REVIEW ARTICLE

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Immunobiography and women's health: repercussions from conception to senility

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INTRODUCTION

In recent years, some researchers have questioned whether changes that occur in the adaptive immune system during aging could explain all the changes observed in the elderly and if the innate response could also have some participation in the process. Currently, it has become evident that both types of immunity participate in immunosenescence[1].

Immunosenescence is a key concept that translates into a growing and permanent decrease in the immune system's cellular growth. Senescent cells in various organs and tissues are inherent in the aging process, but when in great intensity and quantity, they are associated with chronic diseases, autoimmunity, and cancers[2].

The immune system is highly complex, presenting some specific properties, such as each receiver's ability to recognize different molecular patterns, cells capacity to interact and form a network (network), and their adaptability to different situations (plasticity). Based on these particularities, a model was proposed in the form of a "bow tie," called bow-tie architecture[3]. In this model (Figure 1), the bow-tie knot represents the immune system, and each side represents structures that can receive different input signals (fan in) and, after processing, produce a series of output signals (fan out).

Immune system cells are also able to adapt and change according to the numerous stimuli they receive. The type of stimulus, intensity, and temporal sequence are critical for the type of response generated, such as strong or weak, absent (tolerance or anergy), autoimmune, inflammatory, and memory. The immune responses generated will be unique to each individual and will compose the immunological history or "immunobiography" in the timeline, represented by the sum of all immune experiences that may be experienced throughout life[4].

Events during prenatal and neonatal life, as well as the so-called antigenic eco-space to which individuals are exposed from birth to adulthood and into senescence, form the bricks with which immunobiography is constructed[4].

When it comes to women's health, there are some important particularities because care for the biopsychic body becomes necessary in order for the conceptus to be received in a healthy way due to the condition of motherhood. Therefore, this article is intended to describe the behavior of the immune system – immunobiography – in the face of impairments and external agents from conception to senility.

METHODS

The research was carried out from December 2022 to February 2023 in the PubMed/Medline, Lilacs, and SciELO databases, using the following keywords: immunobiography, women's health, immune system, immunosenescence, inflammaging, and autoimmunity, using AND and OR Boolean logic. The filters used to prepare the proposal were as follows: articles published in the past 10 years, in English, Spanish, and Portuguese.

After screening by reading titles and abstracts, publications such as comments, editorials or letters, and duplicate articles were excluded. From then on, the full reading began, including more articles, through the references of the studies that had been preselected initially and reviews published on the subject, through manual search.

After selecting the articles, we tried to divide the theme into three topics in order to build the narrative of the factors that

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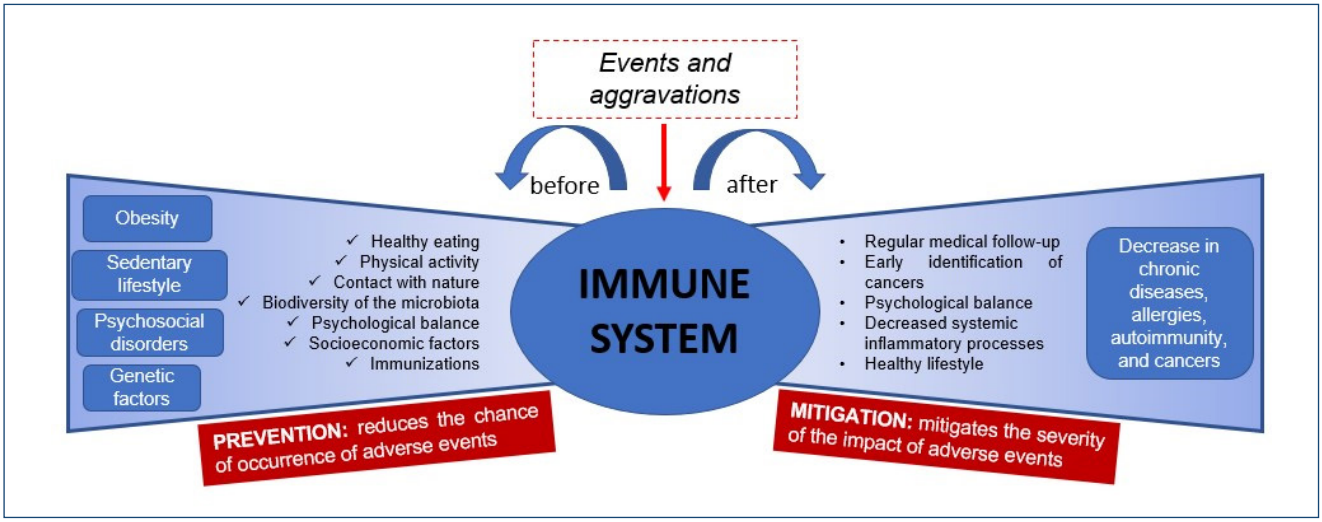

Figure 1. Bow-tie model of representation of factors related to prevention and mitigation of chronic diseases, allergies, autoimmunity, and cancers.

are involved in the immunological development from conception to immunosenescence.

RESULTS

Through the search in the databases, 33 articles were selected that address the following three sections: 1. Early events of conception and the immune system; 2. Exposures in early extrauterine life and the immune system; and 3. Events that occur in adulthood and senescence.

Early events of conception and the immune system

Intrauterine stimuli

Prenatal influences on immunobiography include numerous aspects, such as the health of future parents before conception, genetic predisposition, demographic and economic determinants, maternal health during pregnancy, and influences of the uterine environment and maternal biopsychic and cultural organisms during pregnancy[5].

In the context of individual-environment interaction, the Biodiversity Hypothesis has arisen in view of these new observations of the interaction between the external microbiota (soil, natural waters, plants, and animals) and the internal microbiota (intestine, skin, mucous membranes, and airways), enriching the human microbiome, aiming at promoting balance in immune tolerance and protecting against inflammatory and allergic disorders[6].

Numerous external agents can alter the epigenome, directly and indirectly influencing the development and immune programming of the conceptus. Among them are cited: environmental exposures during pregnancy, including diet, nutrient intake, nutritional status (obesity × malnutrition), use of vitamins and folic acid, smoking, infections and use of antibiotics, effect on the hypothalamus-pituitary-adrenal axis due to psychological stress, alcohol use, and exposure to indoor and outdoor toxins and pollutants (Figure 2). Consequently, understanding some of these factors will be essential in identifying individuals at risk and in the possible development of interventions for the prevention of chronic, allergic, and autoimmune diseases[7].

Maternal diet

The developing fetus depends on the mother to provide molecular precursors, as well as certain vitamins that are essential for immunity and system development[8].

Regarding the maternal diet, the intake of fish and fish oil during pregnancy seems to protect against allergies, although some studies have found the opposite. One study found that increasing intake of fish by mothers during pregnancy protected children against eczema, atopy, and wheezing by the age of 6 years, especially those who were not breastfed. Maternal supplementation with polyunsaturated fatty acids during pregnancy also reduces atopic eczema and egg sensitization in the first year of life[9].

Folate, another important nutrient, is recommended for pregnant women to prevent congenital anomalies (neural tube defects) in the fetus. While most studies report that elevated folate levels are associated with an increased risk of allergic diseases, there are a few publications reporting adverse effects. Thus, there is still no consensus on the subject, but it seems prudent to avoid excess folate during pregnancy[10].

Levels of other vitamins during pregnancy, from diets and supplements, also affect the risk of allergic diseases. Intake of vitamins A and E is inversely associated with the risk of allergic

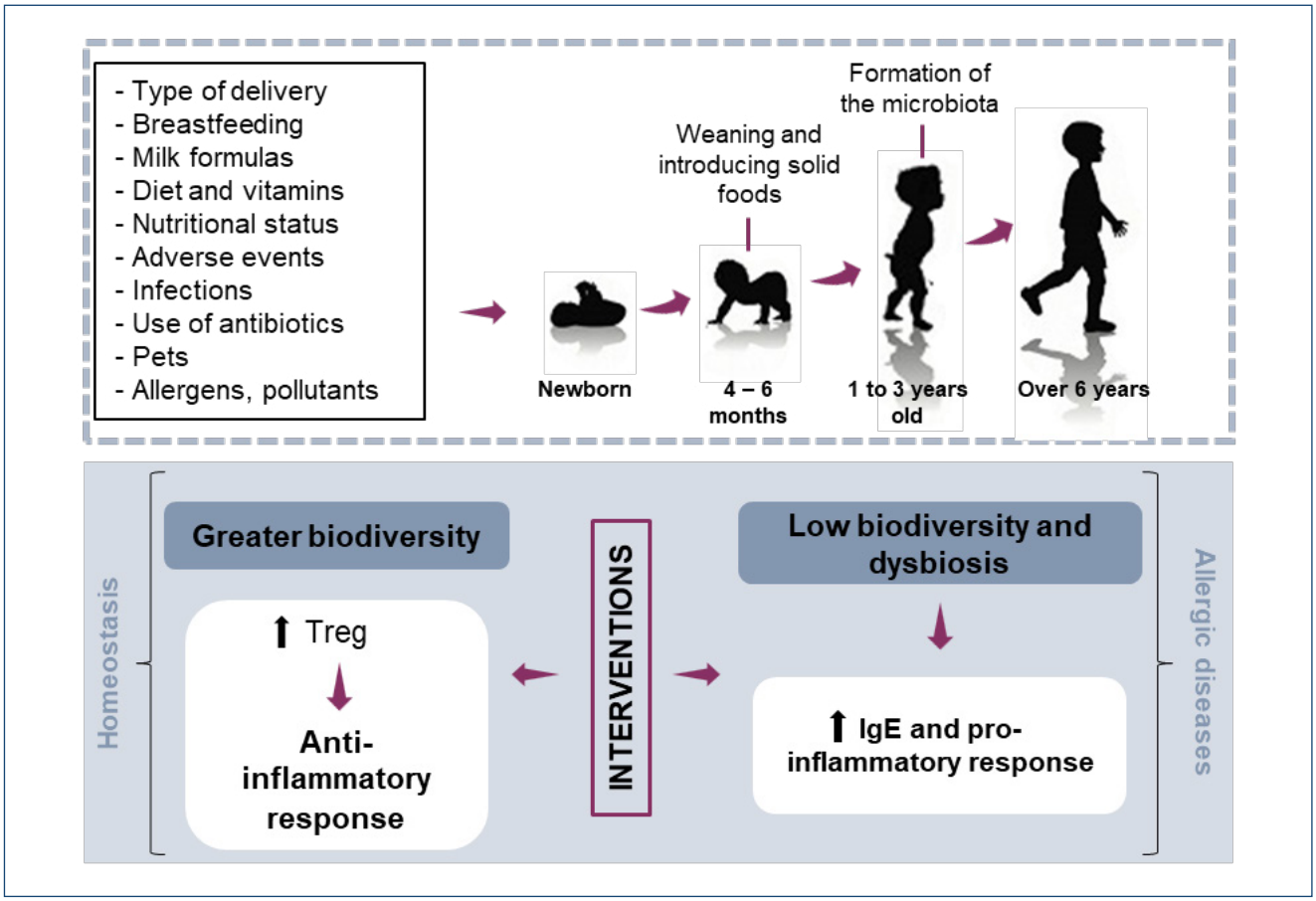

Figure 2. Multiple factors that interact between the host and the environment. Complexity of interactions of prenatal and postnatal factors in immunobiography.

rhinitis in childhood. Higher levels of vitamin C in the maternal diet reduce the risk of allergic diseases and wheezing, and vitamin D consumption during pregnancy alters neonatal airway epithelial cell responses and is inversely associated with the risk of asthma[11].

Some studies, including systematic reviews, have suggested that maternal ingestion of probiotics and prebiotics may cooperate in fetal immune development, with benefits of protection against atopic dermatitis, especially if used during prenatal care and in the first 6 months of postnatal life[12].

All these data seem to indicate that maternal intake of different nutrients may play a relevant role in the development of the immune system and other systems and may modify the risk of atopy in children. However, current knowledge on this topic remains uncertain.

There is still no universal recommendation regarding the prevention of allergic diseases through specific food supplementation during pregnancy or the exclusion of certain foods for consumption by pregnant women[13]. Well-designed intervention studies are needed to resolve these uncertainties.

Type of delivery and intestinal microbiome

The mode of birth influences the risk of allergic diseases: children born by cesarean section have an increased risk of developing allergies due to the acquisition of a microbiota with less diversity and consisting mostly of bacteria that provide little stimulus to the responses of type helper 1 (Th1) cells and regulatory T cells (Tregs). It is important to emphasize that the passage through the birth canal provides a birth experience in respiratory, endocrine, neuroimmune, and vaginal microbiome exchange fullness, which will certainly imprint a favorable potential on the baby's immunobiography[14].

There is suggestive evidence that the human microbiome is seeded in uterus, and it is likely that bacteria play a significant role in the development of the immune system. There is an increased rate of bacterial translocation through the intestine and increased traffic of live bacteria around the fetus in the last trimester, which may suggest that bacterial exposure increases or perhaps begins toward the end of pregnancy[15].

In turn, the administration of antibiotics during pregnancy and at birth acts unfavorably on the neonatal microbiome. It is

known that direct transmission of antibiotics through the placenta or breast milk can occur. As a result, antibiotics can cause temporary dysbiosis in the mother, resulting in transmission of her altered microbiota to her baby during critical early life phases[16].

Premature birth also confers a series of alterations that have been associated with neonatal dysbiosis. In particular, preterm infants are more frequently admitted to neonatal intensive care units, whose environment is likely to influence the neonatal microbiome. These babies are more likely to receive antibiotics and consume formula or pasteurized breast milk, as well as having little skin-to-skin contact with their mothers, negatively influencing the formation of their immune system[16].

Indoor and outdoor environmental factors

It is well known that smoking is one of the most studied environmental factors due to its association with epigenetic alterations. Pre- and postnatal exposure to tobacco is associated with higher levels of DNA methylation, decreased gene expression of IFN-γ (in effector T cells), and FOXP3 (in regulatory T cells). Smoking during pregnancy also interacts with interleukin-13 (IL-13) and may influence the onset of asthma, airway hyperreactivity, and genetic variants in the 17q21 locus associated with the risk of early onset asthma[17].

Similar considerations apply to environmental pollution, both indoors and outdoors, increasing the risk of rhinitis and asthma in childhood. In some parts of the world, there is strong air pollution by toxins and heavy metals generated by industrial processes, pesticides, plasticizers, as well as polluting particles and gaseous emissions resulting from burning fuels, which lead to possible epigenetic effects related to atopy[18].

Exposures in early extrauterine life and the immune system

Breastfeeding and the microbiome

More than a third of the intestinal bacteria of breastfed babies are vertically derived from milk and breast skin contact. Source-tracking studies have shown that the skin around the areola is the source of approximately 10% of an infant's microbiome and that bottle-fed babies may therefore miss out on microbes from their mother's skin. In addition, breast milk contains prebiotics that modulate the infant gut microbiome and metabolome, persistently differing in composition, diversity, and immune function in non-exclusively breastfed infants[19,20].

There is suggestive evidence that the mechanism by which childhood gut bacteria protect against the development of asthma and allergies is through the production of short-chain fatty acids, which are intestinal bacterial metabolites and immune modulators produced as a result of the fermentation of fibers. Elevated serum acetate levels in pregnant women correlated with a reduced risk of wheezing in the offspring in the first year of life. Similarly, intestine with higher concentration of acetate at 3 months of age and of propionate and butyrate at 12 months of age correlated with a decreased risk of wheezing and asthma later in life[19].

Events that occur in adulthood and senescence

Biodiversity of the microbiota and immune system

From an ecological point of view, the human body is an ecosystem of microbes, and in particular, the intestinal microbiome – also called the "second genome" – exerts multiple protective and life-supporting functions by orchestrating the relationship between cells and the environmental metagenome. The lack of interaction with the external microbiota, present in nature, promotes altered immune responses, favoring the risk of inflammatory and allergic diseases in individuals[6] (Figure 3).

This microbiome is established gradually in the first years of life. At birth, the human gut microbiome is highly dynamic, with low biomass and low diversity. Around one year of age, it passes from a developmental stage to a transitional phase, and the composition of the microbiota changes as diversity increases. Finally, at 2 and 3 years of age, the gut microbiome matures into a nearly stable adult microbiome[21].

The diversity and stability of the microbiota are mainly promoted in early life, but the interaction between the microbial components of the outer and inner layers never ceases. Lifestyles with reduced contact with nature lead to a cycle of greater dependency on health care[21].

Responses to infections and vaccines in immunosenescence

The numerous changes that occur in the immune system during aging make immunosenescence a significant contributing factor to increased risk and severity of infections. Although the immune response to antigens may be preserved in elderly individuals, their ability to immunize against new antigens is reduced[22].

Latent Epstein-Barr virus, herpes virus, and cytomegalovirus infections have been associated with telomere shortening in CD8 T cells, specifically due to a reduction in telomerase activity associated with T-cell proliferation. These data indicate that chronic infections during aging produce significant changes in the population of CD8+ T cells. Furthermore, these cytokines are strongly involved in the pathogenesis of immunological disorders that can favor the emergence of different pathologies, including autoimmune diseases[23,24].

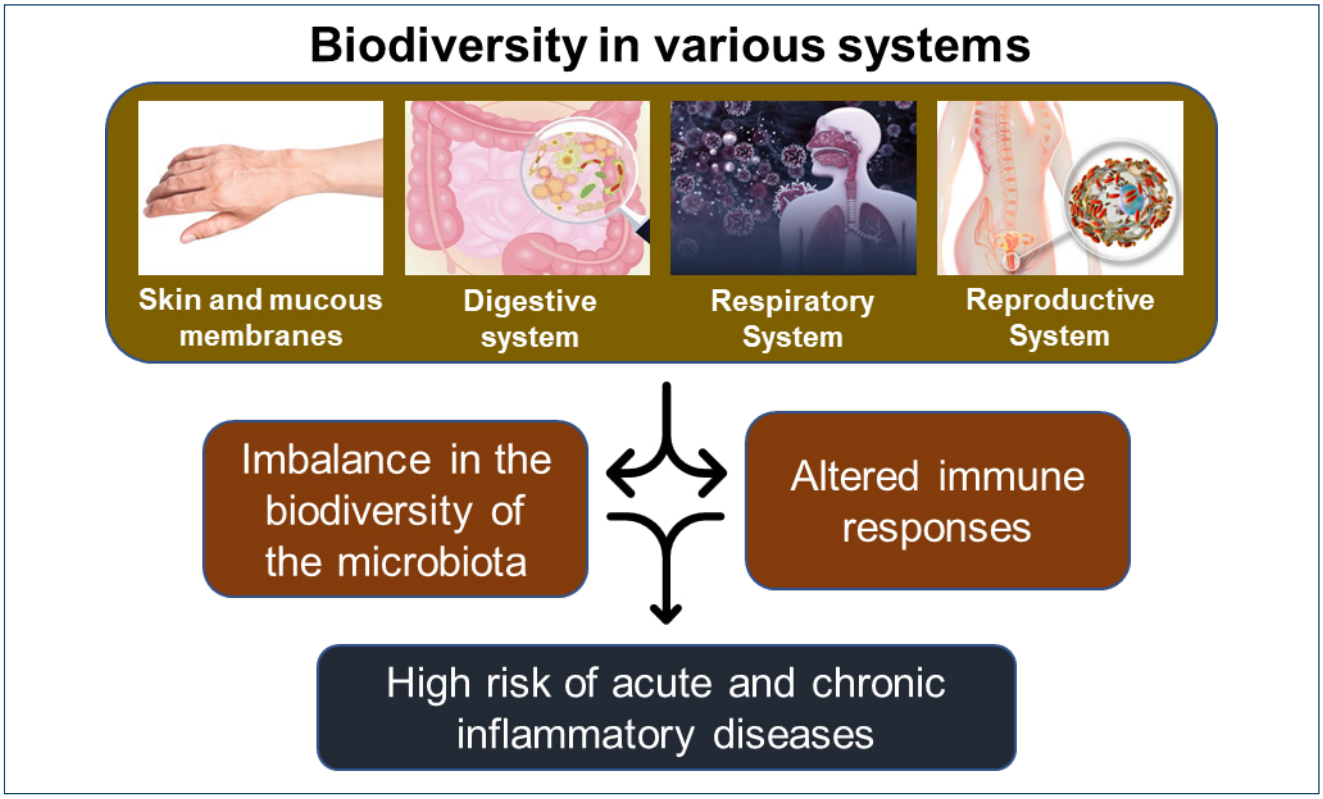

Figure 3. Lower biodiversity of the human body's microbiota and the risk of inflammatory diseases: biodiversity theory.

Among the various preventive strategies for protecting the health of the elderly, one of the most effective is vaccination against the most common infectious diseases in this age group. As a strategy to increase the immune response of the elderly to vaccines, several approaches have been described, the main ones being the increase in antigen concentration and the association of adjuvants in vaccines[25].

Autoimmunity in senility

Currently, there is no doubt that the changes that occur in the immune system during aging influence the onset of autoimmunity. This is due to the fact that aging is related to increased reactivity to self-antigens and loss of tolerance. In addition, it is worth remembering the epigenetic changes that occur in elderly people that can affect important genes involved in the development of autoimmune diseases[26].

Another important aspect of aging is the increase in inflammatory cytokines and chemokines produced by T cells, such as tumor necrosis factor (TNF)-α, c-reactive protein, IL-8, monocyte chemoattractant protein 1 (MCP1), and RANTES, which may contribute to the development of autoimmunity in the elderly[26].

One of the important causes of dysfunctional immune responses that can lead to autoimmunity are telomere abnormalities, and an association has been demonstrated between the mean telomere length of peripheral blood mononuclear cells in different pathologies. These findings were interpreted as evidence of accelerated T-cell proliferation in the autoimmune process. Another striking fact is that the genetic predisposition for short telomeres is strongly related to the HLA-DR4 haplotype, which is shared in rheumatoid arthritis and T1DM in some individuals[27].

Inflammaging and immunobiography

In general, inflammatory processes do not decrease with age, and a sterile, chronic, and low-grade inflammation called inflammaging seems to be an almost universal phenomenon in the elderly, constituting a hallmark of immunosenescence[28].

Inflammaging is mainly associated with changes in innate immunity, where the macrophage plays a central role, characterized by hyperproduction of pro-inflammatory cytokines (IL-6, TNF-α, and IL-1β), simultaneous production of anti-inflammatory mediators (IL-10), and chemokines. It is important to point out that the presence of compensatory anti-inflammatory mechanisms has also been previously described in centenarians, thus constituting adaptation pathways that possibly favor longevity. This apparent paradox can be explained from the perspective of immunobiography, according to which environmental

factors can shape the immune system throughout life, generating effective anti-inflammatory responses[29].

Currently, there is evidence that other types of cells not belonging to the immune system may also contribute to inflammaging, such as adipose cells, skeletal muscle cells, and senescent cells[30].

Lack of response: tolerance

The immunosuppressive network involves several regulatory T (Treg) and B (Breg) cell subtypes, as well as regulatory phenotypes of macrophages (Mreg), dendritic cells (DCreg), natural killer (NKreg), and type II natural killer cells (NKT). The immunosuppressive network also includes monocytic cells and polymorphonuclear cells derived from immature myeloid suppressor cells induced by inflammatory mediators[31].

This immunosuppressive cooperative network has a significant role in the resolution of acute inflammatory conditions, but its persistent activation, as for example in tumors and inflammatory diseases, has harmful effects on the immune system and tissue homeostasis inducing immunosenescence[31].

The immunosenescence process may be associated with the activation of an immunosuppressive network, especially with the functions of myelocytic cells, suppressor macrophages, and Treg cells. Its function is best known in relation to tumor growths, autoimmune diseases, and maternal-fetal immunity[32,33].

Many clinical observations indicate that immune system remodeling occurs with aging, with increased risk of cancers, increased susceptibility to infections, decreased efficacy of vaccine response, and increased tolerance to transplants[33].

CONCLUSION

Each individual's immune responses will be unique depending on their immunobiography. Therefore, immune responses to potential antigens, including pathogens, food, and vaccines, will be quantitatively and qualitatively different according to the host's immunobiographical history, including age, sex, lifestyle, biodiversity, socioeconomic status, and psychological status, and among different populations, whose genetics and immune systems are shaped by their ecosystem and cultural habits.

AUTHORS' CONTRIBUTIONS

GVAGL: Conceptualization, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. **MAMTB:** Conceptualization, Formal Analysis, Methodology, Software, Writing – original draft, Writing – review & editing. **MEBA:** Conceptualization, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing. **FWS:** Investigation, Visualization, Writing – original draft, Writing – review & editing. **FRF:** Investigation, Visualization, Writing – original draft, Writing – review & editing. **FCK:** Investigation, Visualization, Writing – original draft, Writing – review & editing. **ESCS:** Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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