic backgrounds. After the division of the Korean Peninsula, different environmental circumstances modified children's health in the two Koreas, with genetics held constant. Considering the effect of epigenetic modification caused by environmental factors, it would be vital to develop a strategy for improving public health, especially targeting North Korean children if and when unification occurs. In particular, there is a danger that infectious diseases can spread quickly in South Korea and North Korea since people across the Korean Peninsula have not been exposed to each other for a long time. It is likely that infectious diseases such as measles, tuberculosis, malaria, and parasite infection, which are common in North Korea, can spread to

South Korea, while other infectious diseases and socially driven illnesses from South Korea can spread to North Korea [33]. As South Korea established a relatively stronger health infrastructure than North Korea (Table S4), advances in the health care system can contribute to reducing the mortality rate. Thus, access to optimal management and referral systems at the primary care level, stable supply of nutrients, and removing economic barriers in North Korea would be crucial. Based on the children's disease patterns of South Korea and North Korea found in this study, it is projected that infectious diseases will become more prevalent if we do not have preventive measures. Given the significant differences in children's health between South Korea and North Korea which have persisted for more than 7 decades, it is imperative to bridge this gap.

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### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### ORCID iD

Yoorim Bang: https://orcid.org/0000-0003-2128-7947
Jongmin Oh: https://orcid.org/0000-0002-2980-6943
Eun Mee Kim: https://orcid.org/0000-0002-1649-0759
Ji Hyen Lee: https://orcid.org/0000-0002-2234-1055
Minah Kang: https://orcid.org/0000-0002-5262-286X
Miju Kim: https://orcid.org/0000-0002-4563-0634
Seok Hyang Kim: https://orcid.org/0000-0002-7091-5105
Jae Jin Han: https://orcid.org/0000-0002-6499-7642
Hae Soon Kim: https://orcid.org/0000-0002-6976-6878
Oran Kwon: https://orcid.org/0000-0002-2031-7238
Hunjoo Ha: https://orcid.org/0000-0002-5601-1265
Harris Hyun-soo Kim: https://orcid.org/0000-0003-1311-6507
Hye Won Chung: https://orcid.org/0000-0002-6162-9158
Eunshil Kim: https://orcid.org/0000-0001-5984-7802
Young Ju Kim: https://orcid.org/0000-0002-3153-3008
Yuri Kim: https://orcid.org/0000-0001-7606-8501
Younhee Kang: https://orcid.org/0000-0002-7964-5674
Eunhee Ha: https://orcid.org/0000-0002-4224-3858

### Author Contribution

Conceptualization: Bang Y, Lee JH, Kang M
Formal Analysis: Ha H, Kim E, Kim YJ, Kim Y, Kang Y
Investigation: Kim M, Kim SH, Han JJ, Kim HS, Kwon O, Chung HW
Methodology: Kim HH, Oh J
Project Administration: Kim EM, Ha E
Writing – Original Draft: Bang Y, Oh J, Kim EM, Ha E
Writing – Review & Editing: Bang Y, Oh J, Kim EM, Lee JH, Kang M, Kim M, Kim SH, Han JJ, Kim HS, Kwon O, Ha H, Kim HH, Chung HW, Kim E, Kim YJ, Kim Y, Kang Y, Ha E

### Ethics Approval and Consent to Participate

Not applicable.

### Supplementary Materials

Supplementary materials are available from: https://doi.org/10.12771/emj.2022.e14.

Supplementary Table S1. Description of data characteristics

Supplementary Table S2. The analysis of children's health indicators in South Korea and North Korea from 2000 to 2017
Supplementary Table S3. The daily nutrition per person in South Korea and North Korea from 1990 to 2017
Supplementary Table S4. The number of doctors in South Korea and North Korea

Supplementary Fig. S1. The average annual concentration of $PM_{2.5}$ in South Korea and North Korea from 2015 to 2019.
Supplementary Fig. S2. The estimation of birth losses and excess deaths during the North Korean famine from 1994 to 2005.
Supplementary Fig. S3. The time–plot of annual infant mortality rates in South Korea and North Korea from 1990 to 2019.
Supplementary Fig. S4. Coal consumption in South Korea and North Korea from 2000 to 2017.
Supplementary Fig. S5. The undernourished population of South Korea and North Korea.
Supplementary Fig. S6. Major historical events in the Korean Peninsula from 1970 to 2020.
Supplementary Fig. S7. Quality of source drinking water in North Korea in 2017.
Supplementary Fig. S8. Quality of household drinking water in North Korea in 2017.
Supplementary Fig. S9. Disease pattern of North Korea with developing countries (mortality rate per 1,000 live births).
Supplementary Fig. S10. Disease pattern of North Korea with developing countries (prevalence (%)).
Supplementary Fig. S11. Disease pattern of South Korea with developed countries (mortality rate per 1,000 live births).
Supplementary Fig. S12. Disease pattern of South Korea with developed countries (prevalence (%)).
Supplementary Fig. S13. History of health and medical care policy in North Korea from 1970 to 2020.

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# Supplementary Appendix

# List of Supplementary Tables and Figures

## Supplementary Tables



## Supplementary Figures

**Table S1.** Description of data characteristics

| | Name | Definition | Age | Data source |
|---|---|---|---|---|
| Indicator | | | | |
| Mortality rate (per 1,000 live births) | Infant mortality | The number of infants dying before reaching one year of age, per 1,000 live births in a given year. | 0–4 years old | WHO |
| | Stillbirth | The number of babies born with no signs of life at 28 weeks or more of gestation, per 1,000 total births. | | |
| | Neonatal mortality | The number of neonates dying before reaching 28 days of age, per 1,000 live births in a given year. | | |
| | Under 5 years mortality | The probability per 1,000 that a newborn baby will die before reaching age five, if subject to age-specific mortality rates of the specified year. | | |
| | Acute lower respiratory infections | The number of deaths from acute lower respiratory infections, per 1,000 live births. | | |
| | Congenital anomalies | The number of deaths from structural or functional anomalies that occur during intrauterine life, per 1,000 live births. | | |
| | Prematurity | The number of deaths of babies born alive before 37 weeks of pregnancy, per 1,000 live births. | | |
| | Birth asphyxia | The number of deaths from the failure to establish breathing at birth, per 1,000 live births. | | |
| | Diarrheal disease | The number of deaths from the passage of three or more loose or liquid stools per day (or more frequent passage than is normal for the individual), per 1,000 live births. | | |
| | Meningitis/Encephalitis | The number of deaths from a serious infection of the meninges or inflammation of the brain caused by any one of a number of viruses, per 1,000 live births. | | |
| | Sepsis and other infections | The number of deaths from a organ dysfunction caused by a dysregulated host response to infection, per 1,000 live births. | | |
| Prevalence (%) | Anemia | The prevalence of anemia in children under 5 years. | 0–4 years old | WHO |
| | Overweight | The prevalence of overweight among children and adolescents, BMI > +1 standard deviations above the median. | 5–9 years old | |
| | Obesity | The prevalence of obesity among children and adolescents, BMI > +2 standard deviations above the median. | | |
| | Thinness | The prevalence of thinness among children and adolescents, BMI < -2 standard deviations below the median. | | |

**Table S2.** The analysis of children's health indicators in South Korea and North Korea from 2000 to 2017

| Category | | Sen's slope | | | Mann-Kendall methods | | Linear regression | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Sen's slope | 95% CI | | Mann-Kendall statistics | P-value | Estimate | 95% CI | |
| Countries | | | | | | | | | |
| South Korea | Infant mortality | –0.21 | –0.26 | –0.16 | –5.76 | <0.001 | –0.21 | –0.24 | –0.19 |
| North Korea | | –1.28 | –1.50 | –1.10 | –5.76 | <0.001 | –1.46 | –1.70 | –1.23 |
| South Korea | Stillbirth | –0.10 | –0.14 | –0.07 | –5.43 | <0.001 | –0.10 | –0.13 | –0.08 |
| North Korea | | –0.75 | –0.88 | –0.63 | –5.76 | <0.001 | –0.78 | –0.89 | –0.68 |
| South Korea | Neonatal mortality | –0.25 | –0.30 | –0.20 | –5.76 | <0.001 | –0.25 | –0.28 | –0.22 |
| North Korea | | –1.53 | –1.86 | –1.32 | –5.76 | <0.001 | –1.91 | –2.29 | –1.53 |
| South Korea | Under 5 years mortality | –0.25 | –0.28 | –0.22 | –5.72 | <0.001 | –0.25 | –0.27 | –0.22 |
| North Korea | | –0.12 | –0.13 | –0.10 | –5.72 | <0.001 | –0.12 | –0.13 | –0.11 |
| South Korea | Acute Lower Respiratory Infections (mortality) | –0.01 | –0.02 | 0.00 | –3.94 | <0.001 | –0.01 | –0.02 | –0.01 |
| North Korea | | –0.33 | –0.40 | –0.29 | –5.72 | <0.001 | –0.41 | –0.49 | –0.33 |
| South Korea | Congenital anomalies (mortality) | –0.05 | –0.07 | –0.03 | –4.94 | <0.001 | –0.06 | –0.07 | –0.05 |
| North Korea | | –0.10 | –0.11 | –0.09 | –5.57 | <0.001 | –0.10 | –0.11 | –0.09 |
| South Korea | Prematurity (mortality) | 0.00 | –0.06 | 0.03 | 0.19 | 0.847 | 0.01 | –0.02 | 0.04 |
| North Korea | | –0.05 | –0.26 | 0.22 | –0.04 | 0.97 | 0.05 | –0.15 | 0.26 |
| South Korea | Birth asphyxia (mortality) | –0.02 | –0.03 | –0.01 | –3.86 | <0.001 | –0.02 | –0.02 | –0.01 |
| North Korea | | –0.20 | –0.24 | –0.17 | –5.72 | <0.001 | –0.23 | –0.27 | –0.19 |
| South Korea | Diarrheal disease (mortality) | 0.00 | 0.00 | 0.00 | –1.54 | 0.123 | 0.00 | 0.00 | 0.00 |
| North Korea | | –0.16 | –0.23 | –0.14 | –5.72 | <0.001 | –0.26 | –0.33 | –0.19 |
| South Korea | Meningitis/Encephalitis (mortality) | 0.00 | 0.00 | 0.00 | –2.37 | 0.018 | 0.00 | –0.01 | 0.00 |
| North Korea | | –0.09 | –0.10 | –0.07 | –5.43 | <0.001 | –0.09 | –0.11 | –0.08 |
| South Korea | Sepsis and other infections (mortality) | –0.01 | –0.01 | 0.00 | –3.05 | 0.002 | –0.01 | –0.01 | 0.00 |
| North Korea | | –0.08 | –0.09 | –0.07 | –5.34 | <0.001 | –0.08 | –0.09 | –0.07 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| South Korea | Anemia (prevalence) | 0.08 | 0.03 | 0.15 | 4.64 | <0.001 | 0.12 | 0.08 | 0.17 |
| North Korea | | 0.05 | –0.13 | 0.22 | 0.46 | 0.649 | 0.05 | –0.08 | 0.17 |
| South Korea | Overweight (prevalence) | 0.53 | 0.52 | 0.53 | 5.56 | <0.001 | 0.53 | 0.53 | 0.54 |
| North Korea | | 0.74 | 0.70 | 0.78 | 5.56 | <0.001 | 0.74 | 0.72 | 0.77 |
| South Korea | Obesity (prevalence) | 0.26 | 0.26 | 0.27 | 5.56 | <0.001 | 0.26 | 0.26 | 0.27 |
| North Korea | | 0.40 | 0.37 | 0.44 | 5.56 | <0.001 | 0.41 | 0.39 | 0.43 |
| South Korea | Thinness (prevalence) | 0.00 | –0.01 | 0.00 | –2.89 | 0.004 | –0.01 | –0.01 | 0.00 |
| North Korea | | –0.08 | –0.08 | –0.08 | –5.42 | <0.001 | –0.08 | –0.08 | –0.08 |

**Table S3.** The daily nutrition per person in South Korea and North Korea from 1990 to 2017

| | South Korea | | | North Korea | | | South Korea | | | North Korea | | | South Korea | | | North Korea | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total Calorie (Kcal) | Plant calories (Kcal) | Animal calories (Kcal) | Total Calorie (Kcal) | Plant calories (Kcal) | Animal calories (Kcal) | Total protein (g) | Plant protein (g) | Animal protein (g) | Total protein (g) | Plant protein (g) | Animal protein (g) | Total fat (g) | Plant fat (g) | Animal fat (g) | Total fat (g) | Plant fat (g) | Animal fat (g) |
| Year | | | | | | | | | | | | | | | | | | |
| 1990 | 2,853 | 2,457 | 395 | 2,370 | 2,135 | 235 | 89.3 | 56.1 | 33.2 | 75.72 | 59.01 | 16.71 | 72.2 | 46.7 | 25.5 | 46.24 | 28.58 | 17.65 |
| 1991 | 2,876 | 2,506 | 370 | 2,368 | 2,136 | 233 | 88.6 | 56.2 | 32.4 | 74.37 | 59.08 | 15.29 | 71.7 | 48.6 | 23 | 45.89 | 27.77 | 18.13 |
| 1992 | 2,912 | 2,514 | 398 | 2,222 | 2,042 | 181 | 90.1 | 56.5 | 33.6 | 68.05 | 55.48 | 12.57 | 73.6 | 48.2 | 25.4 | 38.77 | 25.09 | 13.68 |
| 1993 | 2,872 | 2,464 | 408 | 2,276 | 2,115 | 161 | 91.7 | 56.2 | 35.5 | 66.73 | 54.91 | 11.82 | 74.1 | 48.6 | 25.5 | 38.45 | 26.55 | 11.91 |
| 1994 | 2,950 | 2,534 | 416 | 2,246 | 2,105 | 141 | 94.5 | 58.1 | 36.4 | 64.89 | 54.98 | 9.9 | 77.3 | 51.2 | 26.1 | 37.25 | 26.66 | 10.59 |
| 1995 | 2,959 | 2,520 | 439 | 2,103 | 1,981 | 122 | 96.9 | 57.6 | 39.3 | 59.28 | 50.79 | 8.49 | 76.9 | 50.6 | 26.4 | 35.51 | 26.29 | 9.22 |
| 1996 | 2,948 | 2,495 | 453 | 2,080 | 1,968 | 112 | 98 | 56.8 | 41.1 | 58.46 | 50.53 | 7.93 | 77.7 | 51 | 26.8 | 32.66 | 24.31 | 8.35 |
| 1997 | 2,957 | 2,525 | 431 | 2,133 | 2,041 | 92 | 97 | 56.8 | 40.2 | 58.79 | 52.1 | 6.7 | 79.6 | 54.7 | 24.9 | 33.7 | 26.95 | 6.75 |
| 1998 | 2,819 | 2,416 | 404 | 2,121 | 2,012 | 108 | 93.6 | 56.2 | 37.4 | 57.43 | 50.18 | 7.25 | 72.8 | 49.3 | 23.5 | 32.59 | 24.32 | 8.27 |
| 1999 | 2,968 | 2,526 | 442 | 2,112 | 1,990 | 122 | 98.2 | 57.4 | 40.8 | 57.49 | 49.61 | 7.88 | 82.5 | 56.8 | 25.6 | 31.72 | 22.2 | 9.52 |
| 2000 | 3,010 | 2,579 | 431 | 2,147 | 2,014 | 132 | 97.1 | 55.9 | 41.2 | 61.15 | 52.36 | 8.78 | 80.1 | 55.9 | 24.1 | 35.82 | 25.6 | 10.23 |
| 2001 | 3,000 | 2,538 | 462 | 2,096 | 1,953 | 143 | 98.3 | 53.6 | 44.7 | 58.87 | 49.03 | 9.85 | 83.9 | 58.2 | 25.6 | 35.39 | 24.51 | 10.88 |
| 2002 | 2,991 | 2,515 | 477 | 2,182 | 2,022 | 159 | 98.5 | 52.6 | 45.8 | 62.11 | 51.75 | 10.36 | 85.2 | 58.7 | 26.5 | 37.43 | 25 | 12.43 |
| 2003 | 2,919 | 2,452 | 467 | 2,189 | 2,040 | 150 | 97.6 | 51.5 | 46.1 | 59.42 | 49.78 | 9.64 | 83.1 | 57.5 | 25.6 | 36.55 | 24.82 | 11.73 |
| 2004 | 2,990 | 2,524 | 466 | 2,206 | 2,054 | 152 | 99.4 | 52.7 | 46.7 | 60.27 | 50.57 | 9.7 | 85.8 | 60.7 | 25.1 | 37.45 | 25.65 | 11.8 |
| 2005 | 2,983 | 2,525 | 458 | 2,180 | 2,024 | 156 | 98.1 | 52.7 | 45.4 | 59.19 | 49.05 | 10.14 | 88.9 | 64.2 | 24.6 | 37 | 24.93 | 12.06 |
| 2006 | 2,989 | 2,511 | 478 | 2,141 | 1,999 | 142 | 100.9 | 52.8 | 48.1 | 57.87 | 48.14 | 9.73 | 88.3 | 62.9 | 25.5 | 34.88 | 24.04 | 10.84 |
| 2007 | 2,981 | 2,497 | 484 | 2,109 | 1,975 | 134 | 100.8 | 52.4 | 48.5 | 57.14 | 47.34 | 9.8 | 89 | 63 | 26 | 34.03 | 24.14 | 9.88 |
| 2008 | 2,957 | 2,484 | 474 | 2,095 | 1,969 | 126 | 96.8 | 50.1 | 46.7 | 56.72 | 46.96 | 9.76 | 88.6 | 62.8 | 25.9 | 34.35 | 25.34 | 9.01 |
| 2009 | 2,909 | 2,429 | 480 | 2,088 | 1,962 | 126 | 95.1 | 48.3 | 46.8 | 56.38 | 46.59 | 9.78 | 89.7 | 63.3 | 26.4 | 33.37 | 24.4 | 8.97 |
| 2010 | 2,990 | 2,504 | 487 | 2,089 | 1,963 | 126 | 97.4 | 50.1 | 47.3 | 55.8 | 46.14 | 9.66 | 94.1 | 67.3 | 26.8 | 33.78 | 24.72 | 9.07 |
| 2011 | 3,067 | 2,569 | 498 | 2,100 | 1,972 | 128 | 97.3 | 49.5 | 47.8 | 56.34 | 46.3 | 10.04 | 96 | 69.5 | 26.4 | 33.96 | 24.78 | 9.18 |
| 2012 | 3,112 | 2,607 | 505 | 2,105 | 1,975 | 130 | 98.8 | 50.1 | 48.7 | 55.36 | 45.26 | 10.1 | 99.7 | 72.7 | 26.9 | 35.94 | 26.61 | 9.33 |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2013 | 2,981 | 2,455 | 526 | 2,094 | 1,964 | 130 | 99.2 | 48.3 | 50.9 | 55 | 44.94 | 10.07 | 89.8 | 61.7 | 28.1 | 36.41 | 27.07 | 9.34 |
| 2014 | 3,058 | 2,503 | 555 | 2,080 | 1,952 | 128 | 102.7 | 48.6 | 54.1 | 54.15 | 43.72 | 10.43 | 98.1 | 68.6 | 29.5 | 37.17 | 28.22 | 8.95 |
| 2015 | 2,844 | 2,327 | 517 | 2,093 | 1,963 | 130 | 104.9 | 49.4 | 55.4 | 54.36 | 43.76 | 10.6 | 94.9 | 68.1 | 26.8 | 37.76 | 28.69 | 9.07 |
| 2016 | 2,860 | 2,323 | 537 | 2,058 | 1,926 | 132 | 104.8 | 48.9 | 56 | 54.33 | 43.49 | 10.83 | 98.6 | 70 | 28.6 | 34.68 | 25.46 | 9.22 |
| 2017 | 2,983 | 2,413 | 571 | 2,032 | 1,905 | 127 | 112.5 | 49.2 | 63.3 | 52.25 | 41.72 | 10.54 | 104.1 | 75.2 | 28.9 | 38.13 | 29.38 | 8.75 |

**Table S4.** The number of doctors in South Korea and North Korea

| | South Korea | | | | | | North Korea | |
|---|---|---|---|---|---|---|---|---|
| | Total | Medical doctors | Dentists | Oriental medicine | Pharmacists | Medical and pharmacists (per 10,000 population) | Total | Medical and pharmacists (per 10,000 population) |
| Year | | | | | | | | |
| 1990 | 95,083 | 42,554 | 9,619 | 5,792 | 37,118 | 22.2 | 58,644 | 29 |
| 1993 | 112,046 | 51,518 | 12,180 | 7,569 | 40,779 | 25.4 | 67,254 | 31.9 |
| 1994 | 117,561 | 54,406 | 12,939 | 8,179 | 42,037 | 26.3 | ·· | ·· |
| 1995 | 122,852 | 57,188 | 13,681 | 8,714 | 43,269 | 27.2 | ·· | ·· |
| 1996 | 127,646 | 59,399 | 14,371 | 9,299 | 44,577 | 28 | 70,018 | 31.8 |
| 1997 | 133,101 | 62,609 | 15,383 | 9,289 | 45,820 | 29 | 70,901 | 31.9 |
| 1998 | 138,469 | 65,431 | 16,126 | 9,914 | 46,998 | 29.9 | 71,330 | 31.9 |
| 1999 | 147,559 | 69,724 | 17,276 | 11,345 | 49,214 | 31.7 | 71,785 | 31.9 |
| 2000 | 153,273 | 72,503 | 18,039 | 12,108 | 50,623 | 32.6 | 72,052 | 31.7 |
| 2001 | 158,848 | 75,295 | 18,887 | 12,794 | 51,872 | 33.5 | 72,332 | 31.6 |
| 2002 | 165,111 | 78,609 | 19,672 | 13,662 | 53,168 | 34.7 | ·· | ·· |
| 2003 | 170,708 | 81,328 | 20,446 | 14,553 | 54,381 | 35.6 | ·· | ·· |
| 2004 | 170,683 | 81,998 | 20,772 | 14,421 | 53,492 | 35.5 | ·· | ·· |
| 2005 | 177,050 | 85,369 | 21,581 | 15,271 | 54,829 | 36.7 | ·· | ·· |
| 2006 | 182,244 | 88,214 | 22,267 | 15,918 | 55,845 | 37.6 | ·· | ·· |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 2007 | 188,509 | 91,475 | 23,126 | 16,732 | 57,176 | 38.7 | .. | .. |
| 2008 | 194,916 | 95,088 | 23,924 | 17,541 | 58,363 | 39.7 | .. | .. |
| 2009 | 201,191 | 98,434 | 24,639 | 18,401 | 59,717 | 40.8 | 77,481 | 32.2 |
| 2010 | 206,921 | 101,443 | 25,390 | 19,132 | 60,956 | 41.8 | 77,881 | 32.2 |
| 2011 | 212,652 | 104,397 | 26,098 | 19,912 | 62,245 | 42.6 | 88,553 | 36.4 |
| 2012 | 218,414 | 107,295 | 26,804 | 20,668 | 63,647 | 43.5 | 88,987 | 36.4 |
| 2013 | 221,619 | 109,563 | 27,409 | 21,355 | 63,292 | 43.9 | 89,416 | 36.4 |
| 2014 | 225,834 | 112,476 | 28,134 | 22,074 | 63,150 | 44.5 | 89,842 | 36.4 |
| 2015 | 233,753 | 116,045 | 28,953 | 23,245 | 65,510 | 45.8 | 90,267 | 36.4 |
| 2016 | 238,860 | 118,765 | 29,643 | 23,460 | 66,992 | 46.6 | 90,691 | 36.4 |
| 2017 | 244,785 | 121,638 | 30,344 | 24,187 | 68,616 | 47.7 | 91,120 | 36.4 |
| 2018 | 248,323 | 123,173 | 30,918 | 24,885 | 69,347 | 48.1 | 91,550 | 36.4 |
| 2019 | 254,931 | 126,795 | 31,640 | 25,592 | 70,904 | 49.3 | 91,980 | 36.4 |

The difference in the number of medical personnel between South Korea and North Korea shows the status of health infrastructure. Despite the limited access to North Korean data, the total number of medical personnel is much smaller in North Korea than South Korea. The health infrastructure in North Korea has been collapsed since 1990 when the financial crisis and natural disaster hit. This indicates that North Korea is less likely to have easier access to vaccination and better hygiene conditions.

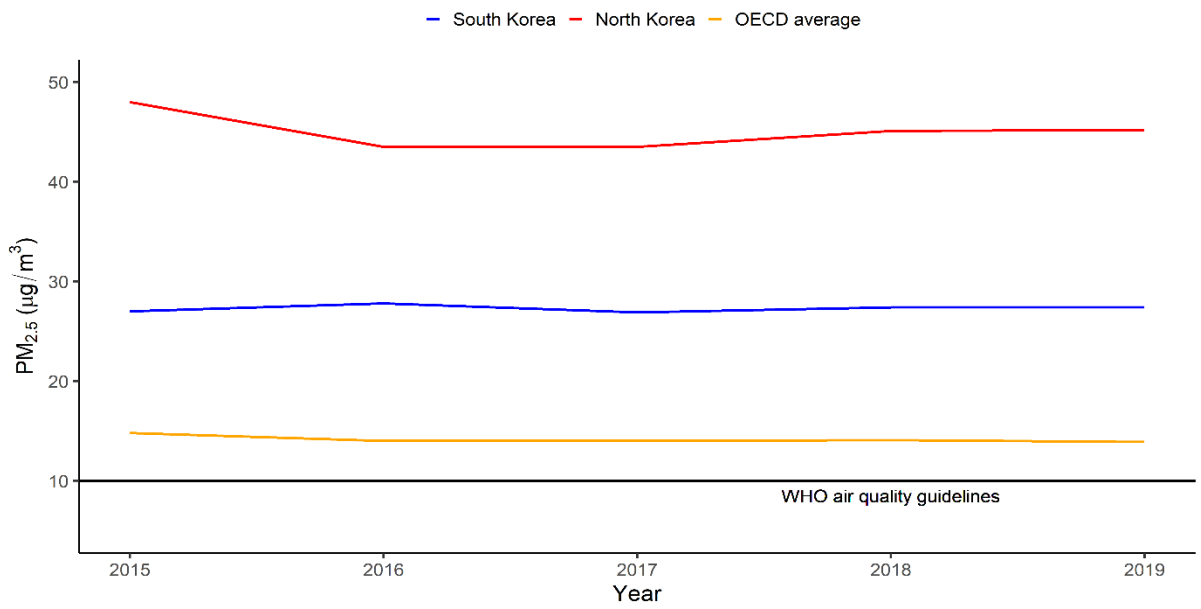


**Fig. S1.** The average annual concentration of $PM_{2.5}$ in South Korea and North Korea from 2015 to 2019.

Internationally comparable measurements of average $PM_{2.5}$ concentrations are derived from satellite observations, chemical transport models, and ground monitoring stations. The x-axis indicates year. The y-axis indicates $PM_{2.5}$ $\mu g/m^3$ concentrations. The red line indicates the average $PM_{2.5}$ concentration in North Korea. The blue line indicates the average $PM_{2.5}$ concentration in South Korea. The orange line indicates the $PM_{2.5}$ concentration in OECD average. The green dash line indicates the WHO air quality guidelines (10 $\mu g/m^3$). Source: OECD Statistics.

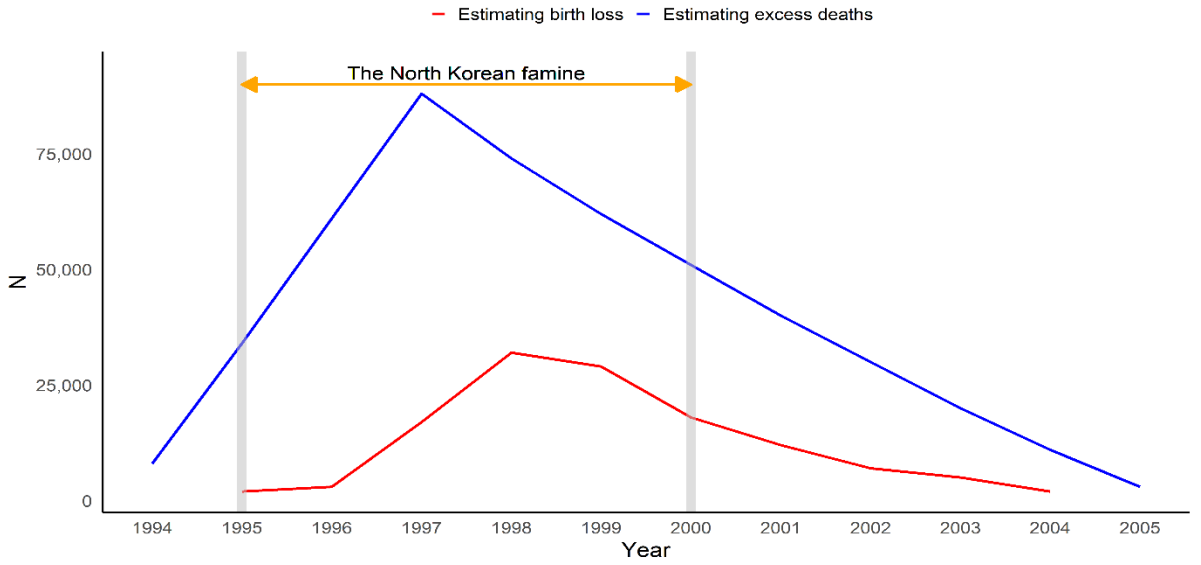


**Fig. S2.** The estimation of birth losses and excess deaths during the North Korean famine from 1994 to 2005.

The x-axis indicates years. The y-axis indicates counts (estimating birth loss or estimating excess deaths). The red line stands for the estimated birth loss and the blue line for the estimated excess deaths; The orange arrow means the period of North Korean famine from 1995 to 2000.

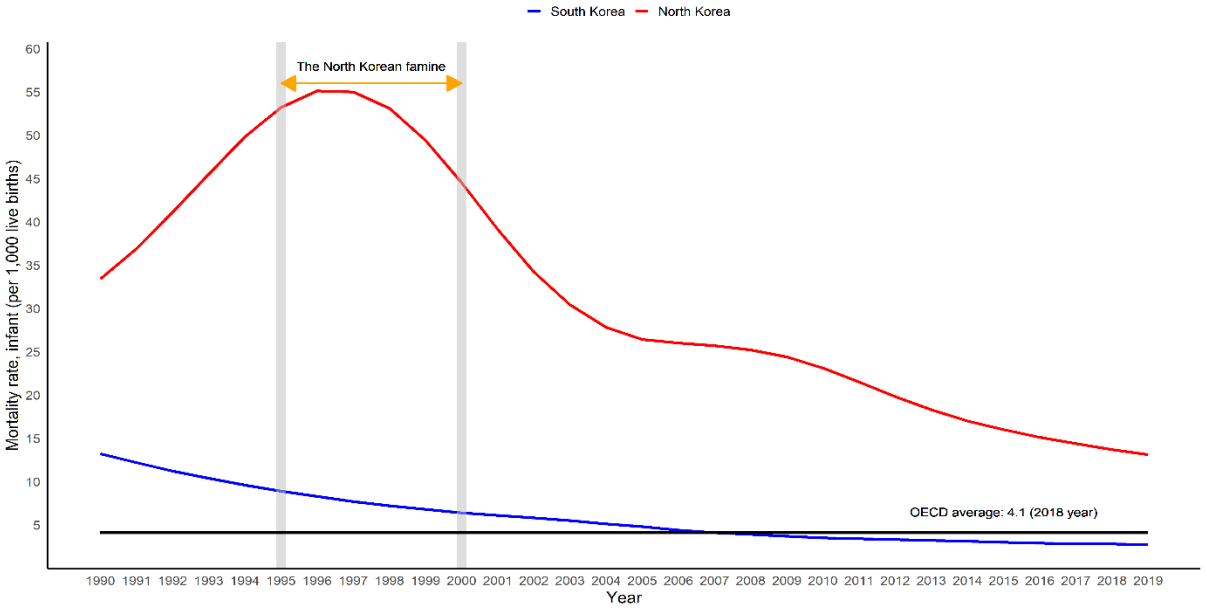


**Fig. S3.** The time–plot of annual infant mortality rates in South Korea and North Korea from 1990 to 2019.

The x-axis indicates years. The y-axis indicates the infant mortality rate per 1,000 live births. The red bar indicates North Korea. The blue bar indicates South Korea. The orange arrow means the period of North Korean famine from 1995 to 2000. The green dash line indicates the OECD average.


**Fig. S4.** Coal consumption in South Korea and North Korea from 2000 to 2017.

The x-axis indicates years. the y-axis indicates coal consumption (Mst). The red bars indicates coal consumption in North Korea.The blud bars indicates coal consumption in South Korea.

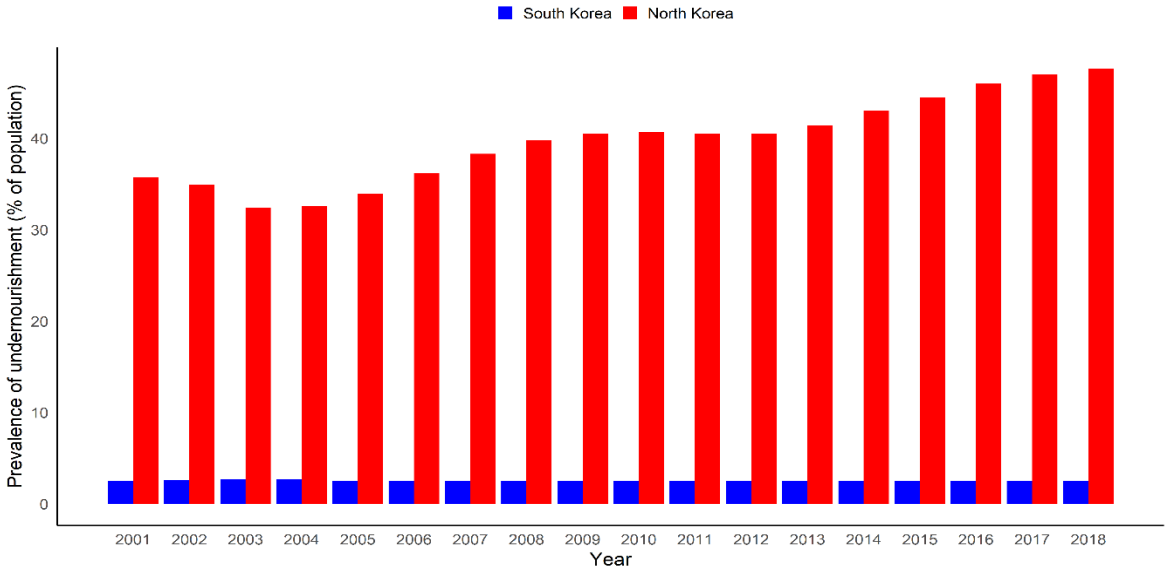


**Fig. S5.** The undernourished population of South Korea and North Korea.

The x-axis indicates years. The y-axis indicates prevalence of undernourishment (%). The red bars indicates prevalence of undernourishment in North Korea. The blue bars indicates prevalence of undernourishment in South Korea.

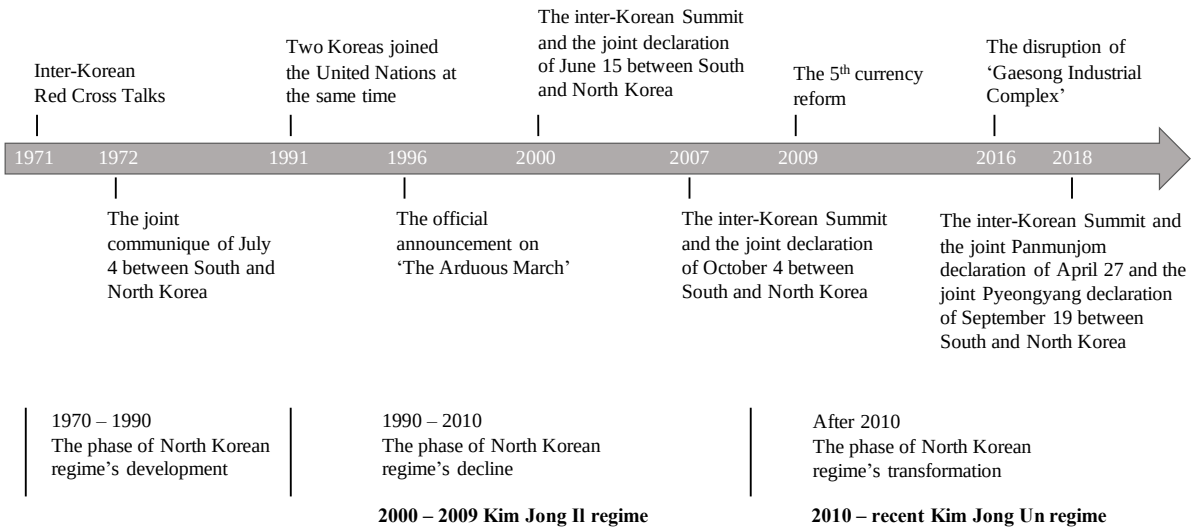


**Fig. S6.** Major historical events in the Korean Peninsula from 1970 to 2020.

The so-called 'Arduous March' was officially announced in 1996 and lasted until 1998 which caused severe malnutrition and stunting among children. This unfortunate event happened during the phase of North Korean regimen's decline (Kim Jong Il government). Although there were few inter-Korean Summits that see the possibility of peaceful cooperation since 2000, North Korea still suffers from economic difficulties. For example, the North Korean government forcibly enforced the 5$^{th}$ currency reform in 2009 that changes the value of money and then brought a disastrous damage to North Korean's financial stability and food supply. It might result in the increasing prevalence of anemia among North Korean children.

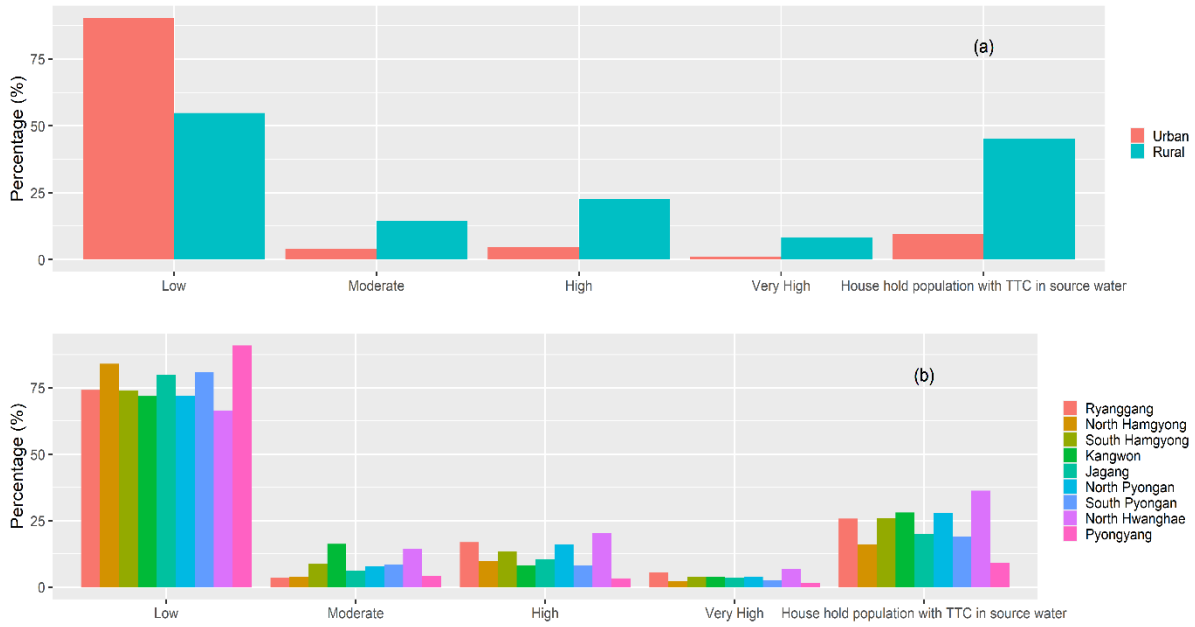


**Fig. S7.** Quality of source drinking water in North Korea in 2017.
(a) Risk level based on number of thermotolerant coliform (TTC) per 100ml by area; (b) Risk level based on number of thermotolerant coliform (TTC) per 100ml by province.

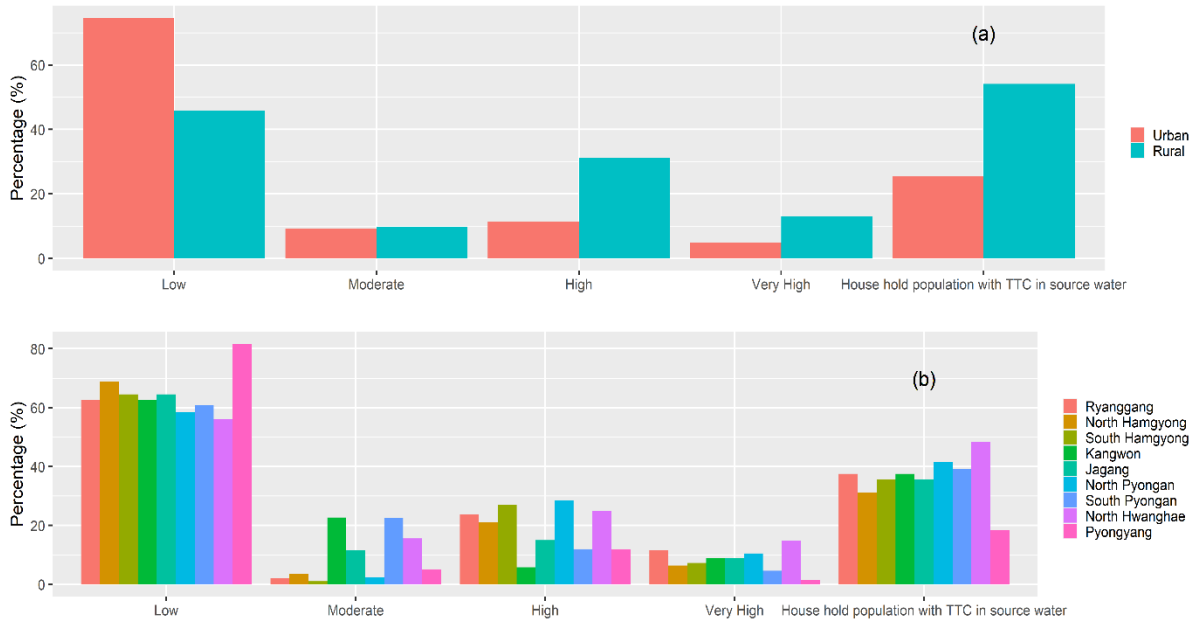


**Fig. S8.** Quality of household drinking water in North Korea in 2017.
(a) Risk level based on number of thermotolerant coliform (TTC) per 100ml by area; (b) Risk level based on number of thermotolerant coliform (TTC) per 100ml by province.

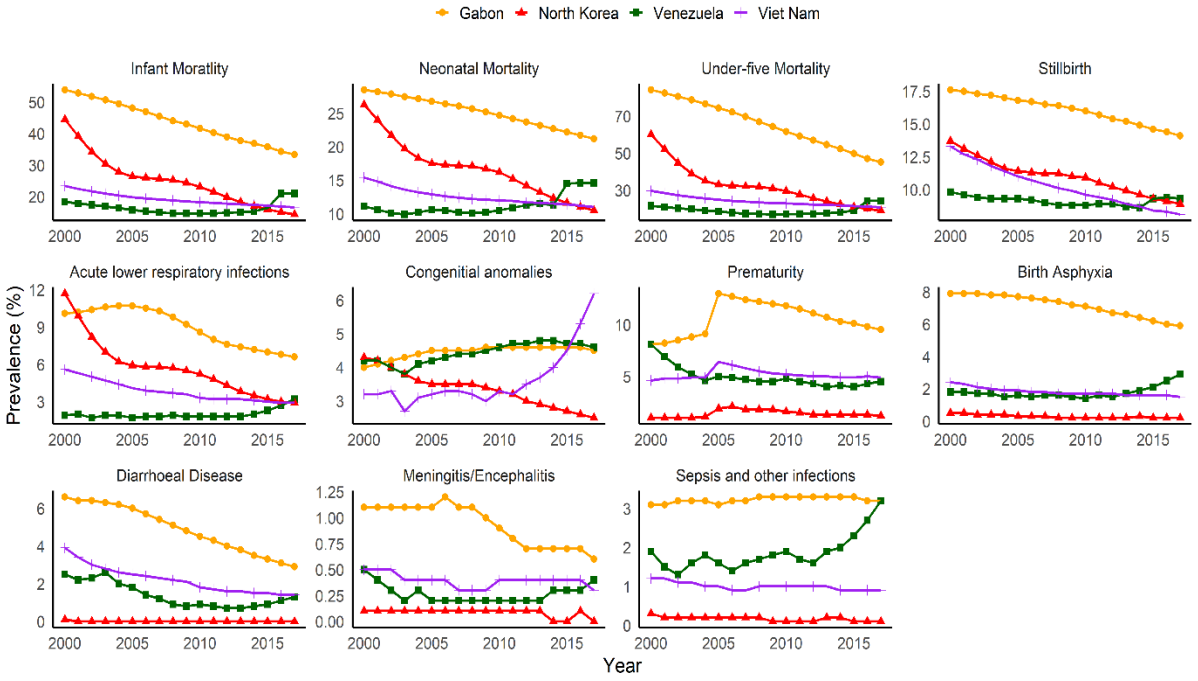


**Fig. S9.** Disease pattern of North Korea with developing countries (mortality rate per 1,000 live births).

The x-axis indiciates year. The y-axis indicates mortality rate per 1,000 live births. The yellow line indicates mortality rate in Gabon, the red line indicates mortality rate in North Korea, the green line indicates mortality rate in Venezuela, and the purple line indicates mortality rate in Vietnam.

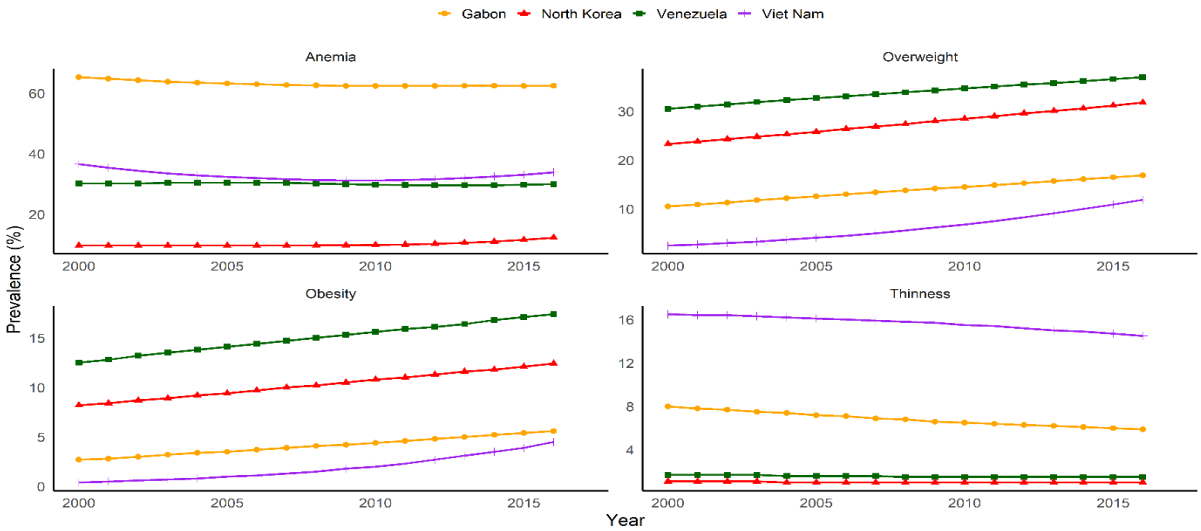


**Fig. S10.** Disease pattern of North Korea with developing countries (prevalence (%)).

The x-axis indiciates year. The y-axis indicates prevalence(%). The yellow line indicates prevalence in Gabon, the red line indicates prevalence in North Korea, the green line indicates prevalence in Venezuela, and the purple line indicates prevalence in Vietnam.

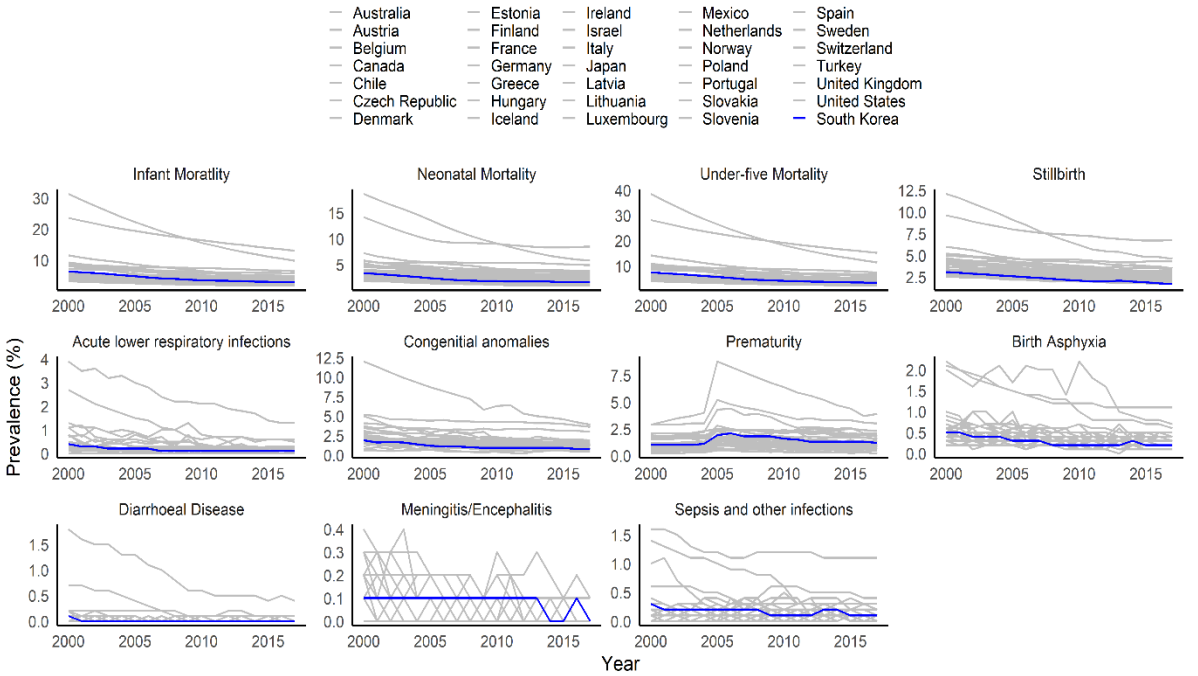


**Fig. S11.** Disease pattern of South Korea with developed countries (mortality rate per 1,000 live births).

The x-axis indiciates year. The y-axis indicates mortality rate per 1,000 live births. The blue line indicates mortality rate in South Korea. The gray line indicates the developed countries.

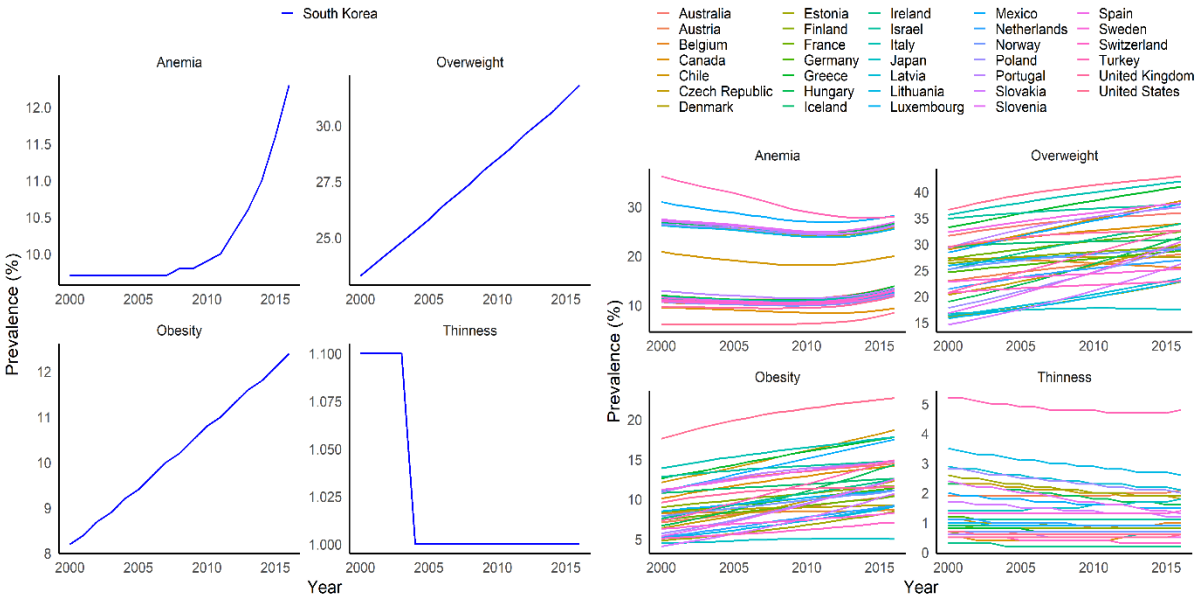


**Fig. S12.** Disease pattern of South Korea with developed countries (prevalence (%)).
The x-axis indiciates year. The y-axis indicates prevalence(%). The blue line indicates prevalence in South Korea.

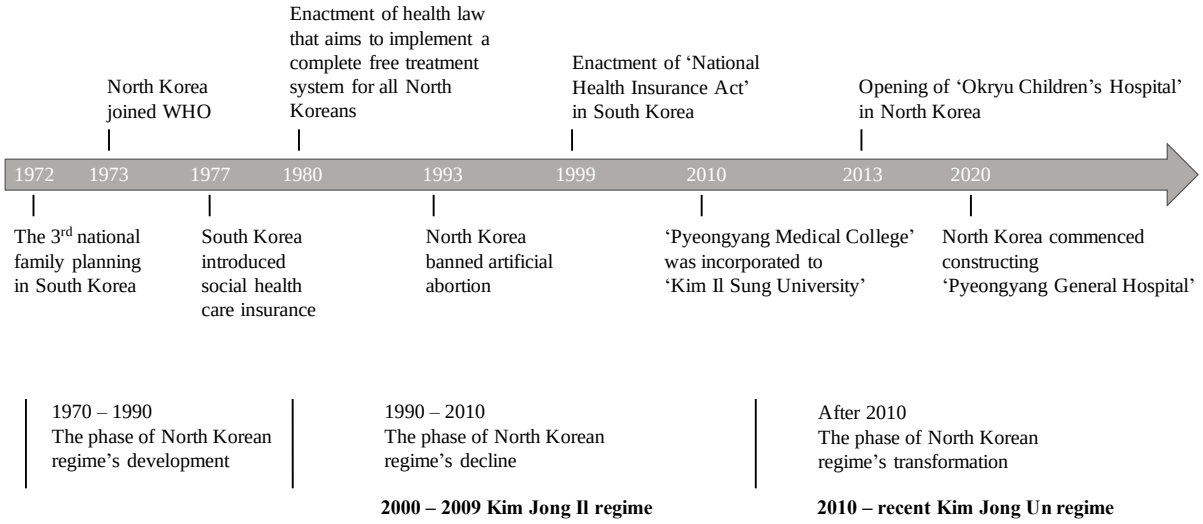


**Fig. S13.** History of health and medical care policy in North Korea from 1970 to 2020.

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# Comparative Analysis of Health Patterns and Gaps due to Environmental Influences in South Korea and North Korea, 2000–2017

**Yoorim Bang[1,*], Jongmin Oh[2,*], Eun Mee Kim[3], Ji Hyen Lee[4], Minah Kang[5], Miju Kim[6], Seok Hyang Kim[6], Jae Jin Han[7], Hae Soon Kim[4], Oran Kwon[8,9], Hunjoo Ha[10], Harris Hyun-soo Kim[11], Hye Won Chung[12], Eunshil Kim[13], Young Ju Kim[12], Yuri Kim[8], Younhee Kang[14], Eunhee Ha[2,9,15]**

[1]Institute for Development and Human Security, Ewha Womans University, Seoul, Korea
[2]Department of Environmental Medicine, College of Medicine, Ewha Womans University, Seoul, Korea
[3]Graduate School of International Studies, Ewha Womans University, Seoul, Korea
[4]Department of Pediatrics, College of Medicine, Ewha Womans University, Seoul, Korea
[5]Department of Public Administration, Ewha Womans University, Seoul, Korea
[6]Department of North Korean Studies, Ewha Womans University, Seoul, Korea
[7]Department of Thoracic and Cardiovascular Surgery, College of Medicine, Ewha Womans University, Seoul, Korea
[8]Department of Nutrition Science and Food Management, Ewha Womans University, Seoul, Korea
[9]Graduate Program in System Health Science and Engineering, College of Medicine, Ewha Womans University, Seoul, Korea
[10]Graduate School of Pharmaceutical Sciences, College of Pharmacy, Ewha Womans University, Seoul, Korea
[11]Department of Sociology, Ewha Womans University, Seoul, Korea
[12]Department of Obstetrics and Gynecology, College of Medicine, Ewha Womans University, Seoul, Korea
[13]Department of Women's Studies, Ewha Womans University, Seoul, Korea
[14]College of Nursing, Ewha Womans University, Seoul, Korea
[15]Institute of Ewha-SCL for Environmental Health (IESEH), College of Medicine, Ewha Womans University, Seoul, Korea

*These authors contributed equally to this work.

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**Corresponding author**
Eunhee Ha
Department of Environmental Medicine, College of Medicine, Graduate Program in System Health Science and Engineering, Ewha Womans University, 260 Gonghang-daero, Gangseo-gu, Seoul 07804, Korea
Tel: 82-2-6986-6234
Fax: 82-2-6986-7022
E-mail: eunheeha@ewha.ac.kr

**Key Words**
Child health; Environmental health; Environmental exposure; Environmental pollution; Environment and public health

**Objectives:** To conduct a comparative study of children's health in South Korea versus North Korea focusing on air pollution.

**Methods:** We used annual mortality rate, prevalence, and environmental indicators data from the World Bank and World Health Organizations (WHO). Trend analysis of the two Koreas was conducted to evaluate changes in health status over time. Spearman's correlation analysis was used to find out the correlation between environmental indicators and children's health status.

**Results:** We found a distinct gap in children's health status between the two Koreas. While North Korea reported a higher death rate of children than South Korea, both showed a decreasing trend with the gap narrowing from 2000 to 2017. The prevalence of overweight and obesity increased and that of thinness decreased in both Koreas. Except $PM_{2.5}$ exposure, South Korea reported higher figures in most indicators of air pollutant emissions (South Korea, mean (SD)=28.3 (2.0); North Korea, mean (SD)=36.5 (2.8), P-value=0.002).

**Conclusion:** This study empirically discovered the gaps and patterns of children's health between South Korea and North Korea. North Korean children experienced more severe health outcomes than children in South Korea. These findings imply that epigenetic modification caused by environmental stressors affect children's health in the two Koreas despite similar genetic characteristics. Considering the gaps in children's health between the two Koreas, more attention and resources need to be directed towards North Korea because the necessary commodities and services to improve children's health are lacking in North Korea.

## Introduction

Children's health is an important theme in public health since its impact covers the life-course from childhood to adulthood. Children have a unique vulnerability to health-related issues and harmful exposures compared to adults [1,2]. Since young children go through rapid growth and development, their metabolism is immature and more vulnerable to environmental stressors [2]. Environmental exposures affect children's health and create a larger burden of diseases, including respiratory diseases (e.g., acute lower respiratory infection [ALRI], pneumonia, and asthma) [1,3,4]. Environmental exposure is known as an important determinant of health in both developed and developing countries, although the patterns of exposure vary [3]. Existing literature discusses the effect of environmental exposure on children's health, which causes a larger burden of diseases [4]. Previous epidemiological studies have reported the association between air pollution exposure and mortality in children under 5 years [5–8]. Health risks caused by air pollution have a great impact in low- and middle-income countries [3,9]. People in wealthier nations may be healthier since economic prosperity allows them to spend more on personal health, leading to better health outcomes [10]. However, economic development has led to a higher level of environmental pollution which damages people's health [11]. We thus argue that environmental exposure is an important determinant of health.

Another body of literature emphasizes the importance of epigenetic modifications caused by environmental stressors such as air pollutants, particulate matter, and metal exposure, thereby affecting children's health [12–14]. Epigenetic change considers genetics as a factor but puts greater emphasis on environmental circumstances that modify one's health [14]. A comparative study of the Republic of Korea (hereafter referred to as South Korea) and the Democratic People's Republic of Korea (hereafter referred to as North Korea) presents a unique opportunity to compare the effects of a shared genetic background versus epigenetic modifications caused by environmental stressors [12,13].

There are few empirical studies on North Korean children's health, despite the ample media reports of widespread malnutrition and infectious diseases. South Korea and North Korea have been isolated from each other due to the politics of the Korean War and the Cold War dynamics on the Korean Peninsula. Such separation from each other while sharing the same ethnicity and early history provides a rich ground for comparative research. However, there are few comparative studies on children's health in these two countries. There are two pertinent points of comparison in this research. First is the impact of the "North Korean Famine (1995–1998)" or "the Arduous March," which has resulted in children's widespread malnutrition and stunting. South Korea did not suffer from famine or malnutrition during the same period. A second point is the remarkably different environmental circumstances due to the different pace and level of economic development.

South Korea and North Korea have been divided since 1945 and their division has solidified after the Korean War in 1950–1953 [15]. Over 7 decades, they have experienced different political regimes and socio-economic development. We assume that the health status of children is conspicuously different between South Korea and North Korea due to socioeconomic, cultural, and environmental factors. Based on this assumption, we hypothesize that harmful environmental circumstances exacerbate the gap in children's health in the two Koreas. Thus, this study aims to analyze the differences in children's health status and the correlation between the environment and children's health in South Korea and North Korea to answer three research questions: (1) How different is the general status of children's health between South Korea and

North Korea, and how has the gap changed over time? (2) What are the disease patterns of children in the two Koreas? and (3) How much do the environmental factors affect children's health in South Korea and North Korea? The comparative analysis will provide interesting findings since many variables have been held constant due to the division. The comparative analysis will help identify the patterns of, and gaps in, children's health in South Korea and North Korea from the perspective of environmental influences on disease patterns across countries of varying levels of economic development.

A comparative study of children's health in South Korea versus North Korea is important for three reasons. First, it can provide a rich comparative analysis of the effect of the environment on children's health with many important health factors held constant. Second, this study will help delineate how a developed, as opposed to a developing, country's environmental factors change as a result of economic progress. Finally, it can contribute as a preparatory study to the understanding of children's health status of the two Koreas to prevent and minimize social disturbances that can be caused by reunification.

## Method

### 1. Data source

We used estimated data for North Korea since the country does not provide official statistics on environmental and health measurements. We utilized data provided by international organizations (for details of data source, see the appendix [Table S1]). The collected (ecological) data are from 2000 to 2017 and included two strands of indicators: (1) environmental indicators and (2) children's health status (mortality rate, prevalence). The collected data were published by the World Bank and the World Health Organization (WHO) [16,17]. Environmental indicators include fine particulate matter ($PM_{2.5}$) exposure and air pollutant emissions, including gas emissions and fossil fuels. In the supplementary material, we provide annual population characteristics and medical and nutritional status collected from the United Nations Children's Fund (UNICEF), Energy Information Administration (EIA), World Bank, Organisation for Economic Co-operation and Development (OECD), and Korea Statistical Information Service. We categorized the indicators of children's health status into four categories: reproductive health, respiratory disease, chronic disease, and nutritional disease.

### 2. Air pollution indicators

The annual mean $PM_{2.5}$ concentration estimates were derived from the Global Burden of Disease study [18–20]. These data are estimates of the population-weighted average exposure and a general air quality indication to inform cross-country comparisons of health risks. The population estimation data are based on the Gridded Population of the World by NASA Socioeconomic Data and Applications Center (version 4). The detailed description of the exposure estimates is based on previous studies of global estimates of air pollution and environmental risks [18–20]. The emission data include carbon dioxide ($CO_2$), nitrous oxide ($N_2O$), methane, and fossil fuel information.

### 3. Outcome indicators

Children's health indicators consist of two types: (1) annual children's mortality rate (infant, stillbirth, neonatal, under-five, ALRI), congenital anomalies, prematurity, birth asphyxia, diarrheal disease, meningitis/encephalitis, sepsis and other infections) and (2) prevalence (anemia,

overweight, obesity, thinness). Infant mortality, stillbirth, and neonatal mortality were calculated as deaths per 1,000 live births (0–4 years old). Mortality of under–five, ALRI, congenital anomalies, prematurity, birth asphyxia, diarrheal disease, meningitis/encephalitis, sepsis and other infections was calculated as deaths per 1,000 children (0–4 years old). We used data on the prevalence of anemia in children under 5 years of age and that of overweight, obesity, and thinness in children 5–9 years of age. Here, overweight is defined as the Body Mass Index (BMI) exceeding +1 SD above the median, obesity as the BMI exceeding +2 SD above the median, and thinness means as a BMI is below median -2 SD.

### 4. Statistical analysis

We performed two analyses to examine how South Korea and North Korea are differently situated after the "North Korean Famine" in terms of air pollution and health status. First, we compared descriptive statistics for South Korea and North Korea. Second, we performed trend analysis to observe how children's health status in South Korea and North Korea has changed over time.

As the children's health indicator data were estimated annually, we focused on observing the changes per year. Overall, we considered three methods for trend analysis of children's health status: (1) Sen's slope, (2) Mann-Kendall trend test, and (3) linear regression. The first two methods are used to analyze the trends for non-parametric data. If the beta coefficient is greater than zero ($\beta > 0$), the data are considered to show a positive trend. When there are many missing values, the Mann-Kendall trend test can be used as a way to adjust missing data. This method validates significance by using Kendall's correlation coefficient.

We analyzed the correlation coefficient between environmental indicators and children's health status. Since our data spans from 2000 to 2017, the number of pair samples for health status is 18. As the sample number is too small to assume a specific distribution, we utilized Spearman's correlation based on the non-parametric method.

### 5. Sensitivity analysis

The sources of data in this study are international organizations. Since the data we use are secondary, a direct comparison between the two Koreas is limited. Thus, we cross-checked our results with the data reported by the OECD and the South Korean government (Statistics Korea) for sensitivity analysis [21,22]. This study also extracted North Korean data from the South Korean database (Statistics Korea).

## Results

Over a total span of 18 years (2000–2017), we found a distinct gap between South Korea and North Korea in two domains: (1) children's health status (mortality rate, prevalence) and (2) environmental indicators. Differences were observed despite similar demographic trends from 2000 to 2018 – growing population, increase in life expectancy, decrease in total fertility rate, and aging (Table 1).

The time-plots show the trends in children's annual mortality and prevalence in South Korea and North Korea, respectively (Figs. 1, 2). The results of the trend analysis are presented in the appendix (Table S2). Child mortality rates in South Korea and North Korea are decreasing, except for prematurity. While North Korea reported a higher death rate of children than South Korea, the gaps in children's mortality and their health status in both Koreas narrowed from 2000 to 2017

**Table 1.** Demographic characteristics of South Korea and North Korea

| Year | Population (1,000 people) | | Life expectancy (yr) | | | | | | Total fertility rate (births per 1,000 women) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | South Korea | North Korea | South Korea | | | North Korea | | | South Korea | North Korea |
| | | | Total | Male | Female | Total | Male | Female | | |
| 2000 | 47,008 | 22,702 | 76.0 | 72.3 | 79.7 | 65.3 | 61.2 | 69.0 | 1.48 | 1.99 |
| 2001 | 47,370 | 22,902 | 76.5 | 72.9 | 80.1 | 66.1 | 62.1 | 69.7 | 1.31 | 1.99 |
| 2002 | 47,645 | 23,088 | 76.8 | 73.4 | 80.3 | 66.9 | 63.0 | 70.4 | 1.18 | 1.99 |
| 2003 | 47,892 | 23,254 | 77.3 | 73.8 | 80.8 | 67.6 | 63.8 | 71.0 | 1.19 | 1.99 |
| 2004 | 48,083 | 23,411 | 77.8 | 74.3 | 81.2 | 68.1 | 64.3 | 71.5 | 1.16 | 1.98 |
| 2005 | 48,185 | 23,561 | 78.2 | 74.9 | 81.6 | 68.4 | 64.7 | 71.7 | 1.09 | 1.98 |
| 2006 | 48,438 | 23,707 | 78.8 | 75.4 | 82.1 | 68.5 | 64.8 | 71.8 | 1.13 | 1.97 |
| 2007 | 48,684 | 23,849 | 79.2 | 75.9 | 82.5 | 68.7 | 65.0 | 72.0 | 1.26 | 1.96 |
| 2008 | 49,055 | 23,934 | 79.6 | 76.2 | 83.0 | 68.9 | 65.3 | 72.2 | 1.19 | 1.95 |
| 2009 | 49,308 | 24,062 | 80.0 | 76.7 | 83.4 | 69.2 | 65.6 | 72.5 | 1.15 | 1.94 |
| 2010 | 49,554 | 24,187 | 80.2 | 76.8 | 83.6 | 69.6 | 66.0 | 72.9 | 1.23 | 1.94 |
| 2011 | 49,937 | 24,308 | 80.6 | 77.3 | 84.0 | 70.0 | 66.4 | 73.3 | 1.24 | 1.93 |
| 2012 | 50,200 | 24,427 | 80.9 | 77.6 | 84.2 | 70.5 | 66.8 | 73.8 | 1.30 | 1.93 |
| 2013 | 50,429 | 24,545 | 81.4 | 78.1 | 84.6 | 70.9 | 67.2 | 74.2 | 1.18 | 1.93 |
| 2014 | 50,747 | 24,662 | 81.8 | 78.6 | 85.0 | 71.2 | 67.6 | 74.5 | 1.21 | 1.93 |
| 2015 | 51,015 | 24,779 | 82.1 | 79.0 | 85.2 | 71.5 | 67.8 | 74.9 | 1.24 | 1.92 |
| 2016 | 51,218 | 24,897 | 82.4 | 79.3 | 85.4 | 71.7 | 68.1 | 75.1 | 1.17 | 1.92 |
| 2017 | 51,362 | 25,014 | 82.7 | 79.7 | 85.7 | 71.9 | 68.3 | 75.3 | 1.05 | 1.91 |
| Average (SD) | 49,229.4 (1,394.1) | 23,960.5 (702.7) | 79.6 (2.1) | 76.2 (2.3) | 82.9 (2.0) | 69.2 (1.9) | 65.4 (2.1) | 72.5 (1.9) | 1.2 (0.1) | 2.0 (0.0) |
| Sen's slope (95% CI) | 260.3 (253, 272.9) | 125.3 (120.0, 134.7) | 0.4 (0.4, 0.4) | 0.4 (0.4, 0.4) | 0.4 (0.3, 0.4) | 0.3 (0.3, 0.4) | 0.4 (0.3, 0.4) | 0.3 (0.3, 0.4) | 0.00 (−0.02, 0.01) | 0.00 (−0.01, −0.00) |
| Mann-Kendall statistics | 5.8 (P–value <0.001) | 5.8 (P–value <0.001) | 5.8 (P–value <0.001) | 5.8 (P–value <0.001) | 5.8 (P–value <0.001) | 5.8 (P–value <0.001) | 5.8 (P–value <0.001) | 5.8 (P–value <0.001) | −0.8 (P–value: 0.425) | −5.3 (P–value: <0.001) |
| β (Slope) (95% CI)* | 260.6 (252.5, 268.7) | 131.2 (125.9, 136.5) | 0.4 (0.4, 0.4) | 0.4 (0.4, 0.4) | 0.4 (0.3, 0.4) | 0.4 (0.3, 0.4) | 0.4 (0.3, 0.4) | 0.3 (0.3, 0.4) | 0.01 (−0.02, 0.00) | 0.00 (−0.01, 0.00) |

*The slope coefficient for simple linear regression.

(Fig. 1). In particular, North Korean children recorded a sharp decline in mortality rate indicators, especially after 2005.

The prevalence of overweight and obesity has increased and that of thinness decreased in both Koreas (Fig. 2). While South Korean children showed an increasing prevalence of anemia, North Korean children decreased and then increased again in North Korean children after 2009. For North Korean children under the age of 5 years who had anemia, a U–shaped pattern was observed since it decreased in the early 2000s and then increased after 2008 (Fig. 2).

We discovered differences in environmental indicators between the two Koreas. Except for $PM_{2.5}$ exposure, South Korea recorded much higher figures than North Korea in most indicators of air pollutant emissions such as $CO_2$, $N_2O$, and methane emissions (Table 2 and Fig. S1). An interesting finding is that $PM_{2.5}$ concentration estimates were higher in North Korea than in

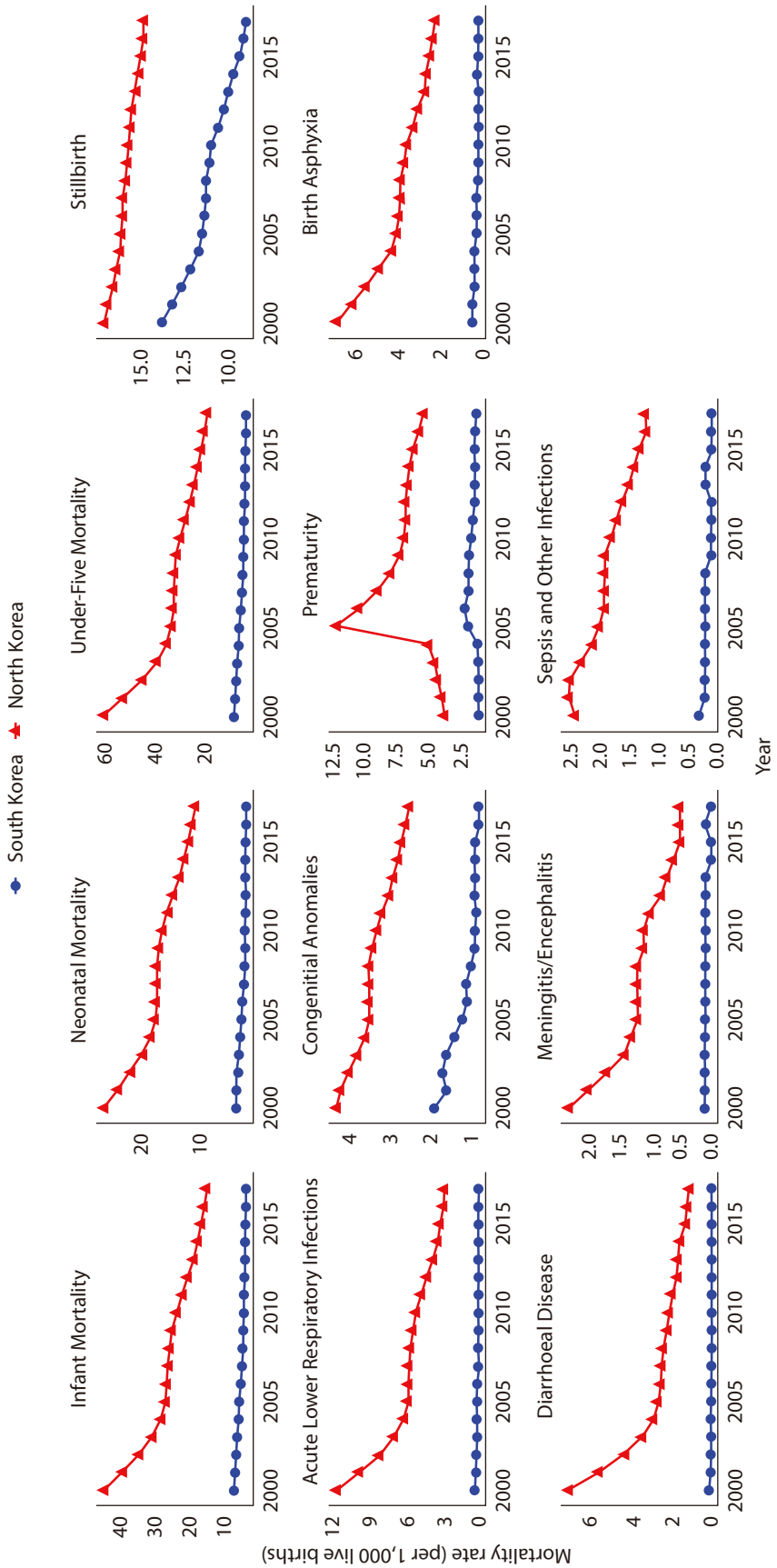


**Fig. 1.** Trends in children's health (mortality) in South Korea and North Korea. The red line stands for children's health status (mortality, per 1,000 live births) in North Korea and the blue line for South Korea.


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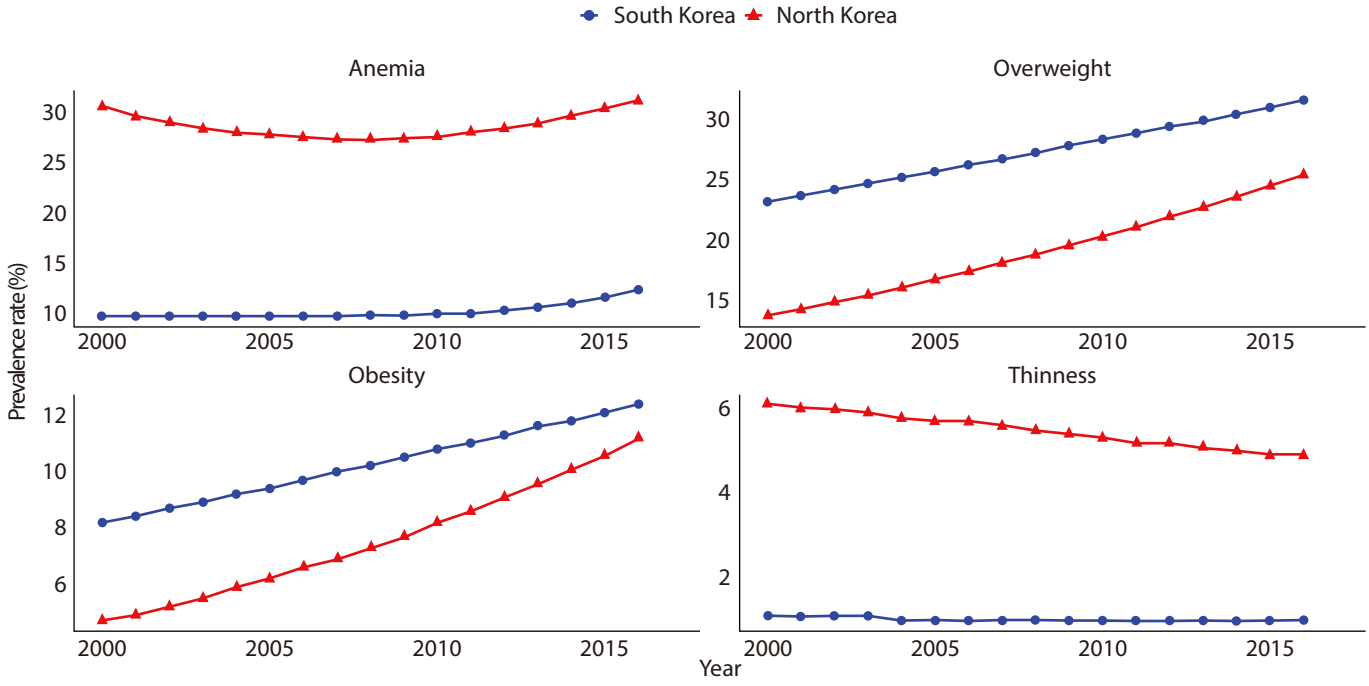


**Fig. 2.** Trends in children's health (prevalence) in South Korea and North Korea. The red line stands for children's health status (prevalence, %) in North Korea and the blue line for South Korea.

South Korea. North Korea is faced with the danger of high $PM_{2.5}$ concentration which is known to increase the risk of children's ALRI.

Given the differences in environmental indicators between South Korea and North Korea, we examined the association between the environment and children's health. $PM_{2.5}$ showed a positive relationship with infant and child mortality indicators and a negative relationship with the prevalence of anemia, overweight, and obesity in the two Koreas (Fig. 3). In the Poisson regression model, North Korea's $PM_{2.5}$ exposure concentrations were related to infant mortality (% increase: 9.07, 95% confidence interval [CI]: 3.06, 15.44), neonatal mortality (% increase: 7.50, 95% CI: 0.52, 14.97), and under-five mortality (% increase: 8.67, 95% CI: 3.44, 14.17). Meanwhile, the correlation of $CO_2$, $N_2O$, and fossil fuel emissions with health effects varied between the two Koreas. It is positive in North Korea, while South Korea has a negative or no correlation.

## Discussion

There is a large gap in children's health status between South Korea and North Korea. Children living in North Korea experienced more severe health outcomes than those in South Korea. The death rate of prematurity, congenital anomalies, and birth asphyxia is higher in North Korea, which indicates that newborns in North Korea are more susceptible to these diseases than their South Korean counterparts. This trend has continued albeit with a decreasing rate over time. The time-plot of infant mortality rate during the North Korean famine is provided in the supplementary appendix (Figs. S2 and S3).

While South Korea recorded higher figures in air pollutant emissions such as $CO_2$, $N_2O$, and methane than North Korea, $PM_{2.5}$ concentration estimates are higher in North Korea (Table 2). Although both Koreas are affected by air pollution, including fine particulate matters and dust


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**Table 2.** Comparison of environmental indicators in South Korea and North Korea

| | South Korea | | | North Korea | | | P–value |
|---|---|---|---|---|---|---|---|
| | n | Mean | SD | n | Mean | SD | |
| Environmental indicator | | | | | | | |
| $PM_{2.5}$ (μg/m³) | 10 | 28.3 | 2 | 10 | 36.5 | 2.8 | 0.002 |
| $CO_2$ emissions (metric tons per capita) | 17 | 10.6 | 1 | 17 | 2.3 | 0.9 | <0.001 |
| $N_2O$ emissions (thousand metric tons of $CO_2$ equivalent) | 13 | 14,338.0 | 1,996.8 | 13 | 3,286.2 | 74.8 | <0.001 |
| Methane emissions (kt of $CO_2$ equivalent) | 13 | 31,680.5 | 703.4 | 13 | 18,390.4 | 671.1 | <0.001 |
| Fossil fuel (% of total) | 16 | 82.4 | 1.2 | 15 | 79.5 | 13.1 | 0.421 |

P-value by Wilcoxon's sign rank test.

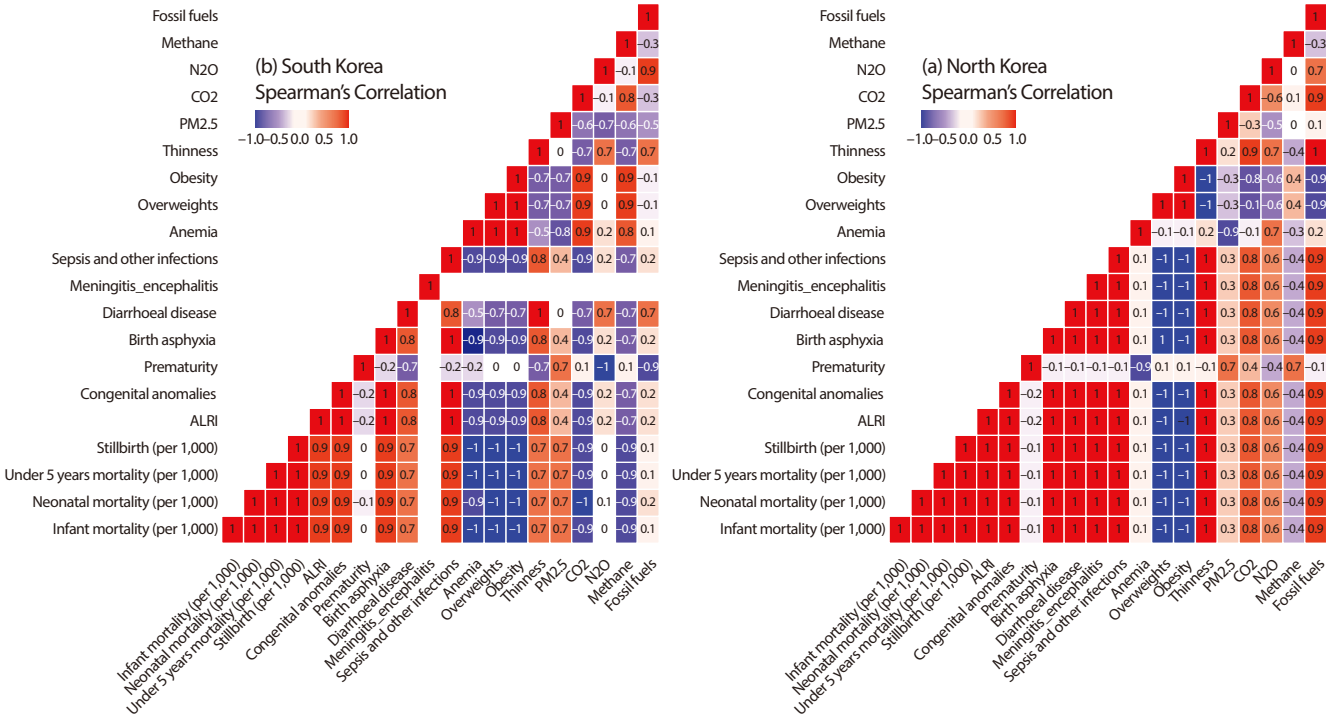


**Fig. 3.** Correlation between air pollution exposure and children's health in South Korea and North Korea.

flying from China, North Korea showed a higher rate of $PM_{2.5}$ concentration estimates than South Korea. We speculate that North Korea's use of cooking and heating fuel with low combustion rate and low thermal efficiency, as well as low-quality coal, has resulted in a higher exposure to $PM_{2.5}$ (Fig. S4). North Korea's use of ineffective domestic fuel is likely to release particulate matter and increase the level of $PM_{2.5}$ concentration over that in South Korea [23]. Fossil fuels, particularly coal and heavy oil, in thermal power plants, industrial boilers, kilns, motor cars, and households are the major pollutants in the largest city of North Korea (Pyongyang) and in nearby industrial districts [24].


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We also found a gap in prevalence indicators between the two Koreas. The prevalence of anemia, overweight, obesity, and thinness is lagged for estimation, and North Korean children are faced with a greater danger of anemia and thinness while those in South Korea experience a higher prevalence of overweight and obesity. More interestingly, the prevalence of overweight and obesity is increasing and that of thinness is decreasing in both Koreas. This trend in prevalence indicators is probably caused by nutritional factors rather than air pollution. The previous study on North Korean refugee children residing in South Korea showed that the gap in growth (height and weight) and obesity rates between South Korean and North Korean children was narrowed after consuming sufficient food [25]. The nutritional status of South Korean and North Korean is provided in the appendix (Table S3 and Fig. S5). It implies that poor nutritional intake in North Korea has led to the children's malnutrition causing anemia and thinness, while the higher prevalence of overweight and obesity in South Korea is most likely caused by a Westernized dietary pattern, which contains high amounts of saturated fatty acids and energy-dense foods that are poor in micronutrients.

The differences in environmental indicators such as air pollutant emissions between South Korea and North Korea created gaps in the children's health status. The higher emissions of environmental pollutants, including $PM_{2.5}$, serve as a trigger for increasing the incidence of respiratory diseases (ALRI, pneumonia, and asthma) [4]. This relationship was supported by another study showing that long-term exposure to ambient fine particulate matter ($PM_{2.5}$) is inversely associated with lung function in children, adolescents, and young adults [26]. In addition to air pollutants, lead is more noxious to children than adults [27]. In particular, anemia is observed in young children who have lead poisoning [27]. Iron deficiency anemia is a risk factor for lead toxicity, as it not only promotes pica behavior but also increases the absorption of lead from the gastrointestinal tract [28]. Lead exposure and nutritional deficiencies, which are prevalent in North Korea, put children in danger of growth retardation and behavioral challenges. For instance, the active use of inefficient cooking and heating fuel such as a tire close to the furnace increases the level of lead exposure among North Korean children. North Korean children have a higher risk of respiratory infections caused by indoor air pollution from low-quality fuels.

Further, this study found an interesting pattern in diseases between South Korea and North Korea. The two Koreas have been isolated from each other since 1945, sharing the same ethnicity and similar genetic characteristics (Fig. S6). The different environmental circumstances for over 7 decades since the division have led to very different disease characteristics. North Korean children suffer from infectious diseases such as parasite infection, tuberculosis, lower respiratory tract infections, acute infectious diarrhea, malaria, meningitis, and sepsis. Infectious diseases are prevalent in North Korea due to poor conditions – pollution of drinking water (Figs. S7 and S8), weak management of vaccination, and unavailability of antibiotics. In contrast, pediatric allergic, autoimmune, and metabolic diseases are prevalent among South Korean children. The so-called "hygiene hypothesis" explains this by assuming that microbes such as bacteria stimulate the immune response and the too-clean environmental and hygienic conditions decrease immunity so that people can be more susceptible to allergies and autoimmune diseases [29,30]. As immune polarization caused by different environmental stressors exists in South Korea and North Korea, the disease patterns are different [14,31,32]. The disease pattern of North Korean children is similar to that of developing countries, whereas the disease pattern of South Korean children is similar to that of developed countries, as illustrated in the appendix based on the mortality rate and prevalence of each disease (Figs. S9–S12).

This study offers two key contributions. First, the study examines the gap in children's health


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between South Korea and North Korea, explores the association between the environment and children's health, and finds the disease patterns of South Korea and North Korea to be similar to the differences found between developed and developing countries. While there have been few studies comparing the children's health status between South Korea and North Korea, this study empirically highlighted the differences and patterns of children's health, which helps to fill the lacunae in the children's health studies. Second, this study is meaningful in that it compared children's health status and environmental circumstances between South Korea and North Korea after the two were forcibly divided in 1945 and further distanced by a war between the two in 1950¬–1953. The two countries in the Korean Peninsula provide an interesting test-bed for a rich comparative analysis as a social experiment to examine how South Korea and North Korea have evolved for over 7 decades since the division in terms of the environment and children's health.

Our findings should be interpreted, however, in light of data limitations. First, official data on North Korean health, environment, or nutrition are not available. Therefore, we used data collected from multiple international organizations including the World Bank and WHO. Second, we cannot determine a direct relationship between air pollution exposure and health effects in South Korea and North Korea due to data constraints. To overcome this, we conducted comparative and trend analyses. The differences in mortality and morbidity of children in the two Koreas might be caused by socioeconomic and cultural factors, as well as environmental factors. Thus, it would be necessary to secure national data for precise research to improve North Korean children's health. Therefore, more reliable data sources representing a larger sample or that enable longitudinal studies such as cohort studies are needed. Third, it is difficult to access prevalence indicators since their availability is limited compared to mortality indicators. Lastly, the dataset does not consider regional disparities within North Korea. It would be important to identify regional differences to help reduce the health status gaps among different regions.

Considering the patterns and gaps in children's health between South Korea and North Korea, more attention and resources need to be directed towards North Korea. The current health status of North Korean children needs intensive international development cooperation because the necessary commodities and services to improve the health of children are lacking in North Korea (Fig. S13). Although the governments of South Korea and North Korea have not had a Summit since 2018, there is hope that future official summits between South Korea and North Korea, and with other countries including the US could open doors for cooperation and unification. Should North Korea become open to international development cooperation, South Korea can play an important role in assisting North Korea although its assistance cannot be counted toward foreign aid as the two do not recognize each other as separate countries. Nevertheless, South Korea's shared ethnicity, language, culture, and geographical proximity would be very useful to assist the international efforts for development cooperation in North Korea.

These findings imply that epigenetic modification resulting from environmental stressors has had an impact on children's health in South Korea and North Korea despite sharing similar genetic backgrounds. After the division of the Korean Peninsula, different environmental circumstances modified children's health in the two Koreas, with genetics held constant. Considering the effect of epigenetic modification caused by environmental factors, it would be vital to develop a strategy for improving public health, especially targeting North Korean children if and when unification occurs. In particular, there is a danger that infectious diseases can spread quickly in South Korea and North Korea since people across the Korean Peninsula have not been exposed to each other for a long time. It is likely that infectious diseases such as measles, tuberculosis, malaria, and parasite infection, which are common in North Korea, can spread to

South Korea, while other infectious diseases and socially driven illnesses from South Korea can spread to North Korea [33]. As South Korea established a relatively stronger health infrastructure than North Korea (Table S4), advances in the health care system can contribute to reducing the mortality rate. Thus, access to optimal management and referral systems at the primary care level, stable supply of nutrients, and removing economic barriers in North Korea would be crucial. Based on the children's disease patterns of South Korea and North Korea found in this study, it is projected that infectious diseases will become more prevalent if we do not have preventive measures. Given the significant differences in children's health between South Korea and North Korea which have persisted for more than 7 decades, it is imperative to bridge this gap.

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### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### ORCID iD

Yoorim Bang: https://orcid.org/0000-0003-2128-7947
Jongmin Oh: https://orcid.org/0000-0002-2980-6943
Eun Mee Kim: https://orcid.org/0000-0002-1649-0759
Ji Hyen Lee: https://orcid.org/0000-0002-2234-1055
Minah Kang: https://orcid.org/0000-0002-5262-286X
Miju Kim: https://orcid.org/0000-0002-4563-0634
Seok Hyang Kim: https://orcid.org/0000-0002-7091-5105
Jae Jin Han: https://orcid.org/0000-0002-6499-7642
Hae Soon Kim: https://orcid.org/0000-0002-6976-6878
Oran Kwon: https://orcid.org/0000-0002-2031-7238
Hunjoo Ha: https://orcid.org/0000-0002-5601-1265
Harris Hyun-soo Kim: https://orcid.org/0000-0003-1311-6507
Hye Won Chung: https://orcid.org/0000-0002-6162-9158
Eunshil Kim: https://orcid.org/0000-0001-5984-7802
Young Ju Kim: https://orcid.org/0000-0002-3153-3008
Yuri Kim: https://orcid.org/0000-0001-7606-8501
Younhee Kang: https://orcid.org/0000-0002-7964-5674
Eunhee Ha: https://orcid.org/0000-0002-4224-3858

### Author Contribution

Conceptualization: Bang Y, Lee JH, Kang M
Formal Analysis: Ha H, Kim E, Kim YJ, Kim Y, Kang Y
Investigation: Kim M, Kim SH, Han JJ, Kim HS, Kwon O, Chung HW
Methodology: Kim HH, Oh J
Project Administration: Kim EM, Ha E
Writing – Original Draft: Bang Y, Oh J, Kim EM, Ha E
Writing – Review & Editing: Bang Y, Oh J, Kim EM, Lee JH, Kang M, Kim M, Kim SH, Han JJ, Kim HS, Kwon O, Ha H, Kim HH, Chung HW, Kim E, Kim YJ, Kim Y, Kang Y, Ha E

### Ethics Approval and Consent to Participate

Not applicable.

### Supplementary Materials

Supplementary materials are available from: https://doi.org/10.12771/emj.2022.e14.

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# Supplementary Appendix

# List of Supplementary Tables and Figures

## Supplementary Tables



## Supplementary Figures

**Table S1.** Description of data characteristics

| | Name | Definition | Age | Data source |
|---|---|---|---|---|
| Indicator | | | | |
| Mortality rate (per 1,000 live births) | Infant mortality | The number of infants dying before reaching one year of age, per 1,000 live births in a given year. | 0–4 years old | WHO |
| | Stillbirth | The number of babies born with no signs of life at 28 weeks or more of gestation, per 1,000 total births. | | |
| | Neonatal mortality | The number of neonates dying before reaching 28 days of age, per 1,000 live births in a given year. | | |
| | Under 5 years mortality | The probability per 1,000 that a newborn baby will die before reaching age five, if subject to age-specific mortality rates of the specified year. | | |
| | Acute lower respiratory infections | The number of deaths from acute lower respiratory infections, per 1,000 live births. | | |
| | Congenital anomalies | The number of deaths from structural or functional anomalies that occur during intrauterine life, per 1,000 live births. | | |
| | Prematurity | The number of deaths of babies born alive before 37 weeks of pregnancy, per 1,000 live births. | | |
| | Birth asphyxia | The number of deaths from the failure to establish breathing at birth, per 1,000 live births. | | |
| | Diarrheal disease | The number of deaths from the passage of three or more loose or liquid stools per day (or more frequent passage than is normal for the individual), per 1,000 live births. | | |
| | Meningitis/Encephalitis | The number of deaths from a serious infection of the meninges or inflammation of the brain caused by any one of a number of viruses, per 1,000 live births. | | |
| | Sepsis and other infections | The number of deaths from a organ dysfunction caused by a dysregulated host response to infection, per 1,000 live births. | | |
| Prevalence (%) | Anemia | The prevalence of anemia in children under 5 years. | 0–4 years old | WHO |
| | Overweight | The prevalence of overweight among children and adolescents, BMI > +1 standard deviations above the median. | 5–9 years old | |
| | Obesity | The prevalence of obesity among children and adolescents, BMI > +2 standard deviations above the median. | | |
| | Thinness | The prevalence of thinness among children and adolescents, BMI < -2 standard deviations below the median. | | |

**Table S2.** The analysis of children's health indicators in South Korea and North Korea from 2000 to 2017

| Category | | Sen's slope | | | Mann-Kendall methods | | Linear regression | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Sen's slope | 95% CI | | Mann-Kendall statistics | P-value | Estimate | 95% CI | |
| Countries | | | | | | | | | |
| South Korea | Infant mortality | –0.21 | –0.26 | –0.16 | –5.76 | <0.001 | –0.21 | –0.24 | –0.19 |
| North Korea | | –1.28 | –1.50 | –1.10 | –5.76 | <0.001 | –1.46 | –1.70 | –1.23 |
| South Korea | Stillbirth | –0.10 | –0.14 | –0.07 | –5.43 | <0.001 | –0.10 | –0.13 | –0.08 |
| North Korea | | –0.75 | –0.88 | –0.63 | –5.76 | <0.001 | –0.78 | –0.89 | –0.68 |
| South Korea | Neonatal mortality | –0.25 | –0.30 | –0.20 | –5.76 | <0.001 | –0.25 | –0.28 | –0.22 |
| North Korea | | –1.53 | –1.86 | –1.32 | –5.76 | <0.001 | –1.91 | –2.29 | –1.53 |
| South Korea | Under 5 years mortality | –0.25 | –0.28 | –0.22 | –5.72 | <0.001 | –0.25 | –0.27 | –0.22 |
| North Korea | | –0.12 | –0.13 | –0.10 | –5.72 | <0.001 | –0.12 | –0.13 | –0.11 |
| South Korea | Acute Lower Respiratory Infections (mortality) | –0.01 | –0.02 | 0.00 | –3.94 | <0.001 | –0.01 | –0.02 | –0.01 |
| North Korea | | –0.33 | –0.40 | –0.29 | –5.72 | <0.001 | –0.41 | –0.49 | –0.33 |
| South Korea | Congenital anomalies (mortality) | –0.05 | –0.07 | –0.03 | –4.94 | <0.001 | –0.06 | –0.07 | –0.05 |
| North Korea | | –0.10 | –0.11 | –0.09 | –5.57 | <0.001 | –0.10 | –0.11 | –0.09 |
| South Korea | Prematurity (mortality) | 0.00 | –0.06 | 0.03 | 0.19 | 0.847 | 0.01 | –0.02 | 0.04 |
| North Korea | | –0.05 | –0.26 | 0.22 | –0.04 | 0.97 | 0.05 | –0.15 | 0.26 |
| South Korea | Birth asphyxia (mortality) | –0.02 | –0.03 | –0.01 | –3.86 | <0.001 | –0.02 | –0.02 | –0.01 |
| North Korea | | –0.20 | –0.24 | –0.17 | –5.72 | <0.001 | –0.23 | –0.27 | –0.19 |
| South Korea | Diarrheal disease (mortality) | 0.00 | 0.00 | 0.00 | –1.54 | 0.123 | 0.00 | 0.00 | 0.00 |
| North Korea | | –0.16 | –0.23 | –0.14 | –5.72 | <0.001 | –0.26 | –0.33 | –0.19 |
| South Korea | Meningitis/Encephalitis (mortality) | 0.00 | 0.00 | 0.00 | –2.37 | 0.018 | 0.00 | –0.01 | 0.00 |
| North Korea | | –0.09 | –0.10 | –0.07 | –5.43 | <0.001 | –0.09 | –0.11 | –0.08 |
| South Korea | Sepsis and other infections (mortality) | –0.01 | –0.01 | 0.00 | –3.05 | 0.002 | –0.01 | –0.01 | 0.00 |
| North Korea | | –0.08 | –0.09 | –0.07 | –5.34 | <0.001 | –0.08 | –0.09 | –0.07 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| South Korea | Anemia (prevalence) | 0.08 | 0.03 | 0.15 | 4.64 | <0.001 | 0.12 | 0.08 | 0.17 |
| North Korea | | 0.05 | –0.13 | 0.22 | 0.46 | 0.649 | 0.05 | –0.08 | 0.17 |
| South Korea | Overweight (prevalence) | 0.53 | 0.52 | 0.53 | 5.56 | <0.001 | 0.53 | 0.53 | 0.54 |
| North Korea | | 0.74 | 0.70 | 0.78 | 5.56 | <0.001 | 0.74 | 0.72 | 0.77 |
| South Korea | Obesity (prevalence) | 0.26 | 0.26 | 0.27 | 5.56 | <0.001 | 0.26 | 0.26 | 0.27 |
| North Korea | | 0.40 | 0.37 | 0.44 | 5.56 | <0.001 | 0.41 | 0.39 | 0.43 |
| South Korea | Thinness (prevalence) | 0.00 | –0.01 | 0.00 | –2.89 | 0.004 | –0.01 | –0.01 | 0.00 |
| North Korea | | –0.08 | –0.08 | –0.08 | –5.42 | <0.001 | –0.08 | –0.08 | –0.08 |

**Table S3.** The daily nutrition per person in South Korea and North Korea from 1990 to 2017

| | South Korea | | | North Korea | | | South Korea | | | North Korea | | | South Korea | | | North Korea | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total Calorie (Kcal) | Plant calories (Kcal) | Animal calories (Kcal) | Total Calorie (Kcal) | Plant calories (Kcal) | Animal calories (Kcal) | Total protein (g) | Plant protein (g) | Animal protein (g) | Total protein (g) | Plant protein (g) | Animal protein (g) | Total fat (g) | Plant fat (g) | Animal fat (g) | Total fat (g) | Plant fat (g) | Animal fat (g) |
| Year | | | | | | | | | | | | | | | | | | |
| 1990 | 2,853 | 2,457 | 395 | 2,370 | 2,135 | 235 | 89.3 | 56.1 | 33.2 | 75.72 | 59.01 | 16.71 | 72.2 | 46.7 | 25.5 | 46.24 | 28.58 | 17.65 |
| 1991 | 2,876 | 2,506 | 370 | 2,368 | 2,136 | 233 | 88.6 | 56.2 | 32.4 | 74.37 | 59.08 | 15.29 | 71.7 | 48.6 | 23 | 45.89 | 27.77 | 18.13 |
| 1992 | 2,912 | 2,514 | 398 | 2,222 | 2,042 | 181 | 90.1 | 56.5 | 33.6 | 68.05 | 55.48 | 12.57 | 73.6 | 48.2 | 25.4 | 38.77 | 25.09 | 13.68 |
| 1993 | 2,872 | 2,464 | 408 | 2,276 | 2,115 | 161 | 91.7 | 56.2 | 35.5 | 66.73 | 54.91 | 11.82 | 74.1 | 48.6 | 25.5 | 38.45 | 26.55 | 11.91 |
| 1994 | 2,950 | 2,534 | 416 | 2,246 | 2,105 | 141 | 94.5 | 58.1 | 36.4 | 64.89 | 54.98 | 9.9 | 77.3 | 51.2 | 26.1 | 37.25 | 26.66 | 10.59 |
| 1995 | 2,959 | 2,520 | 439 | 2,103 | 1,981 | 122 | 96.9 | 57.6 | 39.3 | 59.28 | 50.79 | 8.49 | 76.9 | 50.6 | 26.4 | 35.51 | 26.29 | 9.22 |
| 1996 | 2,948 | 2,495 | 453 | 2,080 | 1,968 | 112 | 98 | 56.8 | 41.1 | 58.46 | 50.53 | 7.93 | 77.7 | 51 | 26.8 | 32.66 | 24.31 | 8.35 |
| 1997 | 2,957 | 2,525 | 431 | 2,133 | 2,041 | 92 | 97 | 56.8 | 40.2 | 58.79 | 52.1 | 6.7 | 79.6 | 54.7 | 24.9 | 33.7 | 26.95 | 6.75 |
| 1998 | 2,819 | 2,416 | 404 | 2,121 | 2,012 | 108 | 93.6 | 56.2 | 37.4 | 57.43 | 50.18 | 7.25 | 72.8 | 49.3 | 23.5 | 32.59 | 24.32 | 8.27 |
| 1999 | 2,968 | 2,526 | 442 | 2,112 | 1,990 | 122 | 98.2 | 57.4 | 40.8 | 57.49 | 49.61 | 7.88 | 82.5 | 56.8 | 25.6 | 31.72 | 22.2 | 9.52 |
| 2000 | 3,010 | 2,579 | 431 | 2,147 | 2,014 | 132 | 97.1 | 55.9 | 41.2 | 61.15 | 52.36 | 8.78 | 80.1 | 55.9 | 24.1 | 35.82 | 25.6 | 10.23 |
| 2001 | 3,000 | 2,538 | 462 | 2,096 | 1,953 | 143 | 98.3 | 53.6 | 44.7 | 58.87 | 49.03 | 9.85 | 83.9 | 58.2 | 25.6 | 35.39 | 24.51 | 10.88 |
| 2002 | 2,991 | 2,515 | 477 | 2,182 | 2,022 | 159 | 98.5 | 52.6 | 45.8 | 62.11 | 51.75 | 10.36 | 85.2 | 58.7 | 26.5 | 37.43 | 25 | 12.43 |
| 2003 | 2,919 | 2,452 | 467 | 2,189 | 2,040 | 150 | 97.6 | 51.5 | 46.1 | 59.42 | 49.78 | 9.64 | 83.1 | 57.5 | 25.6 | 36.55 | 24.82 | 11.73 |
| 2004 | 2,990 | 2,524 | 466 | 2,206 | 2,054 | 152 | 99.4 | 52.7 | 46.7 | 60.27 | 50.57 | 9.7 | 85.8 | 60.7 | 25.1 | 37.45 | 25.65 | 11.8 |
| 2005 | 2,983 | 2,525 | 458 | 2,180 | 2,024 | 156 | 98.1 | 52.7 | 45.4 | 59.19 | 49.05 | 10.14 | 88.9 | 64.2 | 24.6 | 37 | 24.93 | 12.06 |
| 2006 | 2,989 | 2,511 | 478 | 2,141 | 1,999 | 142 | 100.9 | 52.8 | 48.1 | 57.87 | 48.14 | 9.73 | 88.3 | 62.9 | 25.5 | 34.88 | 24.04 | 10.84 |
| 2007 | 2,981 | 2,497 | 484 | 2,109 | 1,975 | 134 | 100.8 | 52.4 | 48.5 | 57.14 | 47.34 | 9.8 | 89 | 63 | 26 | 34.03 | 24.14 | 9.88 |
| 2008 | 2,957 | 2,484 | 474 | 2,095 | 1,969 | 126 | 96.8 | 50.1 | 46.7 | 56.72 | 46.96 | 9.76 | 88.6 | 62.8 | 25.9 | 34.35 | 25.34 | 9.01 |
| 2009 | 2,909 | 2,429 | 480 | 2,088 | 1,962 | 126 | 95.1 | 48.3 | 46.8 | 56.38 | 46.59 | 9.78 | 89.7 | 63.3 | 26.4 | 33.37 | 24.4 | 8.97 |
| 2010 | 2,990 | 2,504 | 487 | 2,089 | 1,963 | 126 | 97.4 | 50.1 | 47.3 | 55.8 | 46.14 | 9.66 | 94.1 | 67.3 | 26.8 | 33.78 | 24.72 | 9.07 |
| 2011 | 3,067 | 2,569 | 498 | 2,100 | 1,972 | 128 | 97.3 | 49.5 | 47.8 | 56.34 | 46.3 | 10.04 | 96 | 69.5 | 26.4 | 33.96 | 24.78 | 9.18 |
| 2012 | 3,112 | 2,607 | 505 | 2,105 | 1,975 | 130 | 98.8 | 50.1 | 48.7 | 55.36 | 45.26 | 10.1 | 99.7 | 72.7 | 26.9 | 35.94 | 26.61 | 9.33 |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2013 | 2,981 | 2,455 | 526 | 2,094 | 1,964 | 130 | 99.2 | 48.3 | 50.9 | 55 | 44.94 | 10.07 | 89.8 | 61.7 | 28.1 | 36.41 | 27.07 | 9.34 |
| 2014 | 3,058 | 2,503 | 555 | 2,080 | 1,952 | 128 | 102.7 | 48.6 | 54.1 | 54.15 | 43.72 | 10.43 | 98.1 | 68.6 | 29.5 | 37.17 | 28.22 | 8.95 |
| 2015 | 2,844 | 2,327 | 517 | 2,093 | 1,963 | 130 | 104.9 | 49.4 | 55.4 | 54.36 | 43.76 | 10.6 | 94.9 | 68.1 | 26.8 | 37.76 | 28.69 | 9.07 |
| 2016 | 2,860 | 2,323 | 537 | 2,058 | 1,926 | 132 | 104.8 | 48.9 | 56 | 54.33 | 43.49 | 10.83 | 98.6 | 70 | 28.6 | 34.68 | 25.46 | 9.22 |
| 2017 | 2,983 | 2,413 | 571 | 2,032 | 1,905 | 127 | 112.5 | 49.2 | 63.3 | 52.25 | 41.72 | 10.54 | 104.1 | 75.2 | 28.9 | 38.13 | 29.38 | 8.75 |

**Table S4.** The number of doctors in South Korea and North Korea

| | South Korea | | | | | | North Korea | |
|---|---|---|---|---|---|---|---|---|
| | Total | Medical doctors | Dentists | Oriental medicine | Pharmacists | Medical and pharmacists (per 10,000 population) | Total | Medical and pharmacists (per 10,000 population) |
| Year | | | | | | | | |
| 1990 | 95,083 | 42,554 | 9,619 | 5,792 | 37,118 | 22.2 | 58,644 | 29 |
| 1993 | 112,046 | 51,518 | 12,180 | 7,569 | 40,779 | 25.4 | 67,254 | 31.9 |
| 1994 | 117,561 | 54,406 | 12,939 | 8,179 | 42,037 | 26.3 | ·· | ·· |
| 1995 | 122,852 | 57,188 | 13,681 | 8,714 | 43,269 | 27.2 | ·· | ·· |
| 1996 | 127,646 | 59,399 | 14,371 | 9,299 | 44,577 | 28 | 70,018 | 31.8 |
| 1997 | 133,101 | 62,609 | 15,383 | 9,289 | 45,820 | 29 | 70,901 | 31.9 |
| 1998 | 138,469 | 65,431 | 16,126 | 9,914 | 46,998 | 29.9 | 71,330 | 31.9 |
| 1999 | 147,559 | 69,724 | 17,276 | 11,345 | 49,214 | 31.7 | 71,785 | 31.9 |
| 2000 | 153,273 | 72,503 | 18,039 | 12,108 | 50,623 | 32.6 | 72,052 | 31.7 |
| 2001 | 158,848 | 75,295 | 18,887 | 12,794 | 51,872 | 33.5 | 72,332 | 31.6 |
| 2002 | 165,111 | 78,609 | 19,672 | 13,662 | 53,168 | 34.7 | ·· | ·· |
| 2003 | 170,708 | 81,328 | 20,446 | 14,553 | 54,381 | 35.6 | ·· | ·· |
| 2004 | 170,683 | 81,998 | 20,772 | 14,421 | 53,492 | 35.5 | ·· | ·· |
| 2005 | 177,050 | 85,369 | 21,581 | 15,271 | 54,829 | 36.7 | ·· | ·· |
| 2006 | 182,244 | 88,214 | 22,267 | 15,918 | 55,845 | 37.6 | ·· | ·· |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 2007 | 188,509 | 91,475 | 23,126 | 16,732 | 57,176 | 38.7 | .. | .. |
| 2008 | 194,916 | 95,088 | 23,924 | 17,541 | 58,363 | 39.7 | .. | .. |
| 2009 | 201,191 | 98,434 | 24,639 | 18,401 | 59,717 | 40.8 | 77,481 | 32.2 |
| 2010 | 206,921 | 101,443 | 25,390 | 19,132 | 60,956 | 41.8 | 77,881 | 32.2 |
| 2011 | 212,652 | 104,397 | 26,098 | 19,912 | 62,245 | 42.6 | 88,553 | 36.4 |
| 2012 | 218,414 | 107,295 | 26,804 | 20,668 | 63,647 | 43.5 | 88,987 | 36.4 |
| 2013 | 221,619 | 109,563 | 27,409 | 21,355 | 63,292 | 43.9 | 89,416 | 36.4 |
| 2014 | 225,834 | 112,476 | 28,134 | 22,074 | 63,150 | 44.5 | 89,842 | 36.4 |
| 2015 | 233,753 | 116,045 | 28,953 | 23,245 | 65,510 | 45.8 | 90,267 | 36.4 |
| 2016 | 238,860 | 118,765 | 29,643 | 23,460 | 66,992 | 46.6 | 90,691 | 36.4 |
| 2017 | 244,785 | 121,638 | 30,344 | 24,187 | 68,616 | 47.7 | 91,120 | 36.4 |
| 2018 | 248,323 | 123,173 | 30,918 | 24,885 | 69,347 | 48.1 | 91,550 | 36.4 |
| 2019 | 254,931 | 126,795 | 31,640 | 25,592 | 70,904 | 49.3 | 91,980 | 36.4 |

The difference in the number of medical personnel between South Korea and North Korea shows the status of health infrastructure. Despite the limited access to North Korean data, the total number of medical personnel is much smaller in North Korea than South Korea. The health infrastructure in North Korea has been collapsed since 1990 when the financial crisis and natural disaster hit. This indicates that North Korea is less likely to have easier access to vaccination and better hygiene conditions.

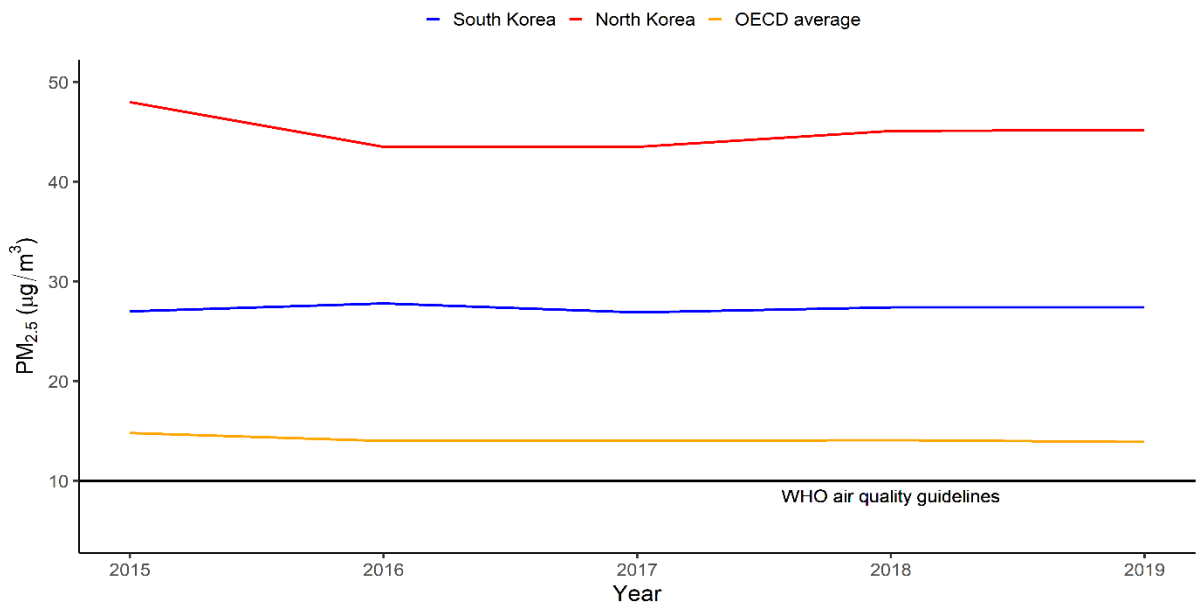


**Fig. S1.** The average annual concentration of $PM_{2.5}$ in South Korea and North Korea from 2015 to 2019.

Internationally comparable measurements of average $PM_{2.5}$ concentrations are derived from satellite observations, chemical transport models, and ground monitoring stations. The x-axis indicates year. The y-axis indicates $PM_{2.5}$ $\mu g/m^3$ concentrations. The red line indicates the average $PM_{2.5}$ concentration in North Korea. The blue line indicates the average $PM_{2.5}$ concentration in South Korea. The orange line indicates the $PM_{2.5}$ concentration in OECD average. The green dash line indicates the WHO air quality guidelines (10 $\mu g/m^3$). Source: OECD Statistics.

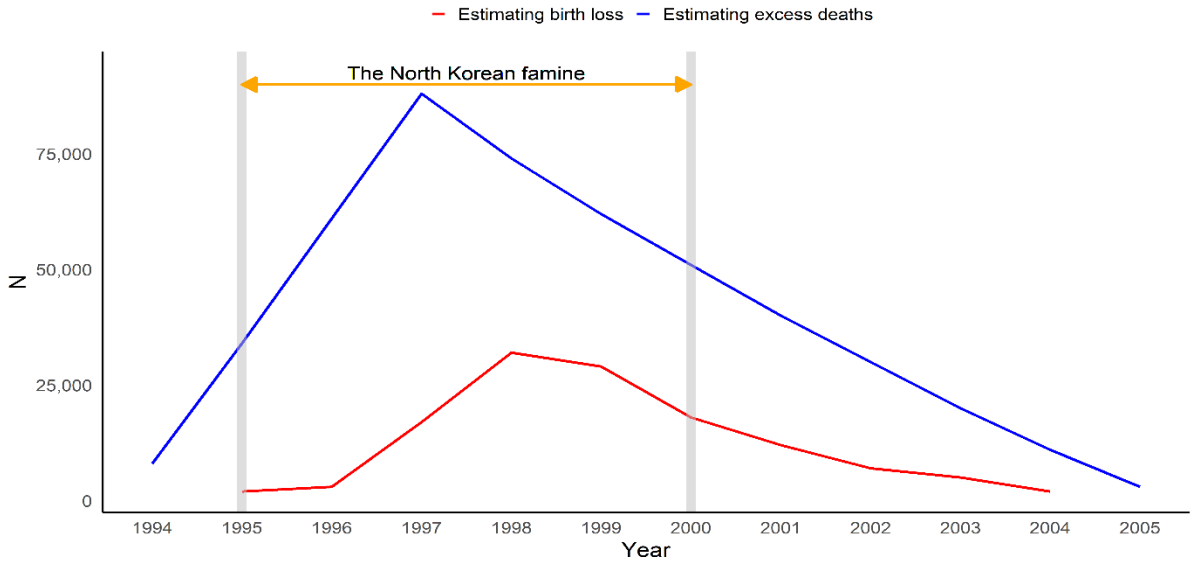


**Fig. S2.** The estimation of birth losses and excess deaths during the North Korean famine from 1994 to 2005.

The x-axis indicates years. The y-axis indicates counts (estimating birth loss or estimating excess deaths). The red line stands for the estimated birth loss and the blue line for the estimated excess deaths; The orange arrow means the period of North Korean famine from 1995 to 2000.

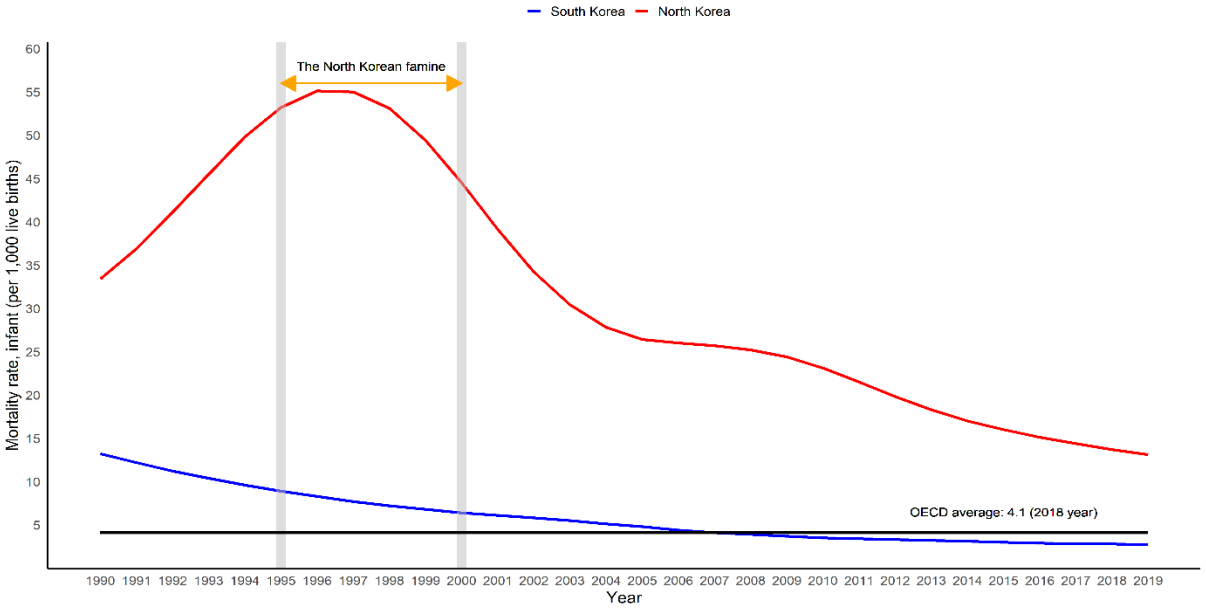


**Fig. S3.** The time–plot of annual infant mortality rates in South Korea and North Korea from 1990 to 2019.

The x-axis indicates years. The y-axis indicates the infant mortality rate per 1,000 live births. The red bar indicates North Korea. The blue bar indicates South Korea. The orange arrow means the period of North Korean famine from 1995 to 2000. The green dash line indicates the OECD average.


**Fig. S4.** Coal consumption in South Korea and North Korea from 2000 to 2017.

The x-axis indicates years. the y-axis indicates coal consumption (Mst). The red bars indicates coal consumption in North Korea.The blud bars indicates coal consumption in South Korea.

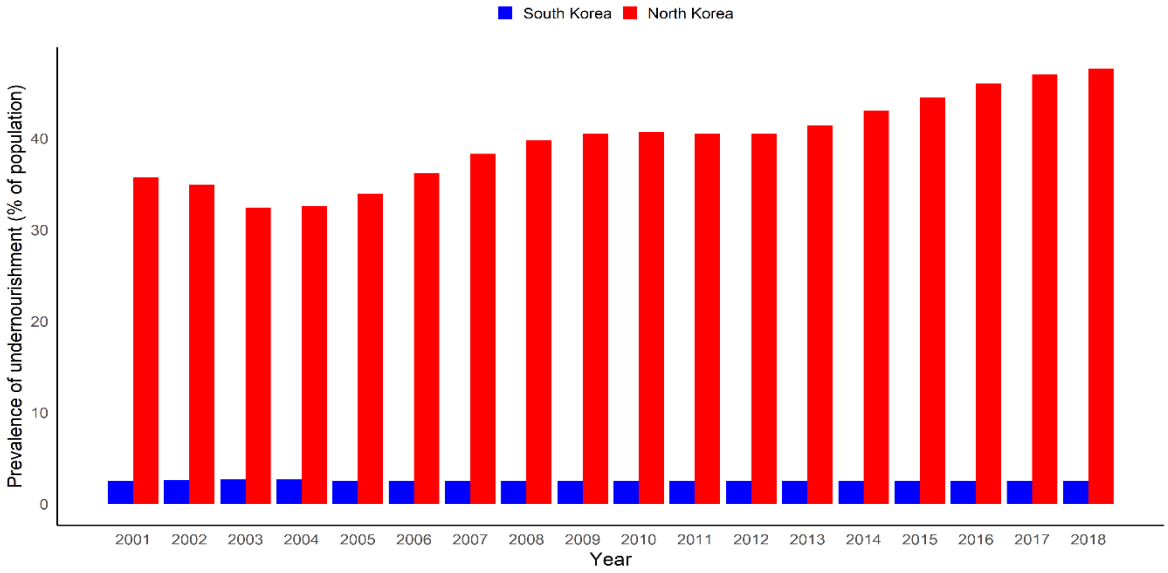


**Fig. S5.** The undernourished population of South Korea and North Korea.

The x-axis indicates years. The y-axis indicates prevalence of undernourishment (%). The red bars indicates prevalence of undernourishment in North Korea. The blue bars indicates prevalence of undernourishment in South Korea.

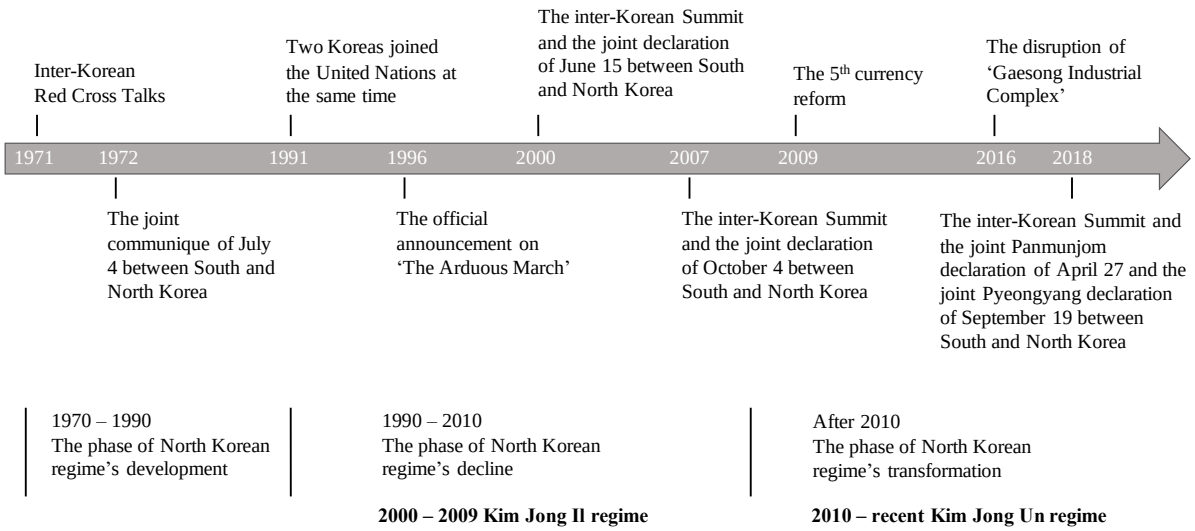


**Fig. S6.** Major historical events in the Korean Peninsula from 1970 to 2020.

The so-called 'Arduous March' was officially announced in 1996 and lasted until 1998 which caused severe malnutrition and stunting among children. This unfortunate event happened during the phase of North Korean regimen's decline (Kim Jong Il government). Although there were few inter-Korean Summits that see the possibility of peaceful cooperation since 2000, North Korea still suffers from economic difficulties. For example, the North Korean government forcibly enforced the 5$^{th}$ currency reform in 2009 that changes the value of money and then brought a disastrous damage to North Korean's financial stability and food supply. It might result in the increasing prevalence of anemia among North Korean children.

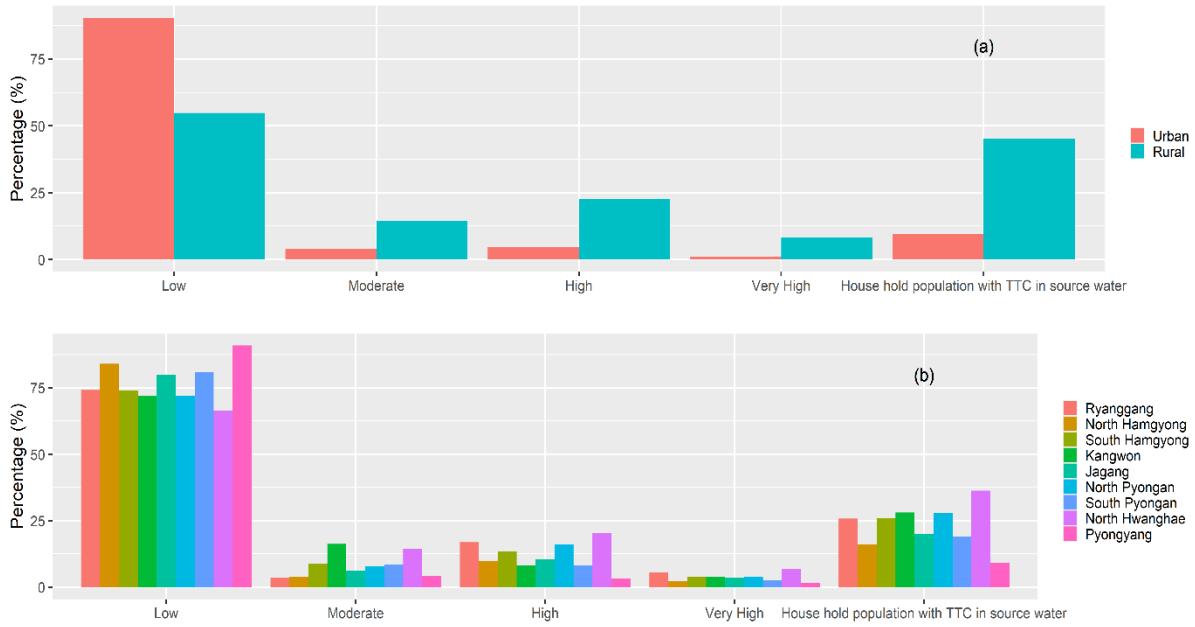


**Fig. S7.** Quality of source drinking water in North Korea in 2017.
(a) Risk level based on number of thermotolerant coliform (TTC) per 100ml by area; (b) Risk level based on number of thermotolerant coliform (TTC) per 100ml by province.

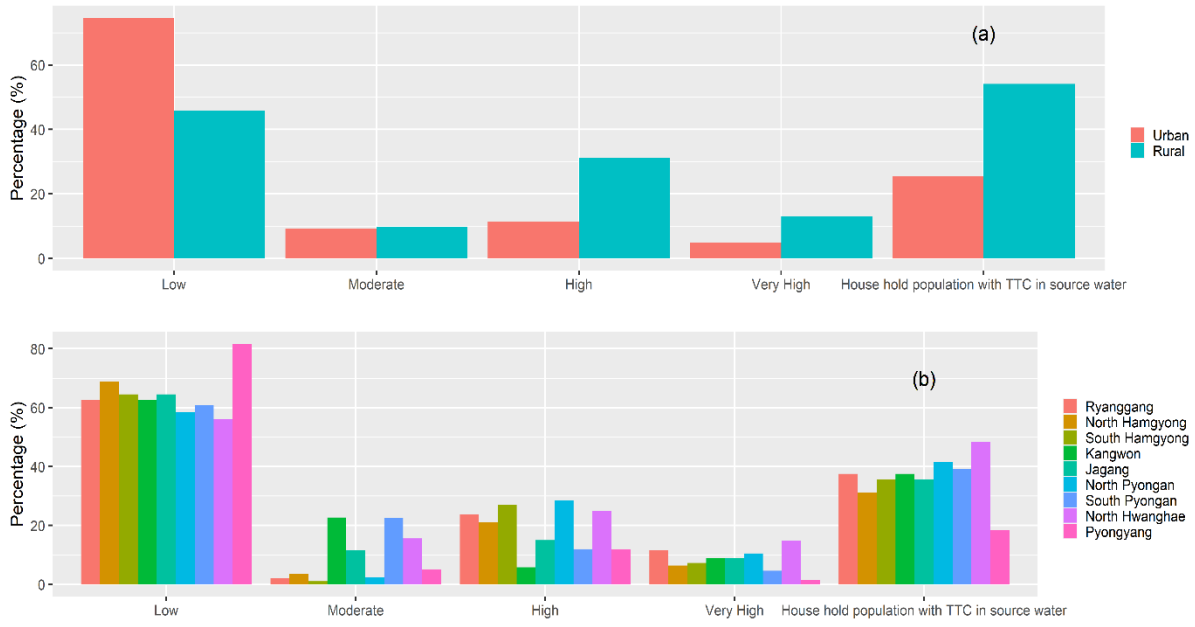


**Fig. S8.** Quality of household drinking water in North Korea in 2017.
(a) Risk level based on number of thermotolerant coliform (TTC) per 100ml by area; (b) Risk level based on number of thermotolerant coliform (TTC) per 100ml by province.

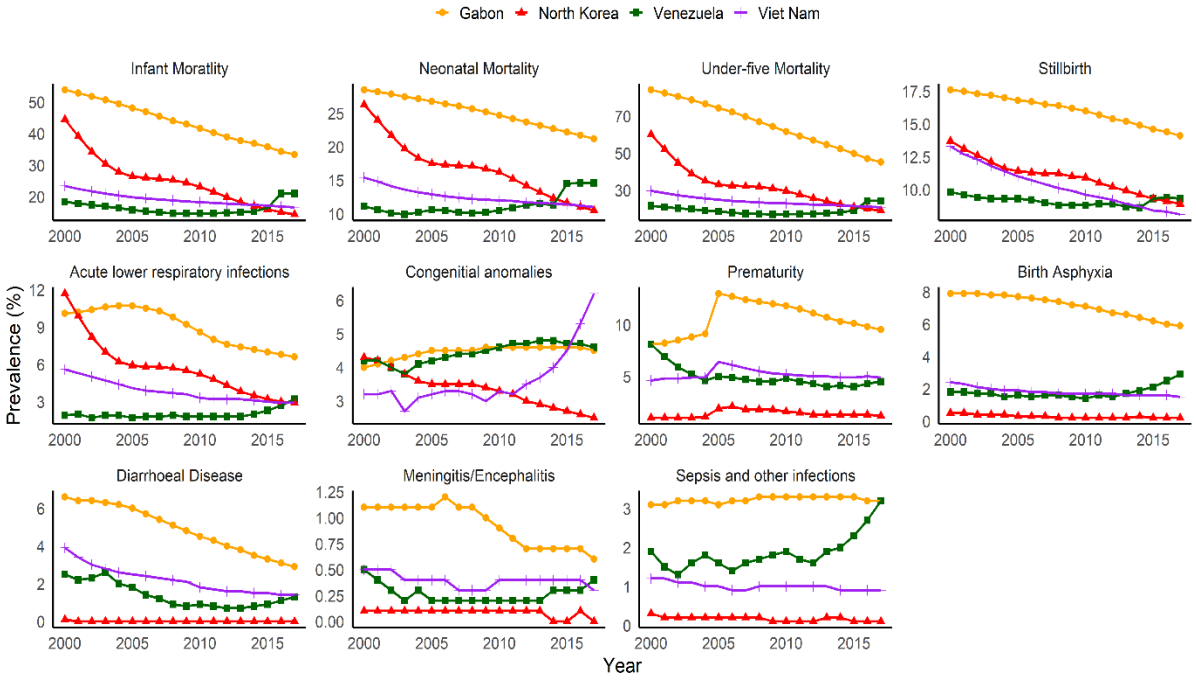


**Fig. S9.** Disease pattern of North Korea with developing countries (mortality rate per 1,000 live births).

The x-axis indiciates year. The y-axis indicates mortality rate per 1,000 live births. The yellow line indicates mortality rate in Gabon, the red line indicates mortality rate in North Korea, the green line indicates mortality rate in Venezuela, and the purple line indicates mortality rate in Vietnam.

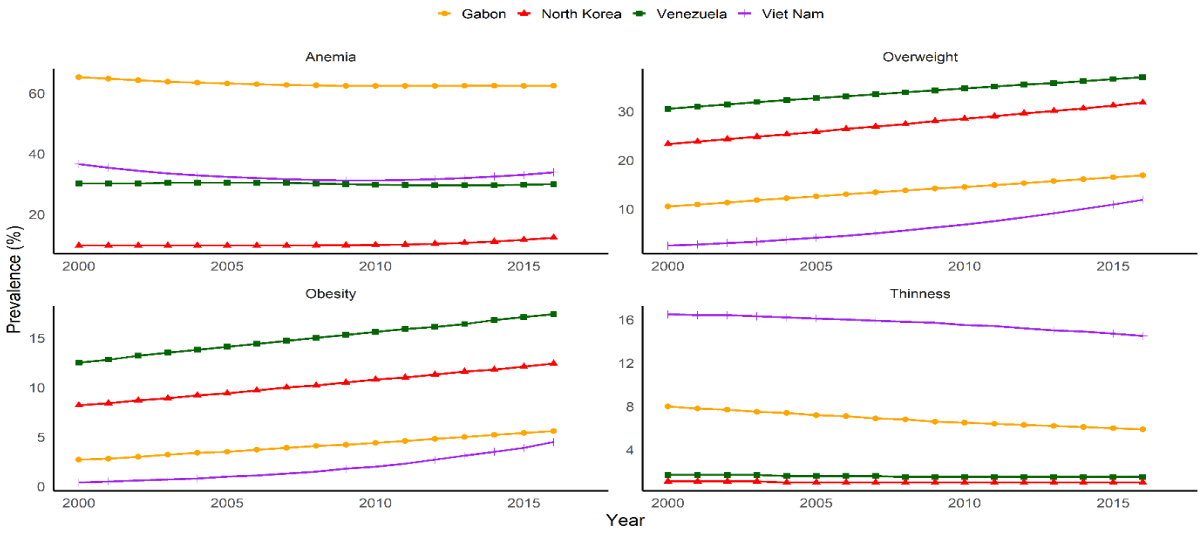


**Fig. S10.** Disease pattern of North Korea with developing countries (prevalence (%)).

The x-axis indiciates year. The y-axis indicates prevalence(%). The yellow line indicates prevalence in Gabon, the red line indicates prevalence in North Korea, the green line indicates prevalence in Venezuela, and the purple line indicates prevalence in Vietnam.

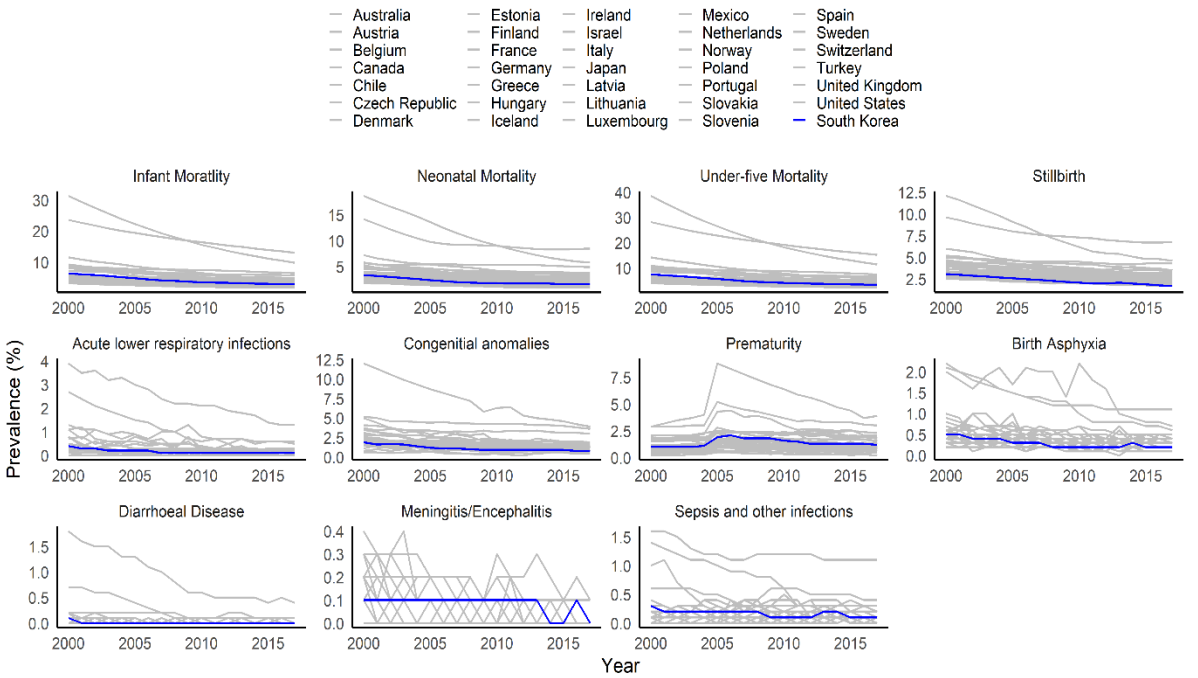


**Fig. S11.** Disease pattern of South Korea with developed countries (mortality rate per 1,000 live births).

The x-axis indiciates year. The y-axis indicates mortality rate per 1,000 live births. The blue line indicates mortality rate in South Korea. The gray line indicates the developed countries.

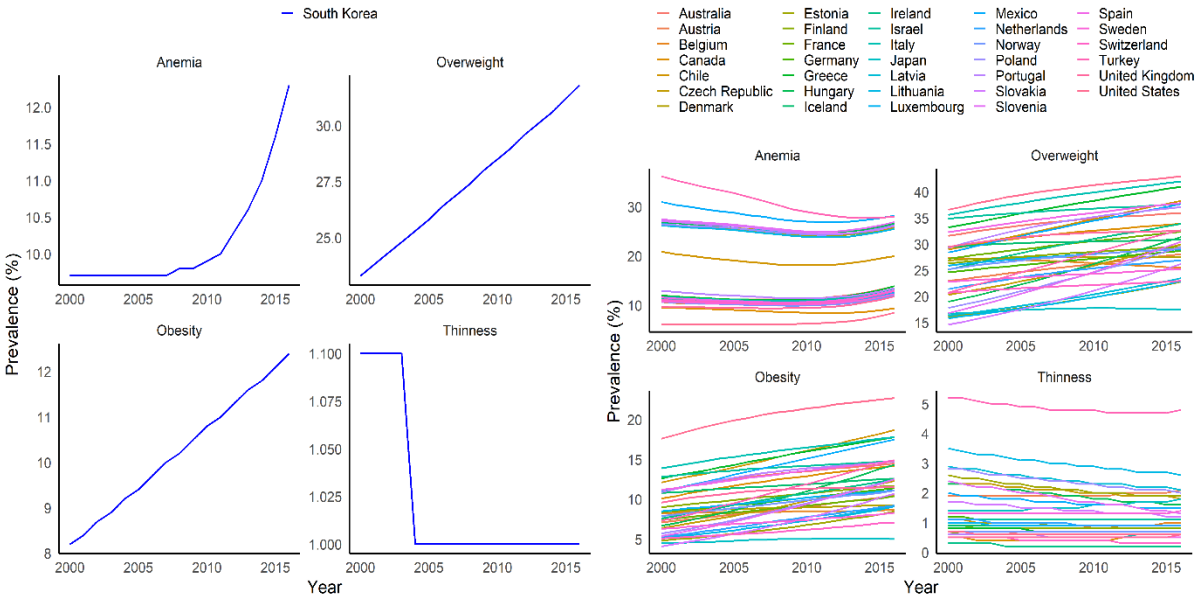


**Fig. S12.** Disease pattern of South Korea with developed countries (prevalence (%)).
The x-axis indiciates year. The y-axis indicates prevalence(%). The blue line indicates prevalence in South Korea.

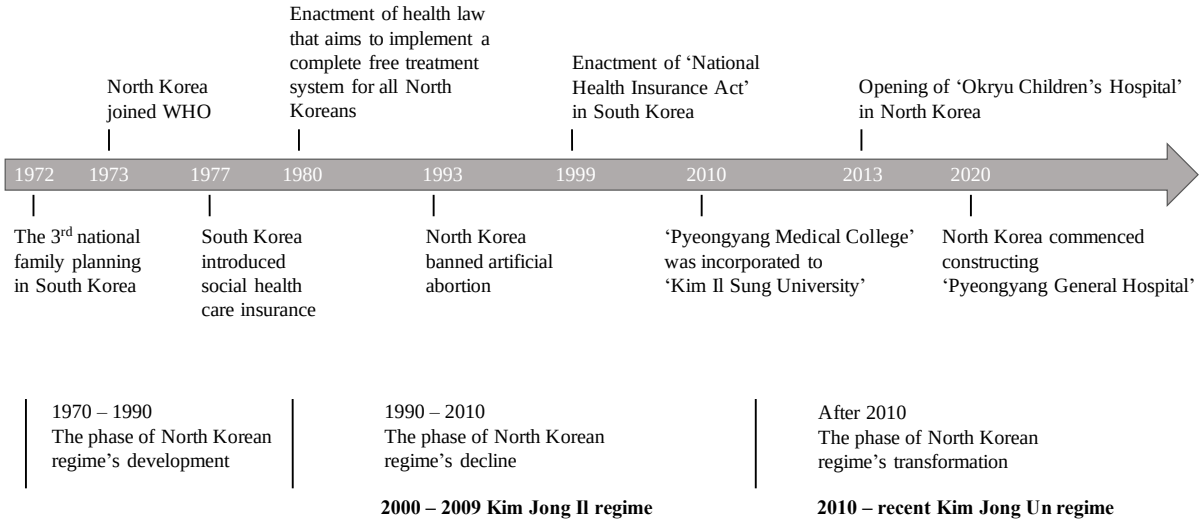


**Fig. S13.** History of health and medical care policy in North Korea from 1970 to 2020.

Case Report

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# Aggressive Clinical Deterioration of Recurrent Extramammary Paget's Disease: A Case Report

**Sewon Lee**[1,*], **Sang Yoon Kim**[2,*], **Heejin Bang**[3], **Kyoung Eun Lee**[1]

[1]Division of Hematology-Oncology, Department of Internal Medicine, School of Medicine, Ewha Womans University, Seoul, Korea
[2]Department of Internal Medicine, Myongji Hospital, Hanyang University College of Medicine, Goyang, Korea
[3]Department of Pathology, Konkuk University Medical Center, Konkuk University School of Medicine, Seoul, Korea

*These authors contributed equally to this work.

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**Corresponding author**
Kyoung Eun Lee
Division of Hematology-Oncology, Department of Internal Medicine, School of Medicine, Ewha Womans University Hospital, 1071, Anyangcheon-ro, Yangcheon-gu, Seoul 07985, Korea
Tel: 82-2-2650-5030
Fax: 82-2-2650-5062
E-mail: oncolee@ewha.ac.kr

**Key Words**
Paget's disease, extramammary; Aggressive extramammary Paget's disease

Extramammary Paget's Disease (EMPD) is a rare intraepithelial malignancy of apocrine bearing glands, which occur usually in the perianal region, vulva, scrotum, penis and ax-illa. Most of the disease are treated by surgical resection and the prognosis is generally good. Even though recurrent disease, it is usually slowly progressed with good prognosis. Here we describe the case of a 70-year-old male who has presented with initially just as an EMPD component of squamous cell carcinoma in inguinal skin, but he showed recur-rence of EMPD. The disease has progressed rapidly, finally he died of that EMPD in 2 months of recurrence. The purpose of this study is to report the rare case of fulminant disease course of EMPD after recurrence.

## Introduction

Paget's disease is a rare intraepithelial neoplasm. It has two sub-types, one is mammary Paget's disease (MPD) and the other is extramammary Paget's disease (EMPD) which occurs in other than mammary area. Morphology and histology of these two subtypes are the same. The origin of EMPD is not clear but suggested that they are originated form apocrine bearing glands, such as the perianal region, vulva, scrotum, penis and axilla. The clinical features of EMPD can be non-specific such as chronic eczematous cutaneous disease, therefore misdiagnosis as an inflammatory or infective skin condition is common. Its final diagnosis is often delayed for a long time. The prognosis of this disease entity is variable according to clinical situation and recent analysis of 2,000 EMPD patients showed that EMPD in scrotal lesion, concurrent malignancy, metastatic lesion, old age and male are the risk factors for mortality [1–4]. Chan et al. reported that 8.3% of EMPD patients showed concurrent malignancy in colon and prostate [5]. Sometimes, there are co-existing squamous cell carcinoma in situ in the skin [6].

Surgical resection with negative margin is the considered to be the standard of care in EMPD, other options include imiquimod 5% topical cream, modified peripheral Mohs surgery and radiation therapy [7,8]. Although recurrence is common, the disease has a slow progression and paucity metastasis, so the prognosis is generally good.

Here, we describe a case of rapid progressed EMPD patient, who showed fulminant disease course in two months.

## Case Report

A 70-year-old man presented with discomfort in the right inguinal area. He had a history of skin malignancy in the right inguinal area three years ago and treated with surgical resection (wide excision and split thickness skin graft from thigh). The histopathological study at that time showed mostly squamous cell carcinoma (3×2.5 cm sized with depth of 4 mm invasion) and focal EMPD component (Fig. 1). During the last three years, he did not visit the clinic. This time he visited the hospital due to right inguinal discomfort. In physical examination, he showed palpable right inguinal lumps without obvious skin change. CT scan showed difuse skin thickening and subcutaneous infiltration at right inguinal and pubic area with mild lymph node enlargements. There was no other visceral lesion in the CT scan (Figs. 2A, 2B). Blood test showed no specific finding except for a mild CEA elevation (10.4 ng/mL, reference range 0–5.0 ng/mL). He underwent a punch biopsy in right inguinal lymph nodes area. The pathology showed the consistent findings of EMPD and immunohistochemical stains showed CK7 (+), CEA (+) and HER2 SISH (–). Further groin dissection was planned. However, he wanted to postpone surgery due to private reasons.

However, two months later, he visited the clinic again due to severe back pain. Spine MRI showed several metastatic lesions in the lumbar spine, sacrum and pelvic bones. The blood test showed anemia with hemoglobin level of 6.1 g/dL and elevated CEA level (21.2 ng/mL) compared with results obtained two months ago. Endoscopic findings including colonoscopy and duodenofiberscopy showed no bleeding tendency or no specific lesion. Subsequent CT scan showed multiple hepatic metastasis, various lymph nodes enlargements, and bony metastasis in abdomen. However no significant change of inguinal lymphadenopathies was documented as EMPD two months ago. FDG PET scan showed similar findings (Figs. 2C–2F). At the time of admission, the level of bilirubin was in normal range, but suddenly he showed jaundice with increasing serum bilirubin level. He underwent liver biopsy and the pathologic results showed mmetastatic carcinoma from the previous EMPD with the same immunohistochemical results of CK7 (+), CEA (+), GCDFP-15(+), HER2 (–) (Fig. 3). We planned chemotherapy for the metastatic EMPD. However just a few days, he showed rapid clinical deterioration with hepatic failure (Fig. 4).

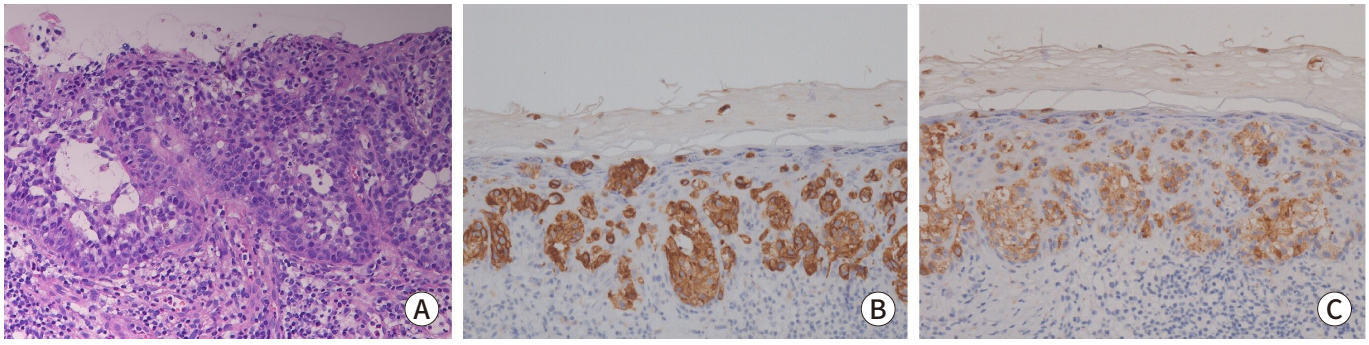


**Fig. 1.** Histopathologic images of skin lesion. (A) Initial skin biopsy of pubic area, the epidermis shows the Paget cells with abundant clear cytoplasm with intracellular and extracellular mucin production (H&E, ×200). (B) Positive staining for CK7 (IHC, ×200). (C) Positive staining for CEA (IHC, ×200). IHC, immunohistochemical.


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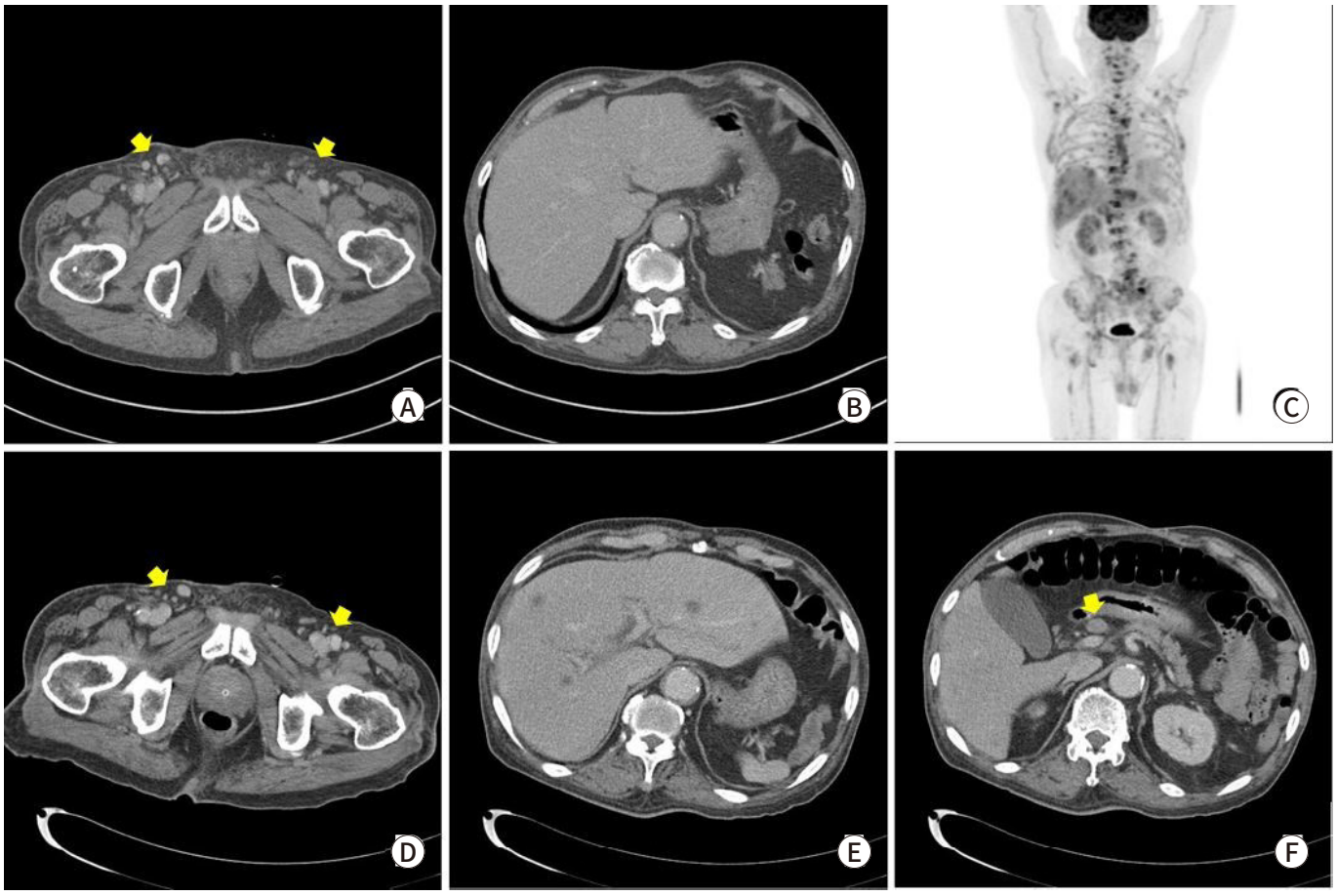


**Fig. 2.** Radiologic findings. (A) Abdomen CT reveals diffuse skin thickening and subcutaneous infiltration at right inguinal and pubic area with lymphadenitis at recurrence (arrows), (B) no other visceral lesion at Abdominal CT of recurrence, (C) FDG-PET CT of after 2 months. (D–F) Abdominal CT after 2 months.

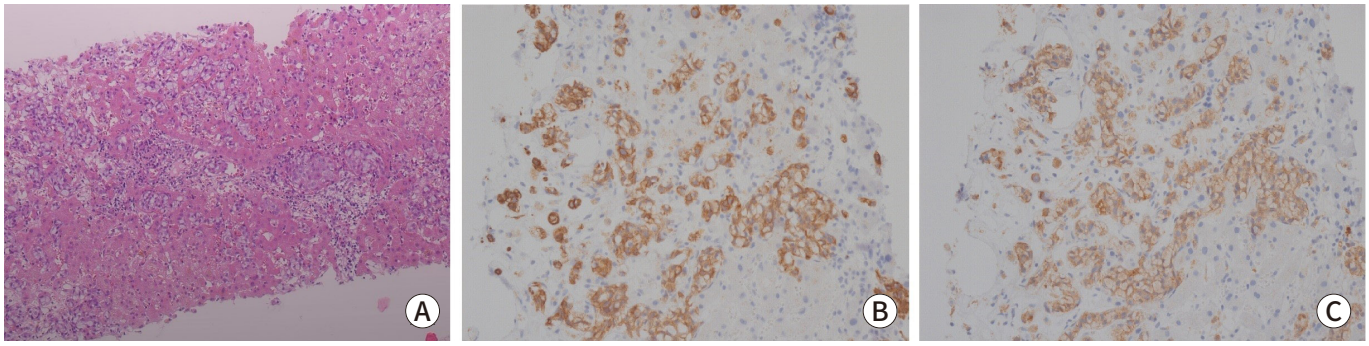


**Fig. 3.** Histopathologic images of liver lesion. (A) Liver biopsy, the Paget cells clusters with clear cytoplasm in hepatic sinusoid (H&E, ×100). (B) Positive staining for CK7 (IHC, ×200). (C) Positive staining for CEA (IHC, ×200). IHC, immunohistochemical.

Eventually, on the 12nd admission day, he died of the disease.

This is the first report about a fulminant disease course of a metastatic, recurrent EMPD to this time in our country.


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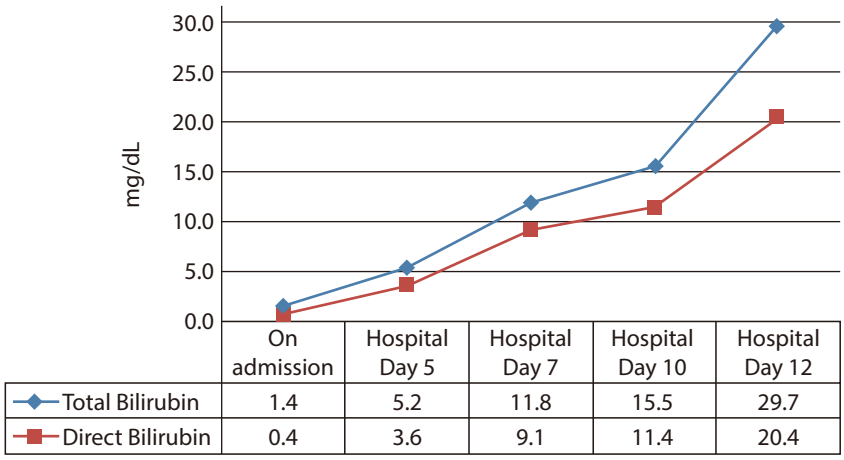


| | On admission | Hospital Day 5 | Hospital Day 7 | Hospital Day 10 | Hospital Day 12 |
|---|---|---|---|---|---|
| Total Bilirubin | 1.4 | 5.2 | 11.8 | 15.5 | 29.7 |
| Direct Bilirubin | 0.4 | 3.6 | 9.1 | 11.4 | 20.4 |

**Fig. 4.** The increment of bilirubin within 2 weeks.

## Discussion

EMPD is a rare slow-growing cutaneous adenocarcinoma that presents as an erythematous, eczematous plaque outside the mammary gland. This neoplastic lesion is often delayed before diagnosis, but usually resulted good prognosis. The range of EMPD recurrence is very wide, for the example, the recurrence of EMPD in vulva varies from 12% to 61% [5,9]. On multiple variate analysis, dermal invasion, lymph node metastasis and elevated serum CEA associated with poor prognosis have been reported [10]. The analysis from large scale patients showed that surgery is a protective factor and radiation is a risk factor for EMPD survival [4]. Although the invasion of dermis is uncommon, if once the EMPD invades into the dermis, that could get metastatic characteristics [11]. Interestingly, Chanda et al. reported that 46% of patients with EMPD associated with an underlying carcinoma developed metastatic disease, compared to 18% of patients with a non-invasive disease [12]. In a large study of 1,439 patients with invasive EMPD, disease specific five year survival was 94.9% (95% CI 92.7%–96.5%) for localized disease, 84.9% (95% CI 77.4%–90.0%) for regional disease and 52.5% (95% CI 29.3%–71.3%) for distant disease. For patients diagnosed with distant spread the outlook was still favorable since more than half of all patients were alive at 5 years of observation [13].

In the case of our patient, he had the risk factor of concurrent skin squamous cell carcinoma, his EMPD presented just as a minor component of that skin squamous cell carcinoma. However, after relapse, EMPD was the only lesion except squamous cell carcinoma. Meanwhile, the most interesting things in this case is that he rapidly progressed to death within three months after diagnosis of relapse. Actually this patient visited EMPD recurrence after 3 years of primary treatment, and there was an evidence of dermal invasion such as subcutaneous infiltrative lesions in the CT scan without visceral or distant metastasis. However, two month's break resulted in distant failure and finally death. Thus, the findings of regional node involvement mimicking lymphadenitis would be a grave sign for rapid distant progression. Recently one study has shown that systemic treatment of EMPD in the disease is metastatic, especially some EMPD showed HER2 positivity and anti-HER2 therapy could result in a durable response and durable survival [14].

It is still uncertain whether long standing local recurrent disease will transform to invasive form. Chang et al. reported that chemokine receptors, CXCR4 and CXCR7 are associated with poor outcome and that they can be used as prognostic biomarkers [15]. In the recent basic and


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translational research, many other disease mechanisms are under elucidation including RAS-RAF-MEK-ERK signaling, PI3K-AKT-mTOR signaling and androgen-AR signaling. In the future, diagnostic and therapeutic application of this research outcome would make the management of EMPD much better.

## Conclusion

EMPD is an intraepithelial malignancy, which shows recurrence and occasional metastasis, with usually good prognosis. Although several studies reported this disease entity, the focus was on the initial skin lesions with limited experience of disease locations and surgical outcomes. This study is the first report of a poor clinical outcome in three months of presentation involving aggressive deterioration of metastatic EMPD. The findings aid physicians in selectively managing EMPD patients, especially those diagnosed with the disease concomitant with squamous cell carcinoma of skin, for enhanced clinical out-comes.

## Acknowledgements

We are grateful to Dr. Min Sun Cho in the Pathology department of Ewha Womans University hospital for her contribution to this work.

### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### ORCID iD

Sewon Lee: https://orcid.org/0000-0003-4334-6856
Sang Yoon Kim: https://orcid.org/0000-0002-1155-1495
Heejin Bang: https://orcid.org/0000-0001-5357-5025
Kyoung Eun Lee: https://orcid.org/0000-0003-1596-8666

### Author Contribution

Conceptualization: Lee KE
Formal Analysis: Kim SY, Bang H, Lee KE
Investigation: Lee S, Bang H, Lee KE
Methodology: Lee S, Bang H, Lee KE
Project Administration: Lee S, Lee KE
Writing – Original Draft: Lee S, Kim SY, Lee KE
Writing – Review & Editing: Lee S, Kim SY, Bang H, Lee KE

### Ethics Approval and Consent to Participate

This study was done in Ewha Womans University Mokdong Hospital and the study was approved by our own Institutional Review Board (No. EUMC 2018-08-031, Ewha Womans Medical Center).

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Case Report

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# Simultaneous Ileocecectomy and Anterior Resection with the da Vinci SP® Surgical System for Patient with Crohn's Disease: A Case Report

**Ho Seung Kim, Gyoung Tae Noh**

Department of Surgery, Ewha Woman's University College of Medicine, Seoul, Korea

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**Corresponding author**
Gyoung Tae Noh
Department of Surgery, Ewha Womans University College of Medicine, 260, Gonghang-daero, Gangseo-gu, Seoul 07804, Korea
Tel: 82-2-6986-1650
Fax: 82-2-6986-5721
E-mail: gtnohlive@gmail.com

**Key Words**
da Vinci SP; Robotic surgical procedures; Crohn disease; Digestive system fistula

A 25-year-old female visited the clinic with abdominal pain and poor oral intake. She was diagnosed with Crohn's disease and had a history of using infliximab for 4 years. She had no previous operative history. Magnetic resonance enterography demonstrated the progression of a penetrating complication that involved the distal ileum and complex entero-enteric fistula between the terminal ileum and sigmoid colon. Surgery was conducted using the da Vinci SP surgical system. In the operative field, severe adhesion was observed between the terminal ileum, adjacent ileum, cecum, and the sigmoid colon. After adhesiolysis of the small bowel and right colon was performed, the fistula tract between the sigmoid colon and terminal ileum was identified and resected. Then, simultaneous ileocecectomy and anterior resection was performed. The operation was completed without any intraoperative complications and patient's recovery was uneventful. She was discharged postoperatively, after 8 days.

## Introduction

Minimally invasive surgery for Crohn's Disease (CD) can be challenging due to thickened and friable mesentery, enteric fistulas, bowel perforation, and frequent occurrence of intra-abdominal abscess. Difficulties in the operative field are reflected by a high rate of conversions and complications following surgical treatment in patients with inflammatory bowel disease [1]. Nevertheless, laparoscopic surgery for patients with intra-abdominal lesions as a result of CD has been widely adopted [2,3]. Moreover, robotic ileocecal resection in patients with CD has been also reported [3–5].

In 2018, Intuitive Surgical launched the da Vinci SP (dVSP) surgical system, which was designed for pure robotic single-incision surgery. It overcame the problem of requiring multiple ports in conventional robotic surgery and addressed concerns involving triangulation and retraction in single-incision laparoscopic surgery. To conduct surgery with a single port, a cannula, which consists of four channels, was applied. Three instruments and one camera can be inserted through a single cannula. Further, the 360° boom can reach anywhere in the abdominal cavity regardless of the surgical target without the need for redocking. For proper triangulation and retraction, each instrument has two joints called the elbow and the wrist joint. In addition, articulating endoscope was adopted to eliminate instrument crashes.

Thus far, there are several reports on the results of minimally invasive approaches, which include

laparoscopic and robotic surgery in patients with intra-abdominal CD [3–5]. However, to the best of our knowledge, there has been no report on the application of the dVSP surgical system. Here we report the patient with intra-abdominal CD who underwent simultaneous ileocecectomy and anterior resection due to the fistula between the distal ileum and sigmoid colon.

## Case

A 25-year-old female visited the clinic with abdominal pain and poor oral intake. She was diagnosed with CD 4 years ago and had been taking infliximab ever since. She had no previous operative history. On admission, her vital signs were non-specific. The blood examination revealed mild elevated leukocyte count (10,010 /mm$^3$; normal, 4.000–10,000 /mm$^3$) and mild elevated C-reactive protein level (3.36 mg/dL; normal, 0–0.5 mg/dL). Colonoscopy showed a whitish scar with inflammatory pseudopolyps in the cecum and a mild structure was observed in the ileocecal valve, although scope passing was possible (Fig. 1A). In the terminal ileum, an ulcer with edematous mucosa and stenosis was observed; here, scope pass was impossible (Fig. 1B). Magnetic resonance enterography demonstrated the progression of a penetrating complication that involved distal ileum with a complex entero-enteric fistula between the terminal ileum and sigmoid colon (Fig. 1C) as well as suspicions regarding another fistula between the distal ileum (Fig.

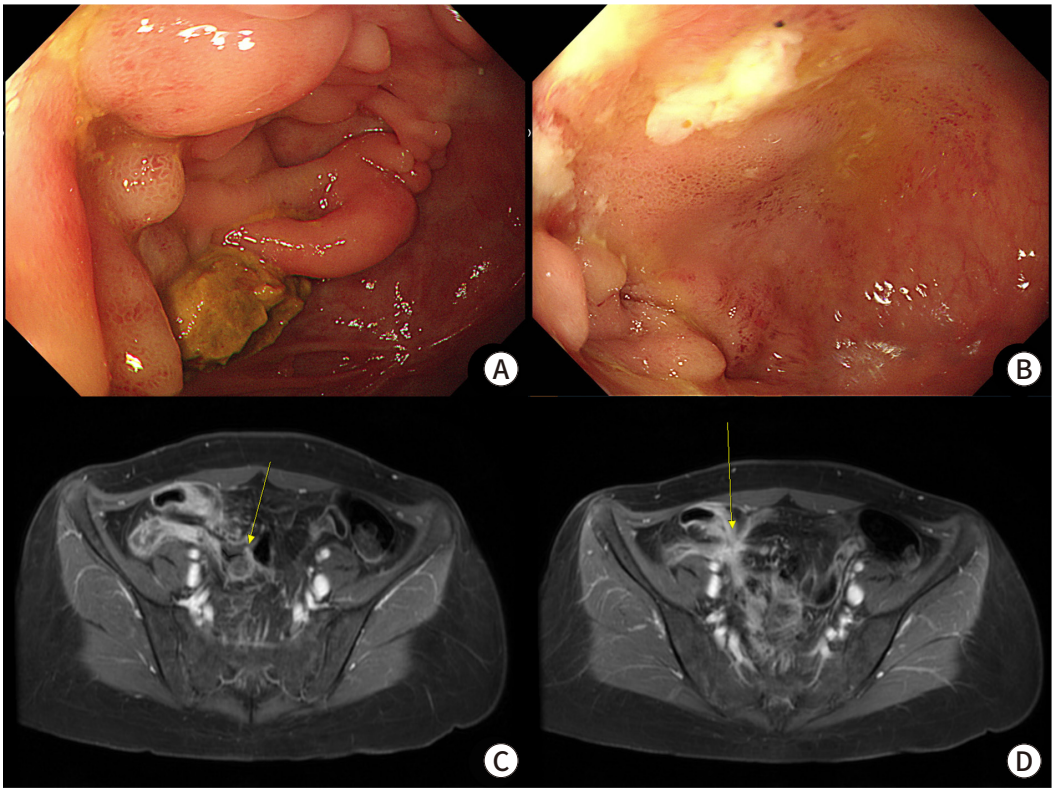


**Fig. 1.** Colonoscopy (A,B) and magnetic resonance enterography (C,D) images. (A) Colonoscopy shows a whitish scar with inflammatory pseudopolyps in cecum and mild stricture is observed in ileocecal valve, (B) in terminal ileum, ulcer with edematous mucosa and stenosis is observed, (C) the magnetic resonance enterography shows progression of a penetrating complication that involved distal ileum with complex entero-enteric fistula between terminal ileum and sigmoid colon, (D) another fistula tract is suspicious between distal ileum.


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1D). Despite conservative treatment with bowel rest and antibiotics for 2 weeks, the patient could not tolerate the diet although abdominal pain was relieved. Contrast-enhanced abdominopelvic CT, following conservative treatment, clearly revealed entero-enteric fistula despite improvements in the inflammatory change in the ileum relative to the previous magnetic resonance enterography (Fig. 2). Hence, consultation with the surgical department was conducted.

After careful discussion on surgical treatment with the patient and her family, an operation with the dVSP surgical system was performed. After making a vertical umbilical skin incision of 3.5 cm, the fascia layer was opened using the open Hasson technique. The single-port entry system was applied through the wound opening and $CO_2$ gas to 12 mmHg was insufflated. The patient was placed in the Lloyd-Davies position (i.e., head-down lithotomy with hips flexed) with a steep Trendelenburg position to expose the surgical target (right lower abdomen and pelvis) clearly. The patient cart of the dVSP surgical system was placed on her right side. The dVSP cannula, which consists of four channels, was inserted into the single-port entry system. Three 6-mm robotic instruments (dVSP monopolar curved scissor, fenestrated bipolar forceps, and Cadiere forceps), along with a 12-mm articulating camera, were inserted into each channel. After the completion of docking, the surgeon started to perform robotic surgery in the console. During the console time, the assistant performed endoscopic suction, inserted suture materials into the abdominal cavity, and stapled for distal sigmoid colon resection through the remaining trocar of the single-port entry system.

In the operative field, severe adhesion among terminal ileum, adjacent ileum, and sigmoid colon was observed. To clarify the exact anatomical state, adhesiolysis of the small bowel and right colon was performed. After mobilizing the bowel, the fistula tract between the sigmoid colon and distal ileum was identified and resected. The hole in the sigmoid colon was closed by robotic suture. To perform ileocecectomy, which included lesions of the distal ileum, right colon mobilization to the hepatic flexure was conducted from the right paracolic gutter, duodenum,

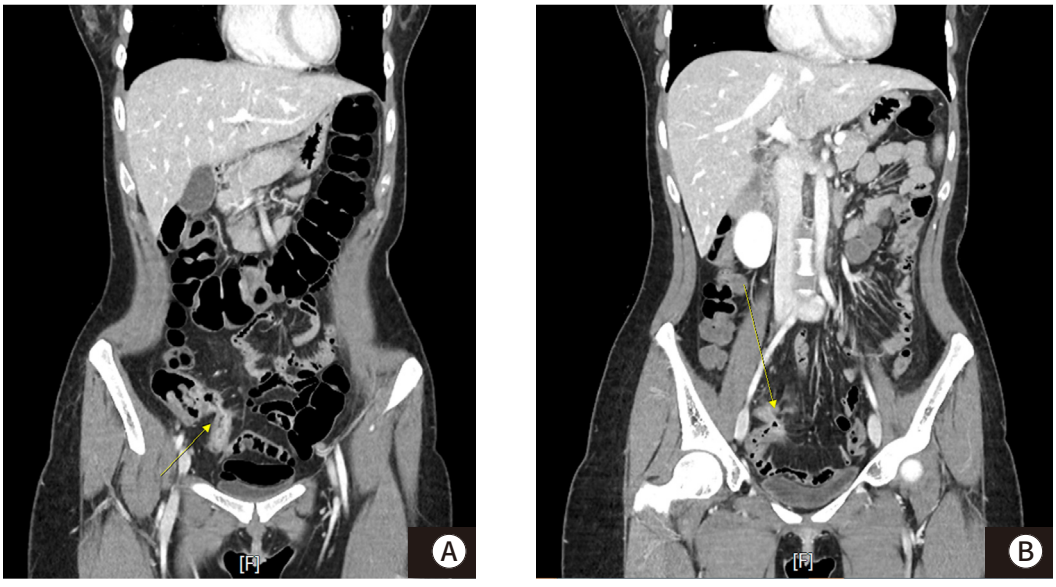


**Fig. 2.** Contrast-enhanced CT image after conservative management for 2 weeks. (A) Contrast-enhanced CT clearly reveals entero-enteric fistula despite improvements in the inflammatory change in the ileum (B) another fistula tract is also observed clearly.


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and Gerota's fascia. After completing right colon mobilization, sigmoid colon mobilization was performed for the anterior resection, which included the fistula tract. After medial dissection followed by lateral dissection was conducted, the distal sigmoid colon was resected, which included the hole of the fistula tract with a linear stapler intracorporeally administered by an assistant. The proximal sigmoid colon was exteriorized through an umbilical incision and the anvil of the circular stapler was inserted. The bowel was placed back into the abdominal cavity and intracorporeal colo-colic end-to-end anastomosis was performed using a circular stapler (Video clip). Then mobilized right colon and the small bowel were exteriorized through an umbilical incision. Extracorporeal end-to-side anastomosis was performed using a circular and a linear stapler after excision of bowel mesentery with vessel sealer for devascularization. At this point, extensive small bowel exploration was conducted to identify small bowel lesions such as obstruction and stricture due to CD. Although multiple skipped strictures were observed in the ileum and jejunum, strictureplasty is unnecessary because the passage was possible. The operation was over as the drain insertion through the umbilical wound and closure of the main wound was completed (Fig. 3, Supplementary Video 1). Docking, console, and total operation times were 12, 200, and 260 mins, respectively. Estimated blood loss was 50 cc and intraoperative transfusion was not necessary. Ileocecectomy and anterior resection without lymph node dissection were performed simultaneously without any intraoperative events.

Diet built up in the order of clear liquid, low residue, and regular diet were 1, 2, and 3 postoperative days, respectively. Gas passing and stool passing was detected postoperatively after 4 days. The Foley catheter was removed postoperatively on the first day. Intravenous patient-controlled analgesia and opioids were held on the first postoperative day. The recovery of the patient was uneventful. She was discharged postoperatively on the 8th day. She has been following up with a physician for CD. During the 18-month follow-up period, the CD was well controlled without postoperative complications.

**Fig. 3.** Immediate wound postoperatively. Drain is inserted through main wound used for single-incision robotic surgery with the da Vinci SP system.


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## Discussion

Ileocecal resection and primary reconstruction are the most common surgical procedures in patients with CD of the distal ileum and/or the ileo-colon. Surgery in CD can be challenging due to thickened and friable mesentery, enteric fistulas, bowel perforation, and frequent occurrence of intra-abdominal abscesses. However, in selected patients with CD, laparoscopy offers well-described short-term benefits such as decreased pain, lower wound complication rates, earlier resumption of diet and bowel function, better cosmesis, and shorter hospital stay [2,3]. In addition, reduced formation of postoperative adhesions was useful, particularly in young patients who are at significant risk of multiple surgeries [6]. Moreover, Maeda et al. [7] reported the results of single-incision laparoscopic ileocecal resection for CD in their systematic review, suggesting that it may be feasible and safe.

Robotic ileocecal resection has been also attempted in patients with CD. Recently, the results of robotic surgery for CD have been published [3–5]. Hota et al. [3] analyzed and performed a retrospective review of the National Surgical Quality Improvement Program (NSQIP) database to select 5,158 patients with CD who underwent ileocecal resection (open, laparoscopic, or robotic-assisted). In this analysis, the robotic group was composed of 121 patients. Though the robotic-assisted group had significantly longer operative times relative to the laparoscopic surgery group, there was no difference in terms of the postoperative short-term outcomes. Hande Aydinli et al. [4] also reported the safety and feasibility of robotic ileocolic resection for CD compared with laparoscopic approaches. This was accomplished with no leaks, major morbidity/mortality, and comparable length of stay, with a 1-day shorter return of bowel function and lower overall complication rates in 33 robotic patients.

However, previous reports were performed with the two most often used robotic platforms, the da Vinci Si and the da Vinci Xi. There has been no report on robotic surgery with the dVSP surgical system in patients with intra-abdominal CD. We thought that dVSP would have advantages for surgery in patients with CD than previous version of the robotic surgical system. As we use the umbilicus for a single-entry site, all procedures could be performed regardless of the lesion's location. In particular, it is possible to predict various surgical conditions due to the disease characteristics of CD. Previous versions of robotic systems have limitations in docking multiple devices in this situation. In addition, re-docking is necessary to perform concomitant procedures, such as in our case. As we used the 360° rotation of single-arm devices, we could perform surgery without re-docking for the different workplaces. Many ports and several re-dockings were inevitable if the operation in our case was performed with the previous version of a robotic system or laparoscopic surgery.

Current dVSP model lacks robotic advanced energy instruments and staplers. Advanced energy devices could help simplify the surgery and reduce the operative time. Inflammation can cause bleeding in the mesentery, particularly in patients suffering from CD. In addition, a robot stapler can make intracorporeal anastomosis easier. Gunnells et al. [8] suggested that extensive mesenteric mobilization is not necessary in case the mesentery is intracorporeally divided and an intracorporeal anastomosis is performed. Also, Calini et al. [5] reported that intracorporeal anastomosis was associated with a faster return to bowel function without any impact on the length of stay or 30-day complications compared with extracorporeal anastomosis in patients who underwent robotic ileocecectomy for intra-abdominal CD. The advantages of single-incision robotic surgery can be maximized if robotic advanced energy instruments and staplers are available.


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We thought that the dVSP surgery could be performed in patients who can be adapted to other minimally invasive surgical techniques. However, the robotic approach is limited in terms of extensive intracorporeal small bowl explorations due to the docking system, as opposed to the laparoscopic approach, which allows for more freedom of port placement. In particular, dVSP has a hardness in the intracorporeal exploration of the small bowel due to the limitation of movement, relative to previous robotic systems. However, as in our case, if the patient does not have adhesions and has a first-time surgery, an extracorporeal exploration can be performed with the main wound used for trocar insertion.

In conclusion, we successfully performed simultaneous ileocecectomy and anterior resection with the dVSP surgical system for enteric-enteric fistula in a patient with CD. There were no intraoperative events and the patient recovered well without any post-operative complications. To the best of our knowledge, there has been no report on dVSP surgery in patients with intra-abdominal CD. Although more cases are essential for evaluating the feasibility of dVSP surgery in patients with intra-abdominal CD, it can be used in patients who can be adapted to other minimally invasive surgical techniques.

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### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### ORCID iD

Ho Seung Kim: https://orcid.org/0000-0002-7378-0584
Gyoung Tae Noh: https://orcid.org/0000-0001-9849-8211

### Author Contribution

Conceptualization: Noh GT
Investigation: Kim HS
Methodology: Noh GT
Project Administration: Noh GT
Writing – Original Draft: Kim HS
Writing – Review & Editing: Kim HS, Noh GT

### Ethics Approval and Consent to Participate

Not applicable.

### Supplementary Materials

Supplementary materials are available from: https://doi.org/10.12771/emj.2022.e16.

Supplementary Video 1. Simultaneous ileocecectomy and anterior resection with the da Vinci SP surgical system.

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Case Report

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# Coronary Spasm during General Anesthesia in a Patient with Previously Undiagnosed Variant Angina

**Gi Year Lee**[1], **Sooyoung Cho**[1,2], **Dong Yeon Kim**[1,2], **Seung Hee Yoo**[1,2]

[1]Department of Anesthesiology and Pain Medicine, Ewha Womans University Medical Center Mokdong Hospital, Seoul, Korea
[2]Department of Anesthesiology and Pain Medicine, College of Medicine, Ewha Womans University, Seoul, Korea

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**Corresponding author**
Sooyoung Cho
Department of Anesthesiology and Pain Medicine, Ewha Womans University Medical Center Mokdong Hospital, 1071 Anyangcheon-ro, Yangcheon-gu, Seoul 07985, Korea
Tel: 82-2-2650-2850
Fax: 82-2-2655-2924
E-mail: sooyoung.cho@ewha.ac.kr

**Key Words**
Coronary vasospasm; Anesthesia, general; Hypotension; Angina pectoris, variant; Ventricular fibrillation

Variant angina, which is associated with coronary artery spam, is difficult to recognize on routine preoperative evaluation. Coronary spasm results in myocardial ischemia and even lethal arrhythmia in severe cases. Since patients are unconscious and cannot complain of symptoms during general anesthesia, early detection of such an event is difficult, and it could lead to severe bradycardia or cardiac arrest. We report a case of a patient with previously undiagnosed variant angina who experienced severe hypotension and ventricular fibrillation during general anesthesia.

## Introduction

Coronary artery spasm or variant angina is rare and difficult to detect on routine preoperative evaluation. The features of ischemic episodes due to variant angina differ from those of typical angina. Such an episode occurs when a patient is resting or in the early morning and is not associated with exercise [1]. Moreover, silent ischemic episodes are frequent, and syncope is occasionally present [2]. In severe cases, transient ST-segment elevation and arrhythmias such as ventricular tachycardia and ventricular fibrillation can follow. Coronary artery spasms can occur during surgery under general or regional anesthesia. Since patients are unconscious and cannot complain of symptoms during general anesthesia, early detection of coronary artery spasms is difficult, which could lead to severe bradycardia or cardiac arrest. We report a case of a patient having variant angina with severe hypotension and ventricular fibrillation during general anesthesia.

## Case

A 70-year-old female was scheduled for laparoscopic cholecystectomy for chronic cholecystitis. Her height and weight were 153.0 cm and 82.1 kg, respectively. Her body mass index was 35.1 kg/m$^2$. The patient had hypertension and type 2 diabetes mellitus and was a hepatitis B carrier. The patient also had prurigo nodularis and was taking 5 mg prednisolone per day. The patient had experienced chest pain 15 years previously and has been taking 100 mg aspirin daily since then.

The patient reported that she had not undergone any diagnostic tests, such as angiography for coronary artery disease, following the episode of chest pain. There were no specific findings on preoperative EKG or transthoracic echocardiogram.

After the patient was transferred to the operating room (OR), standard monitors, including noninvasive blood pressure, EKG, pulse oxygen saturation ($SpO_2$), and bispectral index, were applied. The initial noninvasive blood pressure and heart rate (HR) were 137/62 mmHg and 71 beats/min, respectively. EKG showed a normal sinus rhythm, and $SpO_2$ was 100%. Anesthesia was induced uneventfully after sequential administration of glycopyrrolate (0.2 mg), midazolam (3 mg), 1% propofol (80 mg), fentanyl (50 μg), and rocuronium (32 mg). Following intubation, arterial cannulation was performed, and continuous arterial blood pressure (ABP) monitoring was initiated. Results of arterial blood gas analysis were within the normal range: potential of hydrogen (pH), 7.401; partial pressure of carbon dioxide ($pCO_2$), 33.6 mmHg; partial pressure of oxygen (pO2), 260.9 mmHg; base excess (BE), −4.4 mEq/L; and arterial oxygen saturation (SaO2): 97.7%. Anesthesia was maintained with 1%–2% sevoflurane and intermittent fentanyl injection.

The laparoscopic procedure was conducted uneventfully for 15 min, and carbon dioxide ($CO_2$) insufflation was discontinued. During the surgery, EKG showed a normal sinus rhythm, ABP ranged from 96/54 to 183/91 mmHg, and HR was 80–95 beats/min. $SpO_2$ was maintained at > 99%, and end-tidal $CO_2$ tension was between 31 and 35 mmHg. Five minutes after the beginning of wound suturing, her ABP and HR were 75/49 mmHg and 91 beats/min, respectively, and 5 mg ephedrine was injected intravenously. However, systolic ABP decreased to approximately 50 mmHg. After an additional dose of 5 mg ephedrine, tachycardia with an HR of 130 beats/min was noted. Despite starting norepinephrine infusion, ABP did not increase, and ST-segment elevation (2.5 mm) followed by ventricular fibrillation was noted in the EKG. Chest compression was initiated immediately, and spontaneous circulation (ROSC) was returned after one cycle (2 minutes) of cardiopulmonary resuscitation without defibrillation. Blood samples were collected for cardiac enzyme tests, and 12-lead EKG monitoring was taken.

Despite ROSC, systolic ABP was still low (approximately 60 mmHg). Therefore, an epinephrine infusion was started. ST-segment elevation in the territory of the left anterior descending coronary artery was observed on 12-lead EKG (Fig. 1). Results of post-ROSC arterial blood gas analysis were as follows: pH, 7.283; $pCO_2$, 41.4 mmHg; $pO_2$, 342.5 mmHg; base excess, −7.5 mEq/L; and $SaO_2$, 97.9%. Cardiac enzyme levels at the time of the event were within the normal ranges (high-sensitivity cardiac troponin T, 0.004 ng/mL and a myocardial fraction of creatine kinase, 0.7 ng/mL). At 10 minutes after the event, vital signs began to stabilize, and ST-segment elevation was normalized. The patient was transferred to the intensive care unit under intubation with continuous infusion of epinephrine and norepinephrine (ABP, 93/51 mmHg).

The operation time was 45 minutes, and the anesthesia time (from arrival in the OR to transfer to the intensive care unit) was 100 minutes. Total intake was 1000 mL of crystalloid fluid, and total output was 100 mL (20 mL of blood loss and 80 mL of urine output) in the OR.

Emergency coronary angiography (CAG) was performed 1 hour later, which revealed no stenotic lesions (Fig. 2). To avoid another potentially refractory coronary spasm, a vasodilation test using nitroglycerin (NTG) was performed during CAG. The right coronary artery showed reactive vasodilation following intracoronary administration of NTG (Fig. 2). Therefore, the patient was diagnosed with variant angina. Vital signs stabilized after CAG, and epinephrine and norepinephrine were tapered and stopped the next morning. The patient was extubated and transferred to the general ward the next day and discharged 6 days later with a prescription for a calcium channel blocker and NTG to be used when necessary.

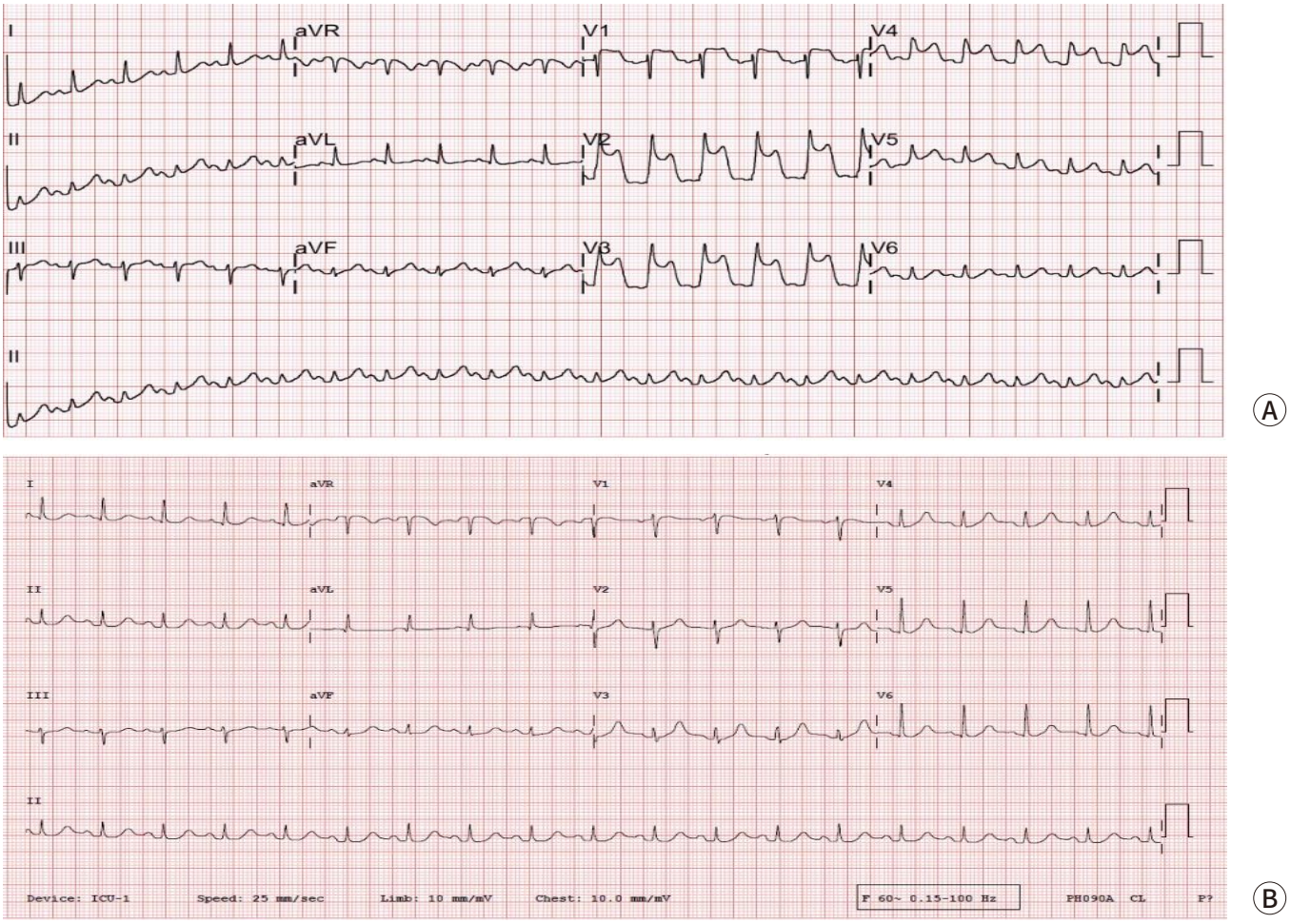


**Fig. 1.** Electrocardiography following coronary vasospasm. (A) ST-segment elevation at the leads V2–V4 was noted when the patient's blood pressure decreased. Immediately following this observation, ventricular fibrillation was noted. After one cycle of cardiopulmonary resuscitation, a return of spontaneous circulation (ROSC) was achieved. (B) ST-segment elevation normalized shortly after ROSC.

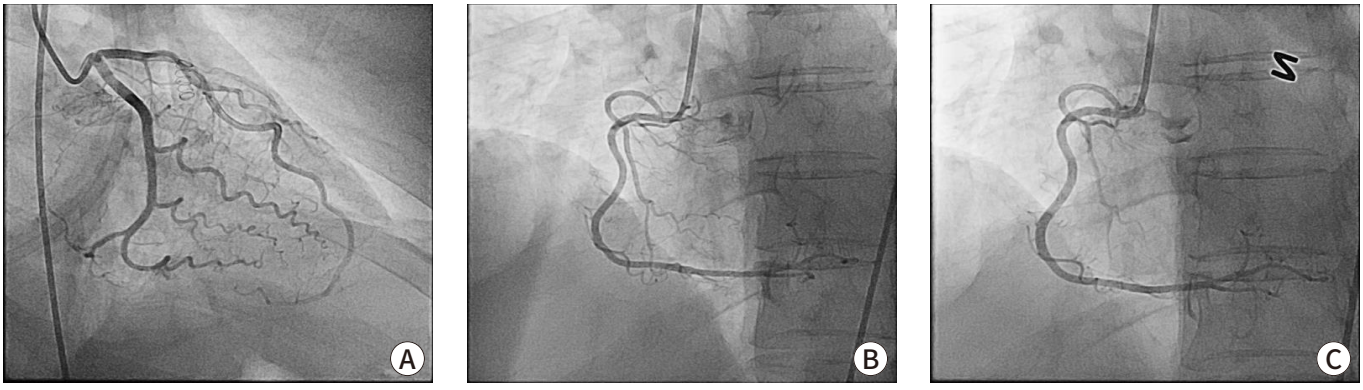


**Fig. 2.** Emergency coronary angiography. (A) and (B) No stenotic lesions were detected in the left and right coronary arteries. (C) Dilation of the right coronary artery was observed after intravenous administration of nitroglycerin.


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## Discussion

In the present case, we experienced coronary vasospasm in a patient with undiagnosed variant angina. The first report of the variant of angina pectoris was by Prinzmetal in 1959 [3]. The pain of variant angina is not provoked by exercise or excessive workload on the heart but occurs spontaneously at rest or during ordinary activity. Coronary vasospasm is accompanied by a characteristic change in the EKG: significant ST-segment elevation and reciprocal ST-segment depression [4]. Moreover, transmural ischemia caused by coronary artery spasms may be silent but serious, leading to lethal arrhythmias such as ventricular tachycardia and fibrillation [5]. It occurs in relatively young individuals with low coronary risk and can be confirmed by provoking local vasospasm by vasoconstrictors such as ergonovine and acetylcholine during CAG [1,6,7].

During general anesthesia, patients cannot complain of the characteristic symptoms. Therefore, ST-segment elevation on EKG is the only clue for recognizing coronary vasospasm. However, sometimes life-threatening arrhythmia can occur without ST-segment change or happens too quickly before anesthesiologists can recognize the changes in the EKG [8,9]. Therefore, careful vigilance and early detection of events are critical for patient management.

Among the drugs used for anesthesia, coronary artery vasospasm has been reported to be caused by vasoconstrictors such as ephedrine, phenylephrine, norepinephrine, and epinephrine [10,11]. Hence, careful observation of any changes in the EKG after the administration of these drugs is necessary. In the present case, the initial decrease in ABP might not have been caused by the spasm. However, we used ephedrine to increase the ABP, which could have caused the spasm. Another potential cause of spasms is abdominal manipulation. At the end of $CO_2$ insufflation, the surgeons pressed down the abdominal wall to pull the gas out, which could have provoked a vagal-mediated reflex [12,13]. Coronary artery spasms may be affected by the autonomic nervous system, and increased sensitivity of the vascular smooth muscles can cause an attack [14].

Initially, we considered the possibility of coronary artery occlusive disease due to a definite ST-segment elevation and a history of chest pain and aspirin consumption. In the present case, the patient had not undergone any diagnostic tests for coronary disease despite a history of chest pain. Similarly, undiagnosed variant angina can be overlooked when coronary vasospasm occurs during surgery. Despite the presence of many risk factors for cardiovascular disease, the preoperative transthoracic echocardiogram was normal, and the possibility of underlying heart disease was believed to be low. Therefore, variant angina remained undiagnosed, and ephedrine was used without the awareness of the potential risk of coronary artery spasm. Since the event was diagnosed as coronary vasospasm, NTG or calcium channel blockers (CCB) would have been helpful in relieving the artery. Generally, the primary treatment for variant angina is NTG and CCB since both of these medications have vasodilatory effects [1]. NTG is a vasodilator that acts independently of vascular endothelial cells, and CCB acts on the vascular smooth muscles. Particularly, the response to these drugs is stronger in variant angina, which is not associated with other factors that reduce intravascular volume, such as vascular stenosis. Therefore, we believe that the rapid administration of these drugs is important.

In addition, sufficient post-surgical evaluation should be conducted for an exact diagnosis so that the patient can continue treatment if necessary. Patients should be educated about the importance of explaining their history to future anesthesiologists. The suspicion of coronary artery spasms can affect the early detection of an event and the choice of drug. Therefore, detailed preoperative history and evaluation are essential.


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In conclusion, coronary artery spasms caused by variant angina can result in fatal arrhythmias and myocardial ischemia. Therefore, caution should be exercised during anesthesia. Furthermore, variant angina cannot be detected easily during anesthesia since the typical symptoms and signs are masked. Therefore, careful vigilance by the anesthesiologists, prompt response, and treatment are essential.

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### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### ORCID iD

Giyear Lee: https://orcid.org/0000-0002-9241-1557
Sooyoung Cho: https://orcid.org/0000-0002-0232-766X
Dong Yeon Kim: https://orcid.org/0000-0002-4414-5653
Seung Hee Yoo: https://orcid.org/0000-0002-6811-7198

### Author Contribution

Conceptualization: Cho S
Investigation: Lee GY, Cho S
Project Administration: Yoo SH
Writing – Original Draft: Lee GY
Writing – Review & Editing: Lee GY, Cho S, Kim DY, Yoo SH

### Ethics Approval and Consent to Participate

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Perspective

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# The COVID-19 Pandemic Response System at University Level: The Case of Safe Campus Model at Ewha Womans University

**Kyunghee Jung-Choi[1], Nackmoon Sung[2], Sun Hwa Lee[3], Misun Chang[4], Hee Jung Choi[5], Chung-Jong Kim[5], Nam-Kyong Choi[6], Hanna Kim[1], Yi-Jun Kim[1,7], Whanhee Lee[8], Hyesook Park[7,9], Eunhee Ha[1,7]**

[1]Department of Environmental Medicine, College of Medicine, Ewha Womans University, Seoul, Korea
[2]Clinical Research Institute, Seegene Medical Foundation, Seoul, Korea
[3]Laboratory Medicine Center, Seegene Medical Foundation, Seoul, Korea
[4]Department of Marketing, Seegene Medical Foundation, Seoul, Korea
[5]Department of Internal Medicine, College of Medicine, Ewha Womans University, Seoul, Korea
[6]Department of Health Convergence, College of Science and Industry Convergence, Ewha Womans University, Seoul, Korea
[7]Graduate Program in System Health Science and Engineering, Ewha Womans University, Ewha Medical Research Institute, College of Medicine, Seoul, Korea
[8]School of Biomedical Convergence Engineering, Pusan National University, Yangsan, Korea
[9]Department of Preventive Medicine, College of Medicine, Ewha Womans University, Seoul, Korea

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**Corresponding author**
Hyesook Park
Department of Preventive Medicine, College of Medicine, Ewha Womans University, 25, Magokdong-ro 2-gil, Gangseo-gu, Seoul 07804, Korea
Tel: 82-2-6986-6013
E-mail: hpark@ewha.ac.kr

Eunhee Ha
Department of Environmental Medicine, College of Medicine, Ewha Womans University, 25, Magokdong-ro 2-gil, Gangseo-gu, Seoul 07804, Korea
Tel: 82-2-6986-6013
E-mail: eunheeha@ewha.ac.kr

**Key Words**
COVID-19; Ewha Safe Campus; Ewha Safe Station; Nasal swab

In response to the changes in the Coronavirus disease 2019 (COVID-19) epidemic situation, Ewha Womans University established Ewha Safe Campus (ESC), an on-campus infection outbreak management system, to allow students and faculty members to safely resume face-to face classes in 2022. The COVID-19 testing station, Ewha Safe Station, is the core element of ESC. Symptomatic students and faculty members perform a combo swab self-PCR test or receive a nasopharyngeal swab PCR test from experts to prevent the spread of COVID-19 through early detection and management. ESC is significant in that it detects infection risks and proactively implements preemptive measures in a university. The COVID-19 health response system model at the university level was applied for the first time in South Korea, reaching a milestone in the history of university health in South Korea. In particular, it is highly valuable that the test was free of charge, as it enabled all of the examinees to have easy access to the test through joint cooperation with the Seegene Medical Foundation. This is a successful example of cooperation between schools and private institutions for public health improvement. In the future, the direct and indirect effects of the establishment and implementation of ESC need to be evaluated and confirmed, and areas requiring improvements need to be identified in preparation for another infectious disease outbreak in the future.

## Background

On March 11, 2020, the World Health Organization (WHO) declared the Coronavirus disease 2019 (COVID-19) a global pandemic [1]. As of January 31, 2022, the global cumulative numbers of confirmed cases and deaths of COVID-19 reached 376,854,195 and 5,695,057, respectively [2]. The first case of COVID-19 infection in South Korea was reported in January 2020 [3]. By the end of January 2022, there had been four epidemics in South Korea. As of January 31, 2022, the

cumulative numbers of confirmed cases and deaths in South Korea were 845,610 and 6,755, respectively [4]. As the pandemic continued, the virus mutated, which affected South Korea. In the fourth epidemic, which lasted about six months starting in July 2021 in South Korea, the Delta variant was the major cause [3]. In November 2021, the South Korean government implemented Living with COVID, a phased recovery to "normal daily lives" [3]. In the end of January 2022, the Omicron variant, which is considered to have a higher transmission rate and lower severity rate than previous variants, spread. Living with COVID was maintained, with high vaccination rates and treatment dissemination [3]. In March 2022, the South Korean government requested the establishment of an autonomous preventative measure system for universities to mark the beginning of the semester which coincided with the fifth epidemic caused by the Omicron variant [5].

## Establishment of the Ewha Safe Campus at Ewha Womans University

In response to the changes in the COVID-19 epidemic situation, Ewha Womans University (EWU) established Ewha Safe Campus (ESC), an on-campus infection outbreak management system, to allow students and faculty members to safely resume face-to face classes in 2022. The COVID-19 testing station, Ewha Safe Station (ESS), is the core element of ESC. Symptomatic students and faculty members perform a combo swab (nasal and oral) self-PCR test or receive a nasopharyngeal swab (NPS) PCR test from experts to prevent the spread of COVID-19 through early detection and management.

### 1. The executive committee for Ewha Safe Campus (ESC)

With the Vice President of the EWU Office of General Administration as the chairperson, the executive committee for the establishment of ESC is comprised of the Medical School, Medical Center, Office of Faculty & Academic Affairs, Office of Student Affairs, Office of General Administration, Office of Facilities Management, Office of Information and Communications, Office of University Relations and Development, Office of Communications, and University Health Service Center. The executive committee divided and coordinated the work of each participating department and supervised the overall implementation of ESC.

### 2. Establishment of a cooperative system with external organizations

The tests were conducted free of charge under cooperation with the Seegene Medical Foundation, a specialized molecular diagnostics company that provided the diagnostic kit supply, which is essential for ESC operation. Unlike NPS specimen, which is a sample collection method for COVID-19 diagnosis that is considered to be the gold standard, but is uncomfortable and requires collection by professional, combo swabs have the advantage of minimal pain (minimally invasive) by self-collecting both nasal swab (scrubbing the inner surface of the nostril with a cotton swab) and oral swab (scraping the inner surface of the mouth with a cotton swab).

In addition to NPS, the US Centers for Disease Control and Prevention (CDC) permits the use of numerous other upper respiratory specimens, such as oropharyngeal swab, nasal swab, saliva, and nasal wash [6]. Numerous prior publications indicate that saliva is a suitable alternative specimen for COVID-19 diagnosis [6–9] and that combination specimens such as oropharyngeal swab and nasal swab have diagnostic performance comparable to NPS [7,10].

Furthermore, a cooperative system was established with Seodaemun Public Health Center in


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Seodaemun District Office for immediate reporting of ESS test results. The immediate reports were then systemized to enable prompt notification, basic epidemiological investigation, and management of the confirmed cases.

### 3. Installation and operation of Ewha Safe Station (ESS)

Installed on the EWU campus, the ESS was piloted on February 22, 2022, and the main test started on March 2nd (Fig. 1) and included students and all faculty members, including staff from service companies (Description of test stations 1 and 2).

After the executive committee discussion, the subjects were defined as follows:

(1) Mandatory testing was required for those who were symptomatic, those who had close contact with confirmed cases, and students in dormitories.

(2) Testing was highly recommended to those who used crowded facilities such as classes with potential droplet exposure, research facilities, the library, examination preparation classes,

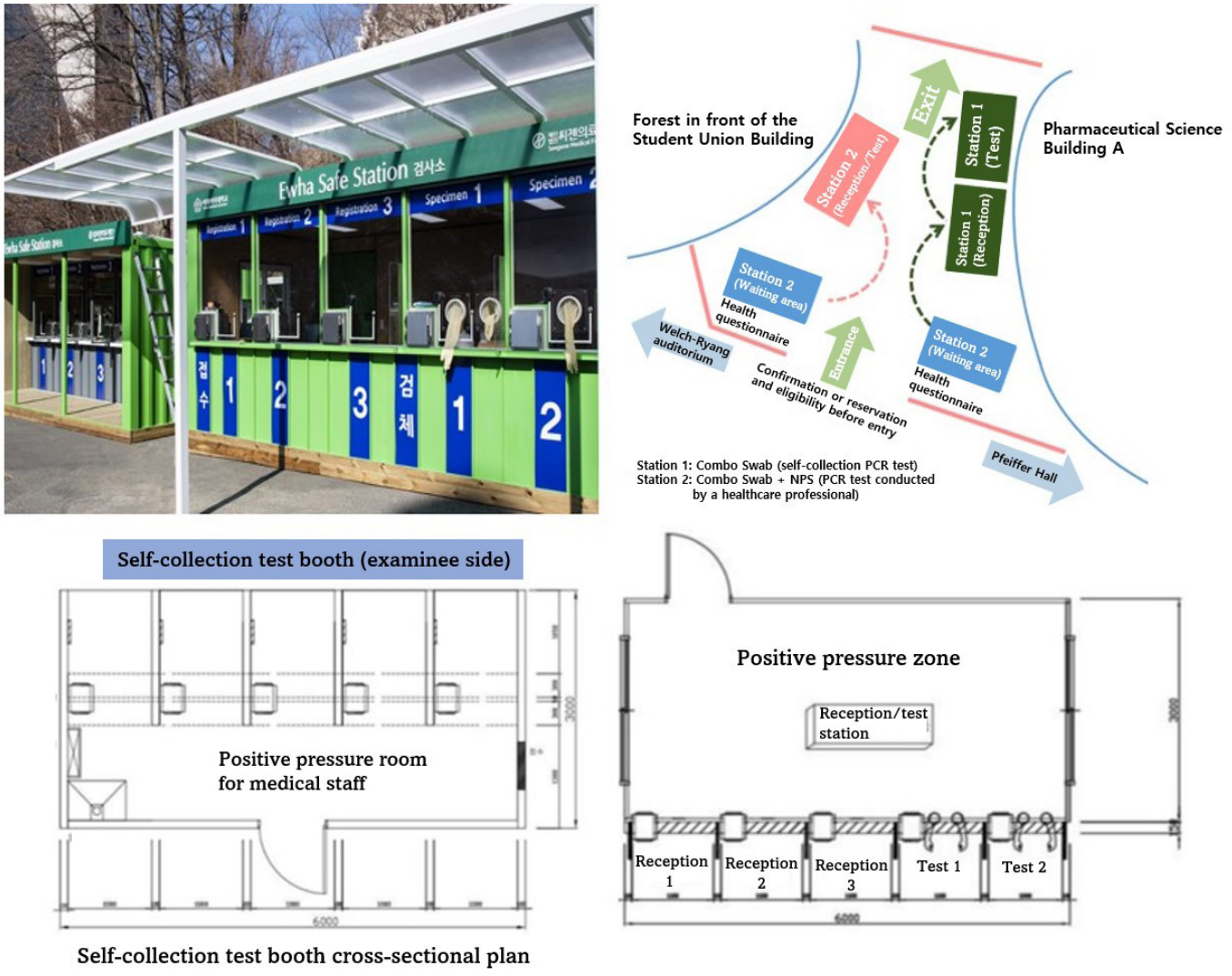


**Fig. 1.** The EWU COVID-19 testing areas (ESSs). The map of Ewha Safe Stations. The combo swab testing area and symptomatic testing area were separately operated. COVID-19, Coronavirus disease 2019.


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and the gym.

(3) Those who tested negative but showed symptoms such as a fever over 37.5°C were required to get re-tested after three days.

(4) When there was a confirmed case, an epidemiological investigation was conducted to identify the mobility trends so the EWU Daily Life Recovery Support Headquarters could inform individual students via text messages. Testing was mandatory for those who had overlapped mobility trends with confirmed cases. Furthermore, for the early detection of asymptomatic patients, weekly tests for vaccinated students and biweekly tests for unvaccinated students were required.

In the ESC, patients with respiratory symptoms were collected Combo Swabs and NPS samples simultaneously, whereas subjects without respiratory symptoms were only collected Combo Swabs. The patient self-collected Combo Swabs under the observation of the health care experts, while the health care experts collected NPS. Patients who are symptomatic, have had close interactions or shared social activities with confirmed patients, and are positive in the Combo Swab test must take both the Combo Swab and the NPS test at the same time during their ESC visit. In all other instances, just the Combo Swab test was performed. The former should take the examination at ESS 2 while the latter should take it at ESS 1, hence reducing contact between subject groups with a high risk of confirmation and those with a relatively low risk.

All exams must be scheduled using Eureka's reservation system (Ewha Womans University Portal). 15-min reservations are restricted to 30 guests. Patients with abrupt onset of symptoms, however, can undergo an on-site test without reservation. The ESC was operational on weekdays from 9 a.m. to 4:30 p.m. for a total of 6 hours and 30 min, omitting one hour for lunch. The test results were communicated through text message before 7 p.m. on the same day or before 10 a.m. the next day. If the test result is positive, the appropriate public health facility is contacted and the subjects are instructed to take follow-up measures, including limits on school and any outside activities. If the student's enrollment was verified, she may seek a make-up class.

## Conclusion and Recommendations

Although the elderly have high ratios of severe COVID-19 and death due to COVID-19, the young and middle-aged, who are socially active, have relatively high infection risks [11]. With active face-to-face contact, preventative measures need to be proactively prepared in universities. ESC from EWU is significant in that it detects infection risks and proactively implements preemptive measures in a university. As one of the factors that contributed to South Korea's successful COVID-19 response, early detection testing was applied at the university level, and the COVID-19 health response system model was applied for the first time in South Korea, reaching a milestone in the history of university health in South Korea. In particular, it is highly valuable that the test was free of charge, as it enabled all of the examinees to have easy access to the test through joint cooperation with the Seegene Medical Foundation. This is a successful example of cooperation between schools and private institutions for public health improvement. In the future, the direct and indirect effects of the establishment and implementation of ESC need to be evaluated and confirmed, and areas requiring improvements need to be identified in preparation for another infectious disease outbreak in the future.

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### Conflict of Interest
No potential conflict of interest relevant to this article was reported.

### ORCID iD
Kyunghee Jung-Choi: https://orcid.org/0000-0002-9800-0994
Nackmoon Sung: https://orcid.org/0000-0001-8951-163X
Sun-Hwa Lee: https://orcid.org/0000-0002-6393-4500
Misun Chang: https://orcid.org/0000-0002-9150-3011
Hee Jung Choi: https://orcid.org/0000-0002-1468-4074
Chung-Jong Kim: https://orcid.org/0000-0002-9987-6533
Nam-Kyong Choi: https://orcid.org/0000-0003-1153-9928
Hanna Kim: https://orcid.org/0000-0002-5190-6334
Yi-Jun Kim: https://orcid.org/0000-0002-1763-4267
Whanhee Lee: https://orcid.org/0000-0001-5723-9061
Eunhee Ha: https://orcid.org/0000-0002-4224-3858
Hyesook Park: https://orcid.org/0000-0002-9359-6522

### Author Contribution
Conceptualization: Jung-Choi K, Sung N, Lee SH, Chang M, Choi HJ, Kim CJ, Choi NK, Kim H, Kim YJ, Lee W, Park H, Ha E
Project Administration: Kim H, Kim YJ
Writing – Original Draft: Jung-Choi K
Writing – Review & Editing: Jung-Choi K, Sung N, Lee SH, Chang M, Choi HJ, Kim CJ, Choi NK, Kim H, Kim YJ, Lee W, Park H, Ha E

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