REVIEW

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Inflammatory bowel disease in Korea: epidemiology and pathophysiology

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Inflammatory bowel disease (IBD) refers to a group of disorders, including Crohn's disease and ulcerative colitis, that exhibit similar but distinct manifestations. These diseases are characterized by refractory and chronic inflammation of the bowel. IBD is usually accompanied by severe symptoms. When a patient presents with suspected IBD, physicians encounter various challenges in terms of diagnosis and treatment. In addition, given such characteristics, the associated medical expenses gradually increase. Although IBD was formerly known as a disease of Western countries, the incidence and prevalence are increasing in Korea. Korean investigators have accumulated a great deal of knowledge about the regional characteristics and epidemiology of the disease, especially via well-organized, joint cohort studies. Against this background, this article describes the epidemiology of IBD in Korea compared to that in the West. In addition, an overview of the pathophysiology of the disease is provided, focusing on the latest results.

Keywords: Inflammatory bowel diseases; Korea; Epidemiology; Pathophysiology

INTRODUCTION

Inflammatory bowel disease (IBD) is difficult to treat and is frequently accompanied by severe and persistent complications. The burden of the disease in Korea is predicted to increase as the prevalence continues to rise [1,2]. IBD usually develops in young adults and frequently causes problems related to immunosuppression; the associated medical costs are high [3,4]. Korea has seen a steep increase in the number of patients with IBD during the last three decades because of recent industrialization, as have other Asian countries [5-7]. However, Korean patients exhibit several distinct characteristics compared to other Asian patients. Adoption of Western guidelines is difficult, because IBD treatment in Korea requires special clinical consideration of regional differences in infectious diseases [8-10]. However, well-designed, epidemiological cohort studies have demonstrated several characteristics of Korean patients with IBD that may be useful when seeking to understand the condition [7-9,11,12]. The results of these studies provide valuable fundamental data allowing improvements in IBD care using both the Internet and IBD center-oriented management [13,14]. This article summarizes recent findings on the epidemiology of IBD in Korea (Table 1) and describes recent advances in our

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understanding of the underlying pathophysiologic mechanism (Table 2).

EPIDEMIOLOGY

Incidence and prevalence

The incidence of IBD is increasing for several reasons, including the increased consumption of a Westernized diet in Korea. The Westernization of Korea is a result of advanced industrialization [15,16]. As in Western countries [17], IBD in Korea began to emerge in the 1980s, underwent acceleration, and recently attained the compounding prevalence (or prevalence equilibrium) stage [17]. Similar trends were observed in many Asian countries [18-20]. Research on the incidence and prevalence of IBD in Korea has relied principally on initial, pioneering cohort studies [7,9,11]. In addition, a study using a nationwide database has recently been commenced; many new (and very important) results have been published [21].

Several Korean epidemiological studies have been conducted during the last two decades (thus in the time since the Songpa-Kangdong cohort study commenced in the 1980s) [6]. In 2020, an official fact sheet was published by the Korean Association for the Study of Intestinal Diseases (KASID) based on the results of a study using the Korea National Health Insurance Service database [22]. The Songpa-Kangdong cohort was the first well-organized cohort in Korea; participants were drawn from a region of Seoul (the capital of Korea) [9]. However, this region is characterized by a high level of education and industrialization. According to the 2020 fact sheet, Seoul City evidenced a high prevalence and incidence of IBD (nearly twice those of other regions in Korea). Therefore, attention must be paid to regional differences when interpreting the results of epidemiological studies [23]. The incidence of IBD, which had not been reported before 1986, increased from 0 to 1.68 per 100,000 and the incidence of ulcerative colitis (UC) from 0.22 to 3.62 per 100,000 over the 20 years to 2005. The results of a 30-year follow-up of the Songpa-Kangdong cohort were published in 2020 [6]. In 2015, the incidence of Crohn's disease (CD) increased to 2.42 per 100,000 and that of UC to 6.58 per 100,000. However, the annual overall growth rate then trended downward from 12% in 1986–1995 to 3% in 2006–2015. According to the KASID 2020 official fact sheet, the total number of patients with IBD increased from 7,700 to 18,463 (CD) and from 16,136 to 37,439 (UC) between 2010 and 2019, representing a 2.37-fold increase

Table 1. Summary of the epidemiological features of IBD in Korea

Incidence and prevalence	Increasing, but recently reached prevalence equilibrium stage
	Incidence rate (CD, 2.7–3.8 per 100,000; UC, 5.4–8.3 per 100,000/over 2010–2019)
Sex	Predominance of CD in young men (female predominance of CD in Western)
Age at onset	Pediatric onset IBD increasing with more extensive colitis and colectomy
	Elderly onset IBD suspected to increase and poor prognosis
Family history	Proportion with a family history is relatively low compared with Western
	Recent increase in familial cases (1.9%–4.9%/over 2002–2015)
Regional differences	Incidence of Seoul is twice compared than Jeollanam-do
	Variations between regions in use of biologic agent and operation
Tuberculosis	Changes in diagnosis between CD and intestinal tuberculosis 14%
	Incidence of tuberculosis (CD, 340.1/100,000 vs. UC, 165.5/100,000)
Viral infections	Both HBV infection and IBD have a worse prognosis
	Checking immunity against VZV, HAV, and measles are required
Fistula	Perianal fistula is risk factor for abscess and non-perianal fistula
	Cumulative frequency (1 year, 40.7%; 5 years, 46.1%; 10 years, 49.7%)
Extraintestinal manifestations	Eyes, skin, hepatobiliary pancreas, and musculoskeletal symptoms are higher

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; HBV, hepatitis B virus; VZV, varicella-zoster virus; HAV, hepatitis A virus.

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in the incidence of CD and a 2.32-fold increase in the incidence of UC [22]. For UC, the incidence increased from 5.4 to 8.3 per 100,000; however, for CD, the incidence seems to have plateaued after attaining 3.8 per 100,000 in 2014. According to regional prevalence data from 2019, Seoul exhibited approximately twice the disease incidence of Jeollanam-do, which had the lowest prevalence of both CD (40.1 per 100,000) and UC (80.7 per 100,000) [22].

Sex

Sex-related differences in the incidence and prevalence of IBD have not been sufficiently investigated. In a recent pooled analysis of 17 cohorts, mainly from Western countries, the incidence of CD was significantly higher in females of all ages, except for those aged 10 to 14 years. No significant sex-related difference in UC incidence was observed in any age group, except for a male predominance in those aged > 45 years [24]. The incidence of CD has been reported to be higher in men than women in East Asian countries, including Korea. In both population-based studies and the Crohn's Disease Clinical Network and Cohort (CONNECT) study of Korea, the incidence of CD was higher among men than women. However, for UC, no significant differences between men and women were observed in any age group [6,7].

The reason for the predominance of CD in young men remains unclear. Although smoking is considered to have an adverse effect, the male-to-female ratio was 1.8:1 among 259 non-smoking patients with CD in the Songpa-Kangdong cohort [6]. In addition, the incidence in men was 37% higher than that in women in 2006 to 2015; this difference was significantly higher than reported in 1986 to 1995 (6%). Therefore, whether the trend of CD male predominance will persist needs to be monitored [6,7].

Age at onset

The prevalence of pediatric-onset IBD is increasing [25,26]. Pediatric cases have been reported to account for up to 25% of all IBD cases in Western countries. Malabsorption can have adverse effects on growth; early and timely management of IBD is required [25]. However, as immunomodulators are difficult to use in pediatric patients, the treatment options are relatively limited. Moreover, studies on pediatric-onset IBD are rare. In a population-based cohort study conducted in Korea in 2021, 131 pediatric patients with IBD (48 with UC and 83 with CD) diagnosed between 1986 and 2015 were compared to adult patients with IBD. The prevalence of extensive colitis at diagnosis (45.8% vs. 22.3%) and the cumulative risk of colectomy (8.9% vs. 1.8%) were significantly higher in pediatric UC than in adult UC cases. In

Table 2. Recent advances in our understanding of inflammatory bowel disease pathophysiology

Genetic factors	Cause difference in individual susceptibility and treatment responses
	In Koreans, association with *NOD2* and *IL23R* rare, *TNFSF15* has stronger association
Environmental factors	Recent increases are consequence of industrialization
	Smoking: not significant in Asians, increase risk of CD, reduce UC, alter thiopurine, anti-TNF-α metabolism
	Unfavorable: smoking (CD), urban living (CD and UC), appendectomy (CD), antibiotics (CD and UC), soft drink (UC)
	Favorable: physical activity (CD), breastfeeding (CD and UC), tea consumption (UC), and *H. pylori* (CD and UC)
Host immunologic factors	Balances between innate and adaptive immunity for preventing excessive immune responses
	Most studies on adaptive immunity are effector T cells or regulatory T cells (Tregs)
	Adhesion molecules related to lymphocyte trafficking are targets for gut-selective lymphocyte capture therapy
	Treg function been considered which can help in remission through anti-inflammatory action
Microbiota	IBD can occur if optimal regulation toward commensal bacteria is not achieved
	Intestinal dysbiosis can lead to disease development
	Homeostasis maintained through the interaction between genetic, environmental, microbiota, and immune system
	Fecal transplantation and customized treatments are methods for correcting intestinal dysbiosis

CD, Crohn's disease; UC, ulcerative colitis; TNF-α, tumor necrosis factor α; IBD, inflammatory bowel disease.

pediatric patients with CD, the ileocecal and inflammatory phenotypes were more common than the other phenotypes [27]. Therefore, pediatric IBD has clinical features that differ from those of adult IBD, even in Korea. Moreover, pediatric UC may exhibit a more severe disease course, characterized by extensive disease involvement, earlier biologic requirement, and a higher surgery rate [25,27].

Although IBD generally occurs in young patients, the prevalence in older patients has been increasing. Studies have predicted that, within the next 10 years, nearly one-third of patients with IBD will be > 60 years of age [28]. The diagnosis and treatment of older patients are often challenging because of underlying diseases [29]. Particular attention should be paid to treatment-related complications such as cardiovascular diseases and malignancies. Moreover, malnutrition is closely associated with a poor clinical course, especially in older patients [28].

Although epidemiological studies on late-onset IBD remain rare in Korea, no significant differences in either proximal extension or the risk of colectomy were found in the Songpa-Kangdong cohort study published in 2021, in which 99 patients with late-onset UC were followed-up for 104 months and compared to young patients [30]. However, the sample size was small, and only two patients underwent colectomy during the observation period [30]. As previous reports found that the prognosis of patients with late-onset disease was usually worse than that of others, consistent follow-up and further studies on the epidemiology and prognosis of IBD in older patients are needed [29,31].

Family history

In general, familial IBD has been reported to be associated with higher rates of biologic use, recurrence, and surgery. The incidence of familial onset is high, especially among first-degree relatives. Compared to Western countries, the proportion of patients with a relevant family history is rather low in Asian countries, including Korea [16]. However, as IBD evolves into the prevalent phase, the number of familial cases is expected to increase. In a recent report, the relative risk of developing IBD among first-degree relatives of patients with IBD was 13.8 (compared to the general population); the figure was similar to that in Western patients [32]. In particular, a significant increase in the number of familial cases, from 1.9% in 2002 to 4.9% in 2015, was observed in one cohort study in Korea [32].

Regional differences

Regional differences in the incidence of IBD have been suggested [33]. These are presumed to reflect differences in environmental risk factors, including lifestyles and diets. In the official IBD fact sheet of 2020, the incidence in urban areas was almost twice that in rural areas, supporting the above hypothesis [22]. An earlier CONNECT study found no significant differences in the cumulative incidence of intestinal complications such as perianal fistulae, perforations, or abscesses between urban and rural areas [33]. Moreover, there were also no differences in the use of immunomodulators and biologics [33]. However, the operation rate during the first year was significantly higher in urban than in rural areas. These differences were not consistently significant; various studies conducted in several locations came to different conclusions [34,35]. However, significant regional variations in treatment strategies were observed in 2019. Specifically, in the seven regions with the highest numbers of patients (all in Seoul), 3.6- and 3.2-fold variations were identified between the regions with the highest and lowest frequency of biologic use for CD and UC, respectively [36]. This suggests that continuous revision of guidelines for treatment of IBD, and the research efforts of academic societies, are warranted [36].

Tuberculosis

The clinical manifestations of intestinal tuberculosis are similar to those of CD, sometimes posing diagnostic dilemmas [37]. In a single-center study conducted between 2010 and 2014 in Korea, a change in diagnosis from CD to intestinal tuberculosis occurred for 14% of patients [38]. The similar manifestations restrict the choices of biologic agents, especially in countries where tuberculosis is prevalent (including Korea) [39]. One study accessed the National Health Insurance Database of Korea to obtain basic demographic results affording appropriate tuberculosis control. The study period was 2011 to 2013, and the incidence of tuberculosis in patients with IBD was significantly higher in those with CD than UC (340.1/100,000 vs. 165.5/100,000, $p < 0.001$). The incidence of tuberculosis in patients treated with 5-aminosalicylic acid, corticosteroids, immunomodulators, and anti-tumor necrosis factor (TNF)-α were 143.5, 208.5, 284.6, and 554.1 per 100,000 person-years respectively. The current prevalence of tuberculosis in Korea creates diagnostic dilemmas (as mentioned above), a risk of reactivation, and a need for an optimized management algorithm [37,39].

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Adhesion molecule antagonists usefully avoid the risk of tuberculosis. Continuous efforts and epidemiological investigations by academic societies are required.

Viral infections

Several viral infections can adversely affect the clinical course of IBD [40]. Recent data have a bearing on the seroprevalence of measles, mumps, rubella, varicella-zoster virus (VZV), hepatitis A virus (HAV), and Epstein-Barr virus (EBV) in the period from 2016 to 2018. The seropositivity rates for measles, mumps, rubella, VZV, HAV, and EBV were 84.0%, 85.2%, 66.5%, 87.4%, 50.0%, and 93.7% respectively [40]. Therefore, clinicians should consider the provision of additional protective immunity against VZV, HAV, and measles. The virus that triggers the worst outcomes in Korean IBD patients is the hepatitis B virus (HBV). Patients with both HBV infection and IBD have poorer prognoses than those with IBD alone [41]. Therefore, an awareness of the risk of HBV reactivation after IBD treatment, and appropriate management, are crucial [42]. The serological prevalence of cytomegalovirus (CMV) is generally high in Asia. The risk factors for CMV colitis in patients with UC are high-dose steroid use and severe uncontrolled disease [43]. Moreover, CMV is a significant predictor of non-response to infliximab [44].

Fistulae

Perianal fistula is a serious manifestation of CD. A perianal fistula at diagnosis or at an early stage of disease is currently considered to be a poor prognostic factor. In a systematic review published in 2021, it was reported that approximately 20% of patients with CD developed perianal disease within 10 years of diagnosis. Approximately two-thirds required perianal surgery, and some eventually required major abdominal surgery [45]. Similarly, in Korea, perianal fistulae are considered risk factors for intra-abdominal abscesses and non-perianal fistulae [46]. The cumulative fistula rate in Korean patients with CD was 40.7% at 1 year after diagnosis, 46.1% at 5 years, and 49.7% at 10 years, all higher than in Western patients [47].

In a recently published, long-term retrospective cohort study with > 10 years of follow-up, patients with perianal CD were more likely to receive corticosteroid, immunomodulator, and anti-TNF-α treatments than those with non-perianal CD [48]. According to the results of the CONNECT study published in 2018, perianal CD was significantly associated with ileal colonic involvement in young male patients who were initially diagnosed in primary clinics. In Korean patients with CD, perianal fistulae were predictive of the development of non-perianal fistulae and intra-abdominal abscesses [48].

Extraintestinal manifestations

The manifestations of IBD are not limited to the bowel. Extraintestinal manifestations can occur in several organs and can significantly reduce the quality-of-life [49,50]. In Western countries, extraintestinal manifestations most frequently involve the joints, skin, and eyes. The frequency of extraintestinal symptoms in Korean patients with IBD is not known. However, in a recent survey using the health insurance database, the prevalence of 17 extraintestinal symptoms (of the eyes, skin, hepatobiliary pancreas, and musculoskeletal system) was higher in patients with IBD than in the general population [51]. In a recent Korean study, the prevalence of subclinical sacroiliitis in CD patients was 13.3%, significantly higher than that of healthy controls (4.8%) [50].

PATHOPHYSIOLOGY

As sustained IBD remission is difficult to maintain, many studies have sought to elucidate the cause of this long-term, refractory, and expensive disease. Investigators have studied genetic aspects, environmental factors, the microbiome, and possible immune mechanisms. However, the underlying pathophysiologic mechanism(s) remain(s) unclear [52,53]. The differences between the two similar but distinct diseases within IBD (CD and UC) are not completely understood. Given recent developments in genomic profiling, disease subclassifications by differences in clinical manifestations and treatment responses have been proposed, even within CD or UC [54]. For example, as the primary non-response rate to even recently introduced biologic agents is only approximately 30% and the secondary non-response rate is gradually increasing, it seems reasonable to conclude that the disease exhibits a heterogeneity over and beyond the traditional classification [52]. This could explain the differences in disease manifestations and treatment responses between the traditional disease classifications, and help elucidate the underlying pathophysiological mechanisms (that remain poorly understood). In this context, we review possible genetic and environmental factors that might cause IBD. The results of recent studies on the microbiota and the

immune system are also described.

Genetic factors

Genetic factors are believed to cause differences in individual susceptibility to IBD [52]. The high proportion of patients with a relevant family history, the tendency of primary relatives to exhibit increased susceptibilities, and the high IBD incidence in identical twins constitute evidence of genetic susceptibility. Genome-wide studies have identified > 240 genomic variants. Mutations in *NOD2* (a gene involved in bacterial pattern recognition), *ATG16L1* (a gene associated with intracellular autophagy), and cytokine-encoding genes (cytokines regulate the innate and adaptive immune responses) are considered to be major genetic variants [55,56]. However, the mutations may exert only minor impacts: CD-related mutations only 8%–13% and UC-related mutations only 4%–7% [53]. Differences between East and West have also been reported. *NOD2* and *IL23R* are associated with the risk of CD in Europeans, but rarely in East Asians [57]. In contrast, *TNFSF15* exhibits a much stronger association in East Asians [57]. A recent cohort study demonstrated that adult CD was clearly separable into two classes based on genomic analyses of colonic tissues [58]. The expression patterns within these CD subclasses highlight large differences in the immune responses and cellular metabolism, and are considered to be associated with multiple clinical phenotypes that explain distinct disease behaviors.

Environmental factors

The recent increase in the prevalence of IBD in Asia is considered to reflect industrialization after World War II. This increase is closely related to technological advances, improvements in health care and sanitation, increased energy utilization, modern transportation, changes in diet, and urbanization [17]. Smoking increases the risk of CD but is believed to reduce the severity of UC [59]. Smoking is associated with alterations in thiopurine metabolism and is considered to shorten the time to disease recurrence. Smoking decreases the efficacy of anti-TNF-α agents and increases the risk of recurrence after surgery. Smoking has been strongly associated with unfavorable CD outcomes in the West; however, such an association has not been proven in Asia [60]. One multivariate analysis revealed that breastfeeding for ≥ 12 months, antibiotic use in childhood, early pet contact, daily tea or coffee consumption, and previous smoking were significantly associated with the development of IBD [60]. In a recent meta-analysis aimed at identifying environmental risk factors, smoking (CD), urban living (CD and UC), appendectomy (CD), tonsillectomy (CD), antibiotic exposure (CD and UC), oral contraceptive use (CD and UC), soft drink intake (UC), vitamin D deficiency (CD and UC), and non-*Helicobacter pylori*-like enterohepatic Helicobacter species (CD and UC), were identified as significant risk factors. Physical activity (CD), breastfeeding (CD and UC), bed-sharing (CD), tea consumption (UC), high levels of folic acid (CD and UC), high levels of vitamin D (CD), and *H. pylori* infection (CD and UC) may reduce the risk of developing IBD [61]. Many investigators have postulated that a Western diet may contribute to the unfavorable results. However, no well-established guideline for any specific (helpful) diet is available [62]. Well-designed clinical trials are needed to confirm whether dietary therapy effectively induces remission [63,64].

Host immunological factors

The immune system features innate and adaptive immunity. The cells of innate immunity include neutrophils, macrophages, and dendritic cells that recognize microbial patterns or products [53]. The cells of adaptive immunity are B and T cells that recognize specific antigens. Innate and adaptive immunity should be maintained in balance to protect the body against excessive immune responses to commensal microbiota [65,66].

The unsatisfactory clinical efficacy of rituximab in UC patients raises fundamental questions on the role played by B cells in the pathogenesis of IBD [67]. Currently, most studies on adaptive immunity explore the efficacies of effector T cells or regulatory T cells (Tregs). Naïve T cells are activated (by dendritic cells) to express chemokine receptors and the α4β7 integrin; the latter binds to mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1). T cells migrating to the epithelial compartment upregulate the αEβ7 integrin, which binds to E-cadherin of epithelial cells [68]. T-cell efflux from lymph nodes is controlled by the sphingosine-1 phosphate receptor family [53]. Adhesion molecules associated with the above three mechanisms serve as targets of gut-selective lymphocyte capture therapy [69,70].

Differentiation of activated T cells is mediated by cytokines [71]. T cells differentiate into Th1 and Th2 cells under the influence of the pro-inflammatory cytokines interleukin (IL)-12 and IL-4, respectively [72]. Th17 cell development requires activation by the retinoic acid receptor-related orphan receptor γ (RORγ) transcription factor; also, IL-1, IL-16,

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and transforming growth factor (TGF)-β are involved in cell differentiation [73]. In Tregs, the forkhead box P3 (FOXP3) transcription factor is activated by TGF-β, and secretion of IL-10 and TGF-β induces anti-inflammatory actions [53,74]. Tregs can also upregulate RORγt, a transcription factor of Th17 and innate lymphoid cells, allowing the Treg subset to specifically suppress the type 17 immune response in the intestinal mucosa [75]. This Treg function may aid IBD remission by promoting anti-inflammatory actions. Drugs that improve Treg function [74] (such as selective inhibitors of the histone deacetylase inhibitor; [6]) have been studied in this context [76]. However, as elevated levels of RORγt+ FOXP3+ Tregs may be caused by inflammation, it remains difficult to determine whether the abundance of Tregs at an inflammatory site is a cause or consequence of intestinal inflammation [53].

Microbiota

Commensal bacteria are required for the development and maintenance of immune system homeostasis and function [66,77-80]. Immune tolerance against commensal bacteria must be maintained; IBD can occur if optimal regulation is not achieved [81]. In addition, not only bacteria but also viruses and fungi, colonize the intestinal lumen; these microbes are collectively termed the intestinal microbiota [78], the study of which accelerated when 16S rRNA gene sequencing became possible [81]. It is now accepted that intestinal microbial imbalance (dysbiosis) can trigger disease [53,80]. However, whether dysbiosis is a cause or consequence of disease remains controversial [53].

Genetic and environmental factors may have decisive impacts on gut microbiota composition; beneficial gut bacteria can regulate the tolerance of the mucosal immune system, including that of Tregs [53]. In other words, normal intestinal homeostasis is maintained via close interactions between genetic predispositions, environmental factors, commensal microbiota, and the immune system. An imbalance in the composition of the intestinal microbiota, particularly when pathogenic bacteria are involved, can negatively influence the intestinal mucosal immune system, increase intestinal permeability by causing mucosal damage, and eventually induce an unregulated mucosal immune response via invasion of various intestinal microorganisms [82,83].

Currently, fecal transplantation is being investigated in terms of intestinal dysbiosis correction, and customized (individualized) treatment is being attempted [84]. In addition, various clinical trials targeting specific harmful bacteria or seeking to suppress the action of such bacteria using genetic technologies, small molecular medicines, and genetically modified bacteria, are underway.

CONCLUSIONS

IBD is predicted to increase continuously in prevalence, imposing high burdens on patients and healthcare systems. Epidemiological studies have revealed distinct characteristics of Korean patients, as compared to their Western counterparts. In particular, appropriate management of tuberculosis and various viral infections is needed. Moreover, continuous knowledge updates and a clear understanding of the underlying pathophysiology, especially in Korean patients, are required to develop an optimal treatment.

Conflict of interest

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

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