

The possible mechanisms of the human microbiome in allergic diseases

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Abstract In the present paper, we discuss the importance of the microbiome in allergic disease. In this review paper, the data from the Medline (PubMed) and search engine of Kırıkkale University were systematically searched for all relevant articles in June 15th, 2015 for the past 30 years. The keywords of “microbiome”, “dysbiosis”, “allergy”, “allergic rhinitis”, “allergic disease”, “mechanisms” and “treatment” were used alone or together. In this paper, microbiomes were presented in terms of “Definition”, “Influence of the human microbiome on health”, “The microbiome and allergic diseases”, and “Modulation of the gut microbiota in terms of treatment and prevention”. Microbiological dysbiosis is also reviewed. The microbiome is the

genetic material of all microbes (bacteria, fungi, protozoa, and viruses) that live on or in the human body. Microbes outnumber human cells in a 10:1 ratio. Most microbes live in the gut, particularly the large intestine. Changes in the immune function of the respiratory tract are (at least in theory) linked to the immunomodulatory activity of the gut microbiota via the concept of a “common mucosal response”. The gut microbiota shapes systemic immunity, thus affecting the lung mucosa. Alternatively, changes in the gut microbiota may reflect alterations in the oropharyngeal microbiota, which may in turn directly affect the lung microbiota and host immune responses via microaspiration. Dysbiosis is defined as qualitative and quantitative changes in the intestinal flora; and modern diet and lifestyle, antibiotics, psychological and physical stress result in alterations in bacterial metabolism, as well as the overgrowth of potentially pathogenic microorganisms. All immune system components are directly or indirectly regulated by the microbiota. The nature of microbial exposure early in life appears to be important for the development of robust immune regulation; disruption of either the microbiota or the host response can trigger chronic inflammation. Dysbiosis is also an important clinical entity. Antibiotics, psychological and physical stress, and dietary factors contribute to intestinal dysbiosis.

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Introduction

Humans are constantly exposed to environmental microbes. Recent microbiome studies have emphasized that mammals require appropriate microbial colonization to

ensure metabolic and immune homeostasis. In Western nations, the burden of chronic inflammatory diseases, including allergic asthma, has increased dramatically over the past several decades. Humans spend 92 % of their time indoors [1]. Thus, most environmental microbial exposure occurs within the household.

The importance of the gastrointestinal (GI) microbiome, in the context of both the local and systemic immune environments, has been shown in several recent studies. Thus, strategies to manipulate that microbiome, in terms of membership and function, may have far-reaching implications in extra-intestinal niches, such as the skin or the joints [2]. In addition, several studies have revealed the importance of the GI microbiome in the airway response to pathogenic agents. Ichinohe et al. [3] recently showed that GI microbial composition is a critical regulator of CD4- and CD8-T cell generation, and the antibody response upon infection with respiratory influenza virus.

Changes in the immune environments studied may be directly attributable to supplementation with specific bacterial species, subsequent enrichment of ancillary species, or depletion of certain species that are outcompeted in a remodeled assemblage. Such changes may differentially program the host immune responses. Although the fundamental mechanisms governing the phenomenon remain unclear, the studies reported here afford proof of the principle that variations in environmental exposure trigger GI microbiome remodeling, in turn impacting host immune responses associated with both the allergic airway response and respiratory viral infection [4].

The gut microbiota consists of a cluster of microorganisms that produce several hormone-like signaling molecules; these are released into the bloodstream to act at distal sites. A growing body of evidence indicates that microbial composition may be modulated by several environmental conditions, including various forms of exercise, and certain pathologies. Increases in bacterial diversity have been associated both with improved health and alterations to the immune system, showing that multiple connections exist between the host and the microbiota. Reduced levels of, and variations within, the bacterial community are associated with health impairments, and increased microbial diversity improves the metabolic profile and immunological responses. To date, very few controlled studies have focused on interactions between acute or chronic exercise and the gut microbiota [5].

The released hormone-like molecules target the brain, among other organs. The microbiota initially releases hormonal products into interstitial tissue, from where they enter capillaries of the blood and lymphoid system. The materials are usually effective at low concentrations in their target organs or tissues remote from the enteric

milieu. Thus, in many respects, the gut microbiota resembles an endocrine organ [5]. For example, GABA, the most significant inhibitory transmitter of the brain, is produced by several strains of lactobacilli [6], whereas monoamines such as noradrenaline, dopamine, and serotonin are produced by many other strains of bacteria [7].

In this review paper, the data from the Medline (PubMed) and search engine of Kirikkale University were systematically searched for all relevant articles in June 15th, 2015 for the past 30 years. The keywords of “microbiome”, “dysbiosis”, “allergy”, “allergic rhinitis”, “allergic disease”, “mechanisms” and “treatment” were used alone or together. In this paper, microbiomes were presented in terms of “Definition”, “Influence of the human microbiome on health”, “The microbiome and allergic diseases”, and “Modulation of the gut microbiota in terms of treatment and prevention”. Microbiological dysbiosis is also reviewed.

Definition of the microbiome

The microbiome is the genetic material of all microbes (bacteria, fungi, protozoa, and viruses) that live on or in the human body. Microbes outnumber human cells in a 10:1 ratio. Most microbes live in the gut, particularly the large intestine. The number of genes of all microbes in the microbiome is 200-fold that of the human genome. The microbiome may weigh as much as 2 kg. The bacteria help digest food, regulate the immune system, protect against other bacteria that cause disease, and produce vitamins (including the B vitamins B12, thiamine, and riboflavin; and Vitamin K, which is required for blood coagulation). The microbiome became generally recognized in the late 1990s [8].

The microbiome is essential for human development, immunity, and nutrition. Bacteria living in and on humans are not invaders but, rather, beneficial colonizers. Autoimmune diseases including diabetes, rheumatoid arthritis, muscular dystrophy, multiple sclerosis, and fibromyalgia are associated with dysfunctional microbiomes. Disease-causing microbes accumulate over time and change genetic activities and metabolic processes, triggering abnormal immune responses against substances and tissues that are, in fact, part of a healthy body. Autoimmune diseases appear to run in families not because of germline inheritance but, rather, by inheritance of the familial microbiome [8].

Humans are essentially sterile during gestation. During and after birth, however, every bodily surface, including the skin, mouth, and gut, becomes host to an enormous variety of microbes: bacterial, archaeal, fungal, and viral. Under normal circumstances, the microbes aid in food

digestion and maintenance of immune systems; dysfunctional human microbiotas have been linked to conditions ranging from inflammatory bowel disease to antibiotic-resistant infections [9].

The gut microbiota is essential to human health throughout life. Exposures in early life [Mode of delivery (maternal microbes); infant diet (selective substrates); antibiotics (selective killing); probiotics (selective enrichment); and physical environment (environmental microbes)] results in colonization of gut microbiota which contributes to the development of the immune system, intestinal homeostasis and host metabolism. Disruption of the gut microbiota is associated with a growing number of diseases [10].

The human microbiome contains unicellular microbes (mainly bacterial, but also archaeal, viral, and eukaryotic) that occur on almost every bodily surface and have been linked to a wide range of phenotypes of health and disease. High-throughput assays were the first comprehensive culture-free techniques allowing the members of such communities to be described and their biomolecular activities assessed at the transcript, protein, and metabolic levels [9].

Dust from homes with dogs negatively affects the immune response to allergens and other triggers of asthma by changing the composition of the gut microbiome. Infants who live in homes with dogs are less likely to develop childhood allergies [8].

Influence of the human microbiome on health

The microbiome influences susceptibility to infectious diseases and contributes to chronic illnesses of the gastrointestinal system (Crohn's disease and irritable bowel syndrome). Some microbiomes affect responses to drug treatment. The maternal microbiome may affect child health. Mapping of the human microbiome has revealed previously unknown species and genes. Studies measuring the relative abundance of different species in the human microbiome have linked various combinations of such species to certain health problems [8].

The emerging field of human microbiome research has revealed the key roles played by microbial communities in several critical mammalian processes, including viability of the ancillary mucosal barrier [11]; metabolism [12, 13]; and the development and modulation of immune responses [14, 15]. This is particularly evident in the gastrointestinal (GI) tract, differing microbial compositions (specifically, the presence or absence of certain bacteria including segmented filamentous forms and those of *Clostridium* clades IV and XIV) of which induce specific T cell repertoires (Th17, and CD4⁺ FoxP3⁺ T regulatory cells, respectively [14, 16, 17].

Changes in the immune function of the respiratory tract are (at least in theory) linked to the immunomodulatory activity of the gut microbiota via the concept of a “common mucosal response” [18–20]. This view suggests that antigen presentation at a single mucosal site stimulates lymphoid cell migration to other mucosal sites, thus influencing the immune responses of remote sites. Regardless of the anatomical pathway (i.e., gastrointestinal, respiratory or, possibly, both) through which microbes affect asthma, the principal challenge is to define the mechanisms responsible for the observed effects. This is not easy; the host genome is complex, as are immunological responses. In addition, unrecognized environmental factors remain in play, and asthma is clinically heterogeneous [21].

Ingestion of bacteria or bacterial products affects human responses to viral respiratory tract infections. Administration of *Lactobacillus acidophilus* and *Bifidobacterium animalis* to children aged 3–5 years reduced fever, rhinorrhea, coughing, and the need for antibiotics [22]. Ingestion of a mixed extract of lyophilized bacteria (OM-85BV) for the first 10 days of each of 3 consecutive months reduced the cumulative number of respiratory tract infections and the number and duration of wheezing episodes [23].

Among healthy subjects, the most commonly reported bacterial phyla in respiratory specimens are *Bacteroides*, *Firmicutes* and *Proteobacteria*. Lower-respiratory tract communities appear related to but distinct from those of the upper airways (Table 1) [24].

A causal pathway may link environmental exposure in early infancy to the later development of allergy and asthma. Thus: (1) environmental exposure shapes the composition of the gut microbiota; (2) the gut microbiota defines the rate and pattern of immune function development; and, (3) differences in immune function shape the nature and intensity of responses to allergens and viruses [21]. The respiratory tract may be an additional (or possibly even more relevant) site of microbial colonization [25, 26].

House dust collected over the first 3 years of childhood life was analyzed in terms of bacterial and allergen contents. Surprisingly, the highest rates of atopic sensitization, and recurrent (presumably virus-induced) wheezing at 3 years of age, were evident in children exposed to the lowest levels of cockroach, mouse, and cat allergens and who had the lowest level of bacterial diversity in the first year of life. The lowest rates of atopy and wheezing were evident in those who had been exposed to the highest levels of allergens and the greatest bacterial diversity [27]. Turnbaugh et al. [28] examined the fecal microbiota of twins who were lean and obese. Between-twin differences in microbial community composition were not necessarily

Table 1 Phyla and genera of human lung microbiomes

Phylum	Genus
Bacteroidetes	<i>Prevotella</i> (commensal)
	<i>Bacteroides</i> (commensal and pathogen)
Firmicutes	<i>Veillonella</i> (commensal and pathogen)
	<i>Streptococcus</i> (commensal and pathogen)
	<i>Staphylococcus</i> (commensal and pathogen)
Proteobacteria	<i>Pseudomonas</i> (pathogen)
	<i>Haemophilus</i> (commensal and pathogen)
	<i>Moraxella</i> (commensal and pathogen)
	<i>Neisseria</i> (commensal)
	<i>Acinetobacter</i> (commensal)
	<i>Escherichia</i> (commensal and pathogen)

Adopted from reference [24]

reflected in the genes and pathways expressed. The implication is that perturbations in core microbial functions, rather than core microbial composition, are key in mediation of disease.

Microbiological dysbiosis

Dysbiosis is defined as qualitative and quantitative changes in the intestinal flora, their metabolic activity and their local distribution. Dysbiosis is a state in which the microbiota produces harmful effects via (1) qualitative and quantitative changes in the intestinal flora itself; (2) changes in their metabolic activities; and (3) changes in their local distribution. According to the dysbiosis hypothesis, modern diet and lifestyle, antibiotics, psychological and physical stress result in alterations in bacterial metabolism, as well as the overgrowth of potentially pathogenic microorganisms. They release potentially toxic products that play a role in many chronic and degenerative diseases [29].

The microbiome and allergic diseases

Commencing at birth, we are continuously exposed to microbial challenges that shape the microbiome. Perturbation of the gut microbiome affects both health and disease. The widespread use of antibiotics means that ancient microbes that formerly resided in the human body are being lost (e.g., *Helicobacter pylori* of the stomach) [30]. The gut microbiota shapes systemic immunity, thus affecting the lung mucosa. Alternatively, changes in the gut microbiota may reflect alterations in the oropharyngeal microbiota, which may in turn directly affect the lung microbiota and host immune responses via microaspiration.

Ultimately, the gut and lung mucosa may function as a single organ, sharing the physiological functions of immune surveillance and shaping of host responses [30].

The role played by the gut microbiota in shaping the mucosal immune system is well-understood [31, 32]. The intestinal microbiota regulates the balance between helper T type 17 cells and T regulatory cells (the Th17:Treg balance) in the lamina propria of the small intestine [31]. Compared to conventionally colonized animals, germ-free mice are defective in terms of the development of immunity, with fewer CD4⁺ and CD8⁺ T cells [33, 34]. However, the symbiosis between the gut microbiome and the intestinal mucosa features barrier mechanisms excluding most bacteria, thus preventing unwanted invasion and development of tolerance via continuous exposure to bacterial products. Loss of barrier function may trigger bacterial invasion and chronic inflammatory processes such as inflammatory bowel disease [35]. In the lung, little is known about the effects of the airway microbiome on immune maturation or the types of tolerance that may develop in the lower airway. These may be very relevant in the context of symbiosis [30].

All immune system components are directly or indirectly regulated by the microbiota. For example, the microbiota per se and metabolic by-products affect dendritic cells and macrophages either directly or via the intermediacy of epithelial cells. This activity is regulated by microbiota-driven epigenetic mechanisms. Similarly, T regulatory cells are induced by microbial metabolic products. The gut microbiota induce B cell maturation and cause such cells to switch their immunoglobulin isotypes. A preference for IgE (rather than IgA) tends to activate basophils and mast cells, in turn modifying the microbiota. Cross-talk between gut flora and the immune system stimulates the development of gut mucosal immunity, preventing the intrusion of exogenous pathogens [36]. Pattern recognition receptors, including toll-like receptors (TLRs) and nucleotide-binding oligomerization domain receptors allow the innate immune system to recognize molecules with foreign characteristics. In turn, this permits recognition of, and the drawing of distinctions between, pathogens and non-harmful materials [37].

The nature of microbial exposure early in life appears to be important for the development of robust immune regulation; disruption of either the microbiota or the host response can trigger chronic inflammation. In this context, reduced exposure to commensals, helminths, and other infectious agents in affluent countries is likely to contribute, at least in part, to the increasing incidences of chronic low-grade inflammation and impaired immune regulation [38–41].

Perturbations in gastrointestinal bacterial numbers disrupt mucosal immunological tolerance, in turn increasing

the incidence of allergic airway disease [42]. Several independent studies have found that reduced gut microbial diversity in infancy is associated with an increased risk of allergic manifestations in school-aged children [43–45]. Associations between the microbial composition of the intestine, asthma, and allergic disease, currently attract considerable research interest [46, 47], although the details of how intestinal microbes interact with the systemic immune system remain poorly defined [48, 49]. Several reviews on the associations between intestinal microbes and asthma have appeared [50–52]. Short-chain fatty acids produced upon fermentation of dietary fibers by intestinal bacteria [53, 54] may be involved in regulation of both local and systemic inflammatory responses.

The critical role played by the gut microbiota in immune system development has been well documented in germ-free animal models. In such animals, normal immune system maturation fails. In particular, the systemic immune regulatory networks fail, triggering both allergic and autoimmune phenomena, as reviewed by Renz et al. [55], Sommer and Bäckhed [56], Garn et al. [57], and West et al. [58]. An early developmental window, during (but not after) which time microbial colonization induces appropriate maturation of the T_H2 response and IgE regulation, has been identified [59]. More recently, it has been shown that microbial diversity is crucial for development of an immunoregulatory network that protects against induction of IgE synthesis by the mucosa [60]. It remains unclear whether humans also have such a window, but the existence of a window would be in line with the observation that gut microbial exposure in infancy influences maturation of the mucosal and systemic immune responses [58, 61, 62].

Alterations in the gut microbiota induced proinflammatory and metabolic effects in animal models of obesity [56]. Notably, subtle manipulations achieved by administration of low-dose antibiotics (at levels likely encountered in human food) early in life increased the risk of adiposity, and exerted significant effects on the levels of short-chain fatty acids (SCFA), and hepatic regulation of lipid and cholesterol metabolism [63]. Intriguingly, changes in behavior and gene expression in the brain develop after manipulation of the gut microbiota [56, 58].

All of delivery via cesarean section (C/S) [64–67], antibiotics (given to the mother or infant) [68], breastfeeding [65, 67], and introduction of solid foods [69], influence establishment of the gut microbiota. Infants born by CS have higher incidences of respiratory distress [70] and appear to be at higher risks of asthma and atopy [71], obesity [72], and type 1 diabetes [73]. It has been hypothesized that delayed, aberrant, microbial intestinal colonization might contribute to the risks associated with CS. Recent DNA-based studies have revealed perturbations of infant gut microbiomes; CS-delivered infants had a

lower diversity of the Bacteroidetes [66] and a reduced abundance of *Bacteroides* [65–67], suggesting that dysbiosis was in play.

Emerging evidence indicates that early establishment of the gut microbiota during critical periods of development may influence the risk of environmentally influenced disease, including allergic conditions. Infants born via C/S are at greater risk of developing asthma and atopy [16, 74, 75], mainly because the Bacteroidetes are less abundant (and less diverse) in the gut [66, 76–78]. More generally, a reduced density and diversity of Bacteroidetes in early infancy preceded the development of allergic manifestations [79–82].

Asthma and the allergies are complex diseases featuring local tissue inflammation triggered by both genetic and environmental factors. The normal commensal microflora play an essential role in inflammatory homeostasis and appropriate immune regulation, and the microbiome may thus significantly affect the development of allergic conditions. New techniques, such as next-generation sequencing, render it possible to comprehensively explore the microbial communities of the human body [83].

Imbalances in the composition of the intestinal microbiota may trigger allergic disease. Although several pre-2006 studies described correlations between microbial compositions and allergic symptoms, it has not been possible to distinguish protective microorganisms from those associated with increased risks of allergic diseases. The early microbiota of children who later developed allergies was characterized by low bacterial diversity, with *Firmicutes* predominating; higher counts of the *Bacteroidaceae*; greater numbers of the anaerobic bacteria *Bacteroides fragilis*, *Escherichia coli*, *Clostridium difficile*, *Bifidobacterium catenulatum*, *Bifidobacterium bifidum*, and *Bifidobacterium longum*; and lower numbers of *Bifidobacterium adolescentis*, *Bifidobacterium bifidum*, and *Lactobacillus*. When the microbiota of allergic children was assessed at the onset of allergic symptoms, higher counts of *Bacteroides*; lower counts of *Akkermansia muciniphila*, *Faecalibacterium prausnitzii*, and *Clostridium*; a higher prevalence of *B. adolescentis*; lower prevalences of *B. catenulatum* and *Staphylococcus aureus*; and lower bacterial diversity overall, were noted [84].

Modulation of the gut microbiota in terms of treatment and prevention

Collectively, the data described above have created intense interest in strategies that might correct dysbiosis. The aims of such work were to treat disease, and to modulate intestinal colonization in efforts to prevent noncommunicable diseases (NCDs) [38].

Environmental microbiota to which humans are exposed, especially during early life, may strongly influence long-term health, and the disease outcomes of many organs and systems. It seems clear that this does not depend on a single or even a few microbial communities, being rather the result of interactions among the host genetic background, the timing of initial microbial contact, and variations in the microbial components to which the host is exposed. It is certainly true that the major efforts made to improve hygiene and treat acute bacterial infections have drastically reduced human morbidity and mortality, especially in infancy, but such efforts may also have radically changed the microbiota to which humans are exposed and the guest microbiomes of human mucosal surfaces [85].

Probiotics

Probiotics have become very popular [86]. In most studies, one or more strains of lactobacilli and/or bifidobacteria are used to treat or prevent allergic disease. However, any useful effect of a particular probiotic strain cannot be extrapolated to another (apparently related) strain. Some probiotics exert immunomodulatory effects, revealed principally in animal models but also in human interventional studies [58, 87]. Mechanistically, it is thought that the TLRs promote T_H1 cell differentiation by enhancing the production of IL-10, TGF- β , and IgA; by inhibiting antigen-induced T cell activation; and by suppressing TNF synthesis [58, 88]. The timing of probiotic administration (when the aim is to promote immune tolerance) appears to be critical [35]; pre/postnatal combinations of probiotics preventing allergy (eczema) have afforded the most consistent benefits, although their routine use cannot be recommended [58, 87, 88].

Probiotics may improve health by modulating local immunity, maintaining gut wall integrity, stimulating systemic immunity, or enhancing both the non-specific and specific arms of the immune system [89]. In the context of innate immune function, probiotics enhance the phagocytic capacities of peripheral blood polymorphonuclear cells and monocytes, and the cytotoxic activity of NK cells. Acquired immunity also seems to improve following administration of probiotics; the levels of specific IgG, IgA, and IgM immunoglobulins rise significantly. Local immunity is strengthened by enhancement of gut barrier functionality and improvement of the local immune response. A principal clinical outcome predicted by such in vitro data is a reduction in the rate of upper respiratory tract illness (URTI) in both children and adults given specific probiotic strains [89]. Although few supplementation studies have been undertaken in athletes, it seems that such persons may benefit from regular probiotics [37]. The most common strains used to promote immune

function are lactic acid bacteria; thus, species of *Lactobacillus* and *Bifidobacterium* [5].

Commencement of supplementation during the second trimester of pregnancy, when circulating fetal T cells have developed, may be optimally effective [58]. Under such conditions, development of asthma may be inhibited (this disease has not been prevented by the probiotic interventions tested to date) [90–93]. Unconventional probiotics, such as bacteria that produce butyrate or propionate, immunomodulatory strains of *Bacteroides* [58, 88], or Clostridia [94], may induce stronger effects. In addition, CS-delivered infants may benefit greatly from probiotics [95].

Dietary fiber and prebiotics

Associations are evident between high-fat/low-fiber Westernized diets and the prevalences of many NCDs, including allergic disease [96]. Thus, dietary substrates of the gut microbiota may be useful to prevent and treat NCDs. Dietary fibers pass through the upper intestine and are fermented by large-bowel anaerobic microbes to produce SCFAs [97], which in turn promote the integrity of the gut epithelium and exert immune effects, including stimulation of G protein-coupled receptors, promotion of innate (TLR 2) immune responses, and induction of regulatory T cells [97].

In experimental models, a switch from a high- to a low-fiber diet triggers dramatic changes in the composition of the gut microbiota, including a decrease in Bacteroidetes numbers [97]. In line with this observation, infants of rural Africa, where both mothers and infants consume traditional diets very high in fermentable carbohydrates, have substantially higher stool Bacteroidetes and SCFA levels compared to European infants who (with their mothers) consume a Western diet [98]. In terms of early-onset NCDs, preliminary evidence suggests that consumption of prebiotics from early infancy may prevent eczema, but confirmation is required [58, 88, 99]. The most recent Cochrane review [99] included 1428 infants at high risk of allergic disease. Addition of prebiotics to infant food reduced the risk of eczema (risk ratio, 0.68; 95 % CI 0.48–0.97) but had no effect on any other allergic outcome.

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) has been suggested to both treat and prevent NCDs [100]. FMT was first used to treat *C. difficile*-induced diarrhea; the clinical resolution rate was high and no adverse event was noted, although the initial trials were not controlled [101]. FMT is predicated on the concept that antibiotic therapy (repeated courses or

overuse of broad-spectrum antibiotics) disrupts the normal microbial ecology, facilitating colonization by *C. difficile*. FMT is used as both an investigational tool in rodent models to study the roles played by microbes in disease development and responses to treatment [56], and as a novel therapeutic intervention that gained clinical credibility upon publication of the first randomized controlled trial showing that FMT effectively treated antibiotic-resistant *C. difficile*-induced diarrhea [102].

Conclusion

Alterations in bowel flora and its activities are contributing factors to many chronic diseases. The microbiome is essential for human development, immunity, and nutrition. Bacteria living in and on humans are not invaders but, rather, beneficial colonizers. They accumulate over time and change genetic activities and metabolic processes, triggering abnormal immune responses. Dysbiosis is also an important clinical entity. Antibiotics, psychological and physical stress, and dietary factors contribute to intestinal dysbiosis.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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