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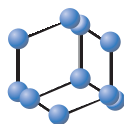
Chronic Systemic Low-Grade Inflammation and Modern Lifestyle: The Dark Role of Gut Microbiota on Related Diseases with a Focus on COVID-19 Pandemic

Tiziana Mundula[1], Edda Russo[1], Lavinia Curini[1], Francesco Giudici[1], Andrea Piccioni[2], Francesco Franceschi[2] and Amedeo Amedei[1,*]

[1]*Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy;* [2]*Emergency Department, Fondazione Policlinico Universitario A. Gemelli, Catholic University of the Sacred Heart, Rome, Italy*

Abstract: Inflammation is a physiological, beneficial, and auto-limiting response of the host to alarming stimuli. Conversely, a chronic systemic low-grade inflammation (CSL-GI), known as a long-time persisting condition, causes damage to the organs and host tissues, representing a major risk for chronic diseases. Currently, a high global incidence of chronic inflammatory diseases is observed, often linked to the lifestyle-related changes that occurred in the last decade. The main lifestyle-related factors are proinflammatory diet, psychological stress, tobacco smoking, alcohol abuse, physical inactivity, and indoor living and working with its related consequences such as indoor pollution, artificial light exposure, and low vitamin D production. Recent scientific evidence found that gut microbiota (GM) has a main role in shaping the host's health, particularly as CSLGI mediator. Based on the lastest discoveries regarding the remarkable GM activity, in this manuscript we focus on the elements of actual lifestyle that influence the composition and function of the intestinal microbial community in order to elicit the CSLGI and its correlated pathologies. In this scenario, we provide a broad review of the interplay between modern lifestyle, GM, and CSLGI with a special focus on the COVID symptoms and emerging long-COVID syndrome.

1. INTRODUCTION

Inflammation is a complex host response to the critical exogenous or endogenous stimuli that, through a network of cells, molecules, and pathways, recognizes, neutralizes, and removes the tissue damage, promoting the healing process and subsequent tissue repair [1, 2]. This mechanism is usually a self-limiting process, leading to a resolution that permits healing [3-6]. After a trauma, the host activates an elimination process called "cell death" that is essential for the homeostasis equilibrium [7]. Correlated to inflammation, there are three types of cell death: necroptosis, pyroptosis, and apoptosis [8-11]. Following this elimination process, the macrophages remove the damaged cells, and the cellular debris is used as a nutrition component to rebuild tissues. This process is known as efferocytosis [12, 13]. Unfortunately, if the stimulus persists for a long time or there is an impairment in the efferocytosis process [2], the inflammatory status persists with a continuous imbalance in the redox state, leading to a low-grade systemic inflammation (CSLGI) [14]. The CSLGI is a common feature of various chronic diseases such as cardiovascular, metabolic, endocrine, autoimmune, oncological, and neurological disorders, including heart attack, hypertension, stroke, diabetes, cancer, obesity, Alzheimer's, *etc* [1, 15-17]. However, the investigation of the persistent mechanisms of the CSLGI condition is in its initial stage and represents a big challenge for the future. Today, scientific evidence suggests a plethora of factors as potential CSLGI triggers, including pro-inflammatory diets, psychosocial

*Address correspondence to this author at the Department of Experimental and Clinical Medicine, University of Florence, Viale Pieraccini, 6 50134 Florence, Italy; E-mail: amedeo.amedei@unifi.it

stress, lifestyle habits such as tobacco smoking, alcohol intake, physical inactivity and indoor living and working (with the correlated air indoor pollution, artificial light exposure and low vitamin D production) [18-21]. In this scenario, the gut microbiota (GM) seems to have an emerging key role. The GM, with its extraordinary variety of microbes, by carrying millions of microbial genes, cooperates with the host's physiological functions and affects the host's health [22]. The main GM roles are the maintenance of intestinal integrity and competition with enteropathogens, the production of vitamins, enzymes, amino acids, and short-chain fatty acids (SCFA), and finally, the development and modulation of the immune system and cognitive function [22]. Currently, the list of GM functions is under incessant updating because of the new contents derived from sophisticated "multi-omics" approaches that integrate genomic, proteomic, and metabolomic data [23]. The GM composition, known as the "microbiota signature," is shaped by host genetics and by environmental factors [24]. If a balanced

GM is synonymous with a healthy host life, in contrast, a perturbed intestinal environment can lead to pathological consequences and potentially fuel an inflammatory condition [25, 26]. In this context, the linkage between GM and CSLGI represents a new attractive field of research [27]. In this manuscript, we summarized the last pieces of evidence on the relationship between GM and CSLGI; additionally, we investigated their impact on particular chronic diseases. We explored in detail the influence of detrimental lifestyles and environmental modern key factors able to shape the microbiota, altering its composition and deregulating the host immune response (IR), thus promoting the CSLGI and its related pathologies. Particularly, we finely discussed the elements involved in the CSLGI trigger through a remodel of GM, such as proinflammatory diets, psychosocial stress, and some dangerous lifestyle factors (diet, stress, smoking, alcohol intake, physical inactivity, and indoor living) (Fig. **1**). Furthermore, a specific focus has been dedicated to the emerging CSLGI contributing to COVID-19 and long-COVID symptoms.
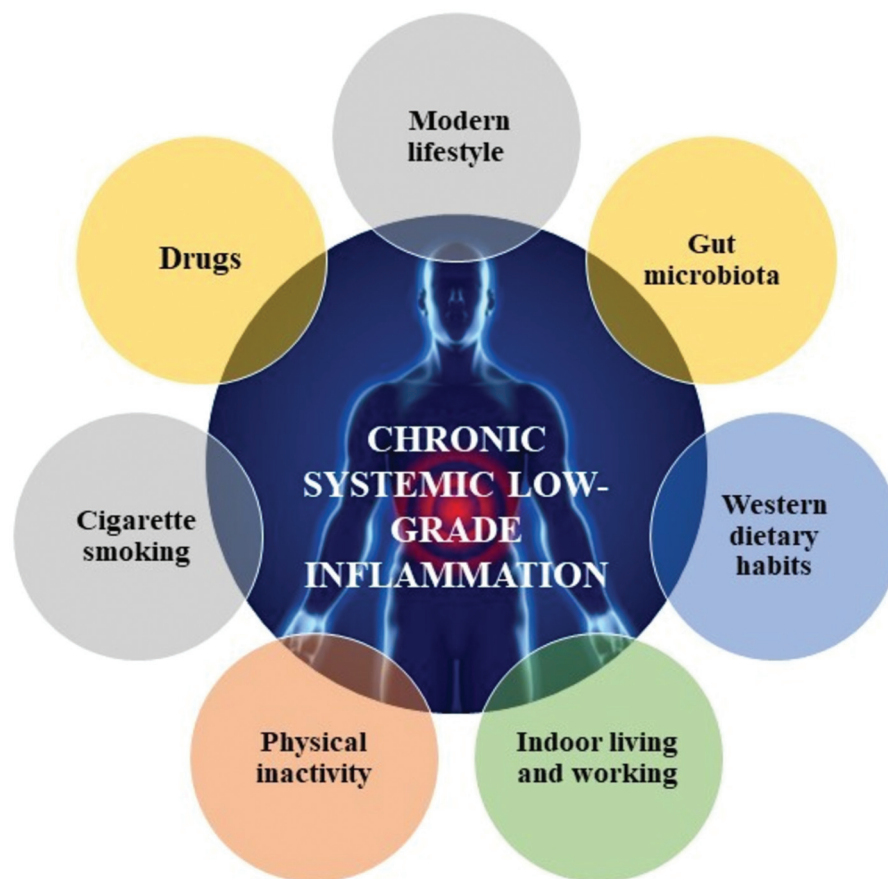
Fig. (1). Main factors related to CSLGI. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

2. CHRONIC DISEASES AND CHRONIC SYSTEMIC LOW-GRADE INFLAMMATION AS A BACKGROUND OF MODERN LIFE

Chronic diseases are defined by the NCCDPHP (American National Center for Chronic Disease Prevention and Health Promotion) as "conditions that last 1 year or more and require ongoing medical attention or limit activities of daily living or both" [28]. In Europe, the major chronic diseases are divided into six categories by the report of the RIVM (National Institute for Public Health and the Environment, the Netherlands): cardiovascular disease, cancer, diabetes, respiratory diseases, mental and neurodegenerative disorders. A milestone in modern medicine consists in the discovery that development, progression, and disease worsening [29-31] are related to the apoptosis process, fibrosis, and organ failure, triggered by inflammatory molecules released by a CSLGI condition [25].

Furthermore, the presence of one of these settings increases the development risk of the others, with only a few exceptions, leading to a condition called "multimorbidity" [32, 33], linking to the low quality of life and increased disability.

Recent evidence highlights that the modern lifestyle continuously exposes the several dangerous stimuli that activate the immune system, increasing immune cells production and proinflammatory CSLGI cytokines such as CRP (C reactive protein) [25], TNF-α (tumor necrosis factor-alpha), IL (interleukin)-6, IL-12 and ROS, feeding a vicious cycle that prevents the inflammation resolution process

2.1. CSGI and Metabolic Syndrome

Western diet and physical inactivity promote insulin resistance, obesity, and metabolic syndrome (MS). MS is defined as three or more of the following traits: central obesity, hypertriglyceridemia, low HDL cholesterol, hypertension, and fasting plasma glucose >7 mmol/L [34]. MS strongly enhances the risk of diabetes and cardiovascular diseases [35]. The western diet is characterized by overnutrition with an excessive intake of calories and some nutrients such as glucose and lipids. Excessive carbohydrate intake can lead to hyperglycemia [36]. If the hyperglycemic condition is prolonged, it can be toxic for several tissues, inducing "glucotoxicity" [37]. In order to clear the glucose in excess in a diabetic state, the body activates the "polyol pathway." This pathway induces the consumption of NADPH with an excess of NADH. Consequently, there are two major effects: a redox imbalance with excessive production of ROS and depletion of antioxidant precursors, resulting in a possible alteration of pro-

teins, lipids and DNA. This process activates cascade reactions (ADP-ribosylation glycation, hexosamine, and the PKC activation pathways) that further contribute to imbalance the redox state and reinforce oxidative stress, inducing cell damage and death [38]. The disequilibrium enhances the activation of the immune response and the release of pro-inflammatory cytokines, exacerbating a CSLGI status. Moreover, an excessive caloric intake can translate into lipid storage, firstly in adipose tissue but also in other tissues (ectopic lipid accumulation), leading to lipotoxicity [39]. In adipose tissue, the deposition of a consistent free fatty acid quantity leads to hypertrophy, hyperplasia, and hypoxia in adipocytes, inducing the activation of the apoptosis process, ROS production, and secretion of adipokines such as leptin. Indeed, leptin is a hormone produced by white adipose tissue that reduces food intake and body weight. Despite elevated leptin peripheral levels, there is a lack of satiating activity in obesity. In this condition, the development of a brain "leptin-resistance" is observed due to a decrease in blood-brain barrier (BBB) permeability [40]. Indeed, this hormone is a strong activator of the innate and adaptive immune system through multiple pathways. Leptin activates the release of several pro-inflammatory cytokines, such as IL-8, IL-12, IL-6, and TNF-α, from dendritic cells and, in neutrophils, promotes the production of ROS [41, 42]. Interestingly, in the CSLGI scenario, leptin increases the expression of the NLRP3 inflammasome [43-45]. In fact, the NLRP3 inflammasome can be activated by a wide range of stimuli such as DAMPs, cholesterol crystals, ROS, lipids during acute and chronic inflammation [46]. This pathway elicits an inflammatory type of cell death (called pyroptosis) and the release of two pro-inflammatory cytokines, notably IL-1β and IL-18 [47]. Compelling evidence suggests that NLRP3 inflammasome has a pivotal role in the perpetuation of CSLGI and its related diseases [48]. In addition, the inflamed adipose tissue partially loses its lipid-storing capacity, contributing to the storage of lipids in other alternative ectopic sides, such as liver, heart, kidney, skeletal muscles, and pancreas, altering metabolic functions with further cells damage, ROS production, organ dysfunction, and thus worsening the CSLGI [49].

2.2. CSLGI and Mental-cognitive Disorders

A CSLGI milieu is also related to the rise of mental and cognitive disorders, mainly caused by chronic psychological stress. Indeed, a stress condition activates the hypothalamic-pituitary-adrenal (HPA) axis and the release of glucocorticoids by adrenal glands [50]. Glucocorticoids are hormones with dual effects: in low

doses, they act as immunostimulants, while in high doses, they are immunosuppressive [51, 52]. The persistent secretion of glucocorticoids due to a prolonged stressful condition can activate the immune system through the induction of the NLRP3 inflammasome, responsible for the enhanced production of TNF-α, IL-6, and IL-1β [53]. Increasing evidence demonstrated that inflammatory cytokines directly influence the levels of neurotransmitters in the nervous system. In particular, TNF-α accelerated the catabolism of precursors as tryptophan with a reduction of serotonin and an increase in glutamate, inhibiting the glutamate transporters. Moreover, patients affected by multi-organ inflammatory disease and long-term inflammation are at high risk of anxiety and depression, mostly in earlier stages [54-56]. Indeed, data derived from meta-analyses revealed the increase of pro-inflammatory biomarkers in mental illness. These findings are confirmed by neuroimaging studies that revealed how peripheral cytokines affect brain health, changing neurotransmitters' production and their release in several neural circuits [57-59]. In addition, the above-mentioned results confirm the idea that psychiatric disorders can also be considered inflammatory diseases, and their treatment with anti-inflammatory drugs can be beneficial [60-62]. Furthermore, a very recent study on inflammatory bowel diseases (IBD) indicates that the inflammatory process causes the gut vascular barrier to become more permeable, resulting in the spread of inflammation beyond the intestine. On the other hand, the vascular barrier in the choroid plexus becomes less permeable in response to intestinal inflammation due to bacteria-derived lipopolysaccharide. This reaction protects the brain from inflammation but also potentially damages the communication between organs, impairing some brain functions. By using a choroid plexus model of genetically driven closure in endothelial cells, the authors observed a deficit in short-term memory and anxiety-like behavior, suggesting that choroid plexus closure may correlate with mental deficits as consequences of a deregulated gut-brain vascular axis [63]. In addition, in neurodegenerative pathologies such as Alzheimer's and Parkinson's disease is evident the CSLGI role. Indeed, a high level of TNF-α is related to cognitive decline and amyloid plaques in the brain [56]. Recently, it has been demonstrated that systemic inflammation and consequent microglia overactivation have an essential role in the neurotoxicity process, inducing progressive neurodegeneration [64, 65].

2.3. CSLGI and Cancer

Finally, another condition characterized by an inflammatory environment is cancer. Epidemiological studies have revealed that cancer incidence is higher in high-income countries compared to low-income countries due to environmental and lifestyle changes [64].

From the first hypothesis of the interplay between cancer and inflammation, described by Rudolf Virchow in 1863, several pieces of work have focused their attention on this topic [66].

It is clear that CSLGI can contribute in all carcinogenesis phases to the onset, progression, and metastatic spread [67]. As previously reported, during CSLGI, an enormous ROS quantity is produced. ROS can interact with cells inducing DNA mutations and damaging proteins and lipids, causing their dysfunction [68-70]. These negative effects are the first step versus tumor development and can generally be counteracted by the antioxidant system and other host defensive strategies [71]. If these defensive pathways are inadequate, cancer initiation and progression can sometimes occur with metastatic colonization [72]. In addition, pro-inflammatory cytokines of CSLGI are the main actors in tumor development through multiple mechanisms. Some cytokines that have a role in tissue repair can elicit cancer survival, implantation, and progression [73]. Indeed, cytokines could have a double role in carcinogenesis. High acute production can have anti-cancer activity, while a low-prolonged release, as seen in the CSLGI context, can have a pro-cancerogenic effect [66].

2.4. The Interplay Between Chronic Systemic Low-Grade Inflammation and Gut Microbiota as an Emerging Element of Exacerbation in COVID-19 Infection

The new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of the COVID-19 pandemic, which, as of October 2021, has infected more than 250,000,000 million people worldwide and caused 5,000,000 deaths [74]. The disease is characterized by several manifestations, including fever, dry cough, rhinorrhea, headache, dyspnoea, myalgias, nausea/vomiting or diarrhea, weakness, anosmia, and ageusia. Complications are pneumonia, acute liver, cardiac or kidney injury, and prothrombotic coagulopathy resulting in venous and arterial thromboembolic events. In hospitalized patients, inflammatory serum changes such as elevated serum C-reactive protein, erythrocyte sedimentation rate, ferritin, TNF-α, IL-1, and IL-6 are observed [75].

It is estimated that around 60% to 90% of hospitalized people have one or more comorbidities (especially hypertension and diabetes mellitus), increasing morbidity and mortality [76]. The risk of developing severe

disease manifestations, including death, is increased in senescent and obese patients and those with cardiovascular disease, cancer, or chronic obstructive pulmonary disease.

A chronic increase of inflammatory cytokines like IL-6, TNF-α, and IL-1-β, has been observed in all high-risk categories for developing severe COVID-19. In high-risk patients with CSLGI, SARS-CoV-2 infection will elicit a cellular immune response mediated mainly by Th-1, Th-17, and proinflammatory macrophages [77], so dysregulated immune responses could potentially drive the COVID-19 hallmark syndromes such as acute respiratory distress syndrome (ARDS), cytokine release syndrome, and lymphopenia. In a recent article, a bibliographic search was carried out on 124 articles to assess the implications of low-grade inflammation in SARS-CoV-2 immunopathology [78]. The result of this study indicates that the mechanisms involved in acute inflammation on SARS-CoV-2 infection overlap with the patient's pre-existing pro-inflammatory tone, causing immune system dysfunction. SARS-CoV-2 infection amplifies already-existing alterations, triggering failures in the immune system's control processes. The resulting hypercytokinemia (cytokine storm) provides an uncontrolled systemic inflammatory response marked by high serum levels of inflammatory biomarkers with decompensation of underlying diseases. Interestingly, in asthma, chronic eosinophilic inflammation protects against infection by producing a reduced interferon-mediated response and a reduced number of ACE2 receptors [78]. In general, the CSLGI, typical of advanced age and chronic diseases (but not in bronchial asthma), seems to produce a pro-inflammatory state that triggers a dysregulated immune response, favoring the development of severe forms of COVID-19 and increasing lethality.

Moreover, infiltrating pro-inflammatory macrophages in SARS-CoV-2 target tissues (lungs, brain, gut, and kidney) and lymphocytes also contribute to the cytokine storm that accompanies CSLGI in metabolic syndrome (MetS) patients [79]. It has been observed that the risk of respiratory failure for patients with IL-6 levels of ≥ 80 pg/ml was 22 times higher than for patients with lower IL-6 levels [80]. Even a "normal" pro-inflammatory response may increase cytokine levels further above those of the underlying CSLGI, hence substantially increasing the risk of developing life-threatening forms of COVID-19. In the case of SARS-Cov-2 infection, a "normal" anti-viral immune response combined with CSLGI may trigger deleterious effects. However, severe effects of COVID-19

in children and healthy adults without any apparent underlying CSLGI-inducing/high-risk conditions still remain unexplained.

Today, reducing the intensity of CSLGI in high-risk categories is a realistic goal for diabetics. A better effort to diagnose diabetes and hypertension can increase awareness about a higher risk of developing severe COVID-19. A recent prospective cohort study on newly diagnosed diabetics starting prescribed insulin therapy compared TNF-α and IL-6 levels pre-and post-insulin treatment [81]. Starting insulin therapy in undiagnosed diabetics markedly reduced CSLGI intensity. Moreover, a retrospective, multi-centered study done in 7,337 COVID-19 cases, among which 952 had pre-existing type 2 diabetes mellitus (T2DM), showed that the well-controlled blood glucose levels group had a significantly lower in-hospital death rate relative to the poorly controlled group [82].

In addition, all the available evidence indicates a complex interaction between CSLGI and the GM in COVID-19. Current results, such as the enteric microbiota dysbiosis [83, 84] and persistent detection of viral RNA in faecal samples [85, 86], suggest a significant role for the gastrointestinal (GIT) tract also in SARS-CoV-2 infected individuals. The SARS-CoV-2 virus infects and actively replicates in enterocytes [87, 88], indicating that SARS-CoV-2 may interact with the commensal bacteria in the GIT. Two different studies found that COVID-19 patients with chronic dysbiosis had a rise in opportunistic microorganisms in their enteric system [83, 84]. However, although recent data showed a link between opportunistic infections and the GM, the fine nature of opportunistic pathogen enrichment and pathogenicity remained unknown. When the host immune system is compromised, these pathogens may play a role in secondary bacterial infection [83]. Analogously, COVID-19 patients showed a microbial dysbiosis with an excess of opportunistic infections [83-91]. Moreover, even though the mechanism of GM alteration underlying severe diseases is unclear, it has been found to be a predisposing factor for pro-inflammatory settings [92]. A recent cohort study investigated how the GM of COVID-19 patients links to disease severity and is associated with increased inflammatory markers [93]. When the microbiota structure of hospitalized COVID-19 patients was compared to that of non-COVID-19 subjects, *Bacteroidetes* were found to be more numerous in positive patients, whereas *Actinobacteria* were found to be more abundant in non-COVID-19 subjects. The GM of COVID-19 patients was predominantly enriched with *Ruminococcus torques, Ruminococcus gnavus*, and *Bacteroides dorei*
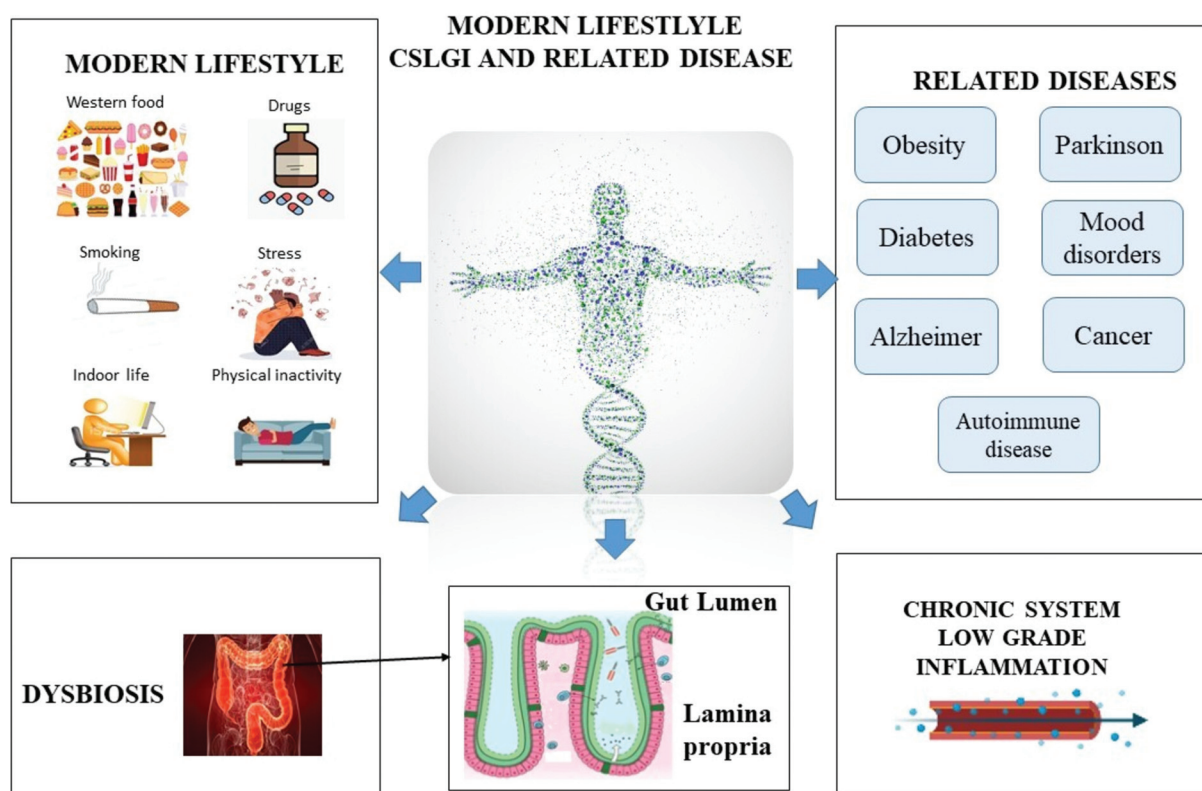
Fig. (2). The link between modern lifestyle and CSLGI with related diseases through the microbiome dysbiosis. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

and deficient with *Bacteroides adolescentis, Faecalibacterium prausnitzii,* and *Eubacterium rectale* [93]. In addition, in the same study, the enteric microbiome dysbiosis remained after SARS-CoV-2 clearance, which might be a cause of the development of chronic symptoms or multisystem inflammatory syndromes reported in certain patients after the virus was cleared (Long COVID-19) [93].

In general, an altered microbiome promotes the activation of the inflammatory cascade and of the innate and adaptive immune response (IR) [94, 95]. Activated IR means increased secretion of chemokines and especially cytokines (*e.g.*, TNF-α, IFN-α, IFN-γ, IL-6, IL-1β, and IL-12) favouring a critical hyper inflammation status and a life-threatening outcome [96]. On COVID-19, the IR can be influenced by the GM and *vice versa*, involving also intestinal microbial metabolites, such as endotoxins damaging the lung tissue. As a result, an altered microbiota promotes the production of pro-inflammatory cytokines and the presence of opportunistic microbial species, both of which are known to exacerbate the SARS-CoV-2 infection [97, 98]. Individual susceptibility to COVID-19 is likely to be influenced by the pre-existing host-microbiome-inflammation axis that changes after SARS-CoV-2 infection, as

shown in Fig. (**2**) [99]. In fact, COVID-19 replication triggers the development of a severe acute IR with an increasing gut permeability that brings to the activation of pro-inflammatory bacteria, thus increasing the inflammatory response [100, 101]. This process can result in a leaky gut, allowing microbial pathogens and metabolites to enter the bloodstream. Identifying a putative link between intestinal microflora, CSLGI and COVID-19 might lead to the discovery of microbial species implicated in the pathogenesis and/or microbial biomarkers for disease severity, which could be used as a predictor of disease progression. Furthermore, early GM manipulation (*e.g.*, by symbiotics, probiotics, fermented foods, and fecal transplant) might be helpful in terms of prevention and treatments.

Additionally, current and emerging infection-correlated issues are the long-COVID and chronic COVID syndromes [102]. Indeed, COVID-19 has had an unprecedented impact thus far, and long-term symptoms could have much more serious consequences [103]. Recent data suggest that in many COVID-19 patients, a variety of symptoms can persist after the acute infection has cleared, a condition known as persistent or long-COVID. The National Institute for Health and Care Excellence (NICE) defines long-COVID as symp-

toms that persist or increase from four to twelve weeks after acute COVID-19 infection and are not due to another illness. On the other hand, the National Institutes of Health (NIH) uses the CDC's (Centers for Disease Control and Prevention) definition of long-COVID, which classifies the illness as lasting more than four weeks following infection [104]. The structure and function of numerous organs are involved and impaired in people with extended COVID. Long-term symptoms after COVID-19 have been reported across the disease severity spectrum; in fact, patients with mild acute symptoms also develop long-COVID symptoms [104], and studies show that the prevalence of long-COVID symptoms differs little between hospitalized and non-hospitalized patients. Asthenia, myalgia, dyspnea, heart anomalies, cognitive decline, sleep disturbances, post-traumatic stress disorder symptoms, concentration issues, and headache are the most common symptoms [105]. The COVID-19 prognosis and its sequelae may depend on the CSLGI level and are worse in aged people. Indeed, as a number of causes have been proposed to explain the persistence of long-term COVID symptoms (from the presence of persistent low viral load and reinfection to changes in immune cell activity and tissue damage caused by the initial infection), an interesting report has explored insights gained in recent decades from several large-scale studies of chronic fatigue syndrome, fibromyalgia, depression and other mental health disorders that show immune abnormalities [106-108]. Several possible pathways could be relevant to the persistence of long-COVID, like the involvement of glial cells and the permeability of the blood-brain barrier. Some of the long-COVID symptoms, depression, and other mental health problems, are related to CSLGI. As such, current treatment strategies for depressed patients include anti-inflammatory drugs. Finally, psychosocial factors are also very important in regulating immune activation. It is clear that strategies tackling a patient's level of stress with increased social support, physical exercise, and an adjusted diet could also be useful in managing long-term symptoms related to COVID-19 [108].

2.5. CSLGI and Ageing

Population ageing in high-income countries is another factor involved in CSLGI. Indeed, ageing is a natural and unavoidable process accompanied by a low-grade inflammation background, named "inflammaging" [109]. The mechanisms underpinning the "inflammaging" are probably linked to numerous age-associated changes, particularly related to immunosenescence, cell debris, procoagulant factors, dysbiosis, etc

[110]. Data derived from a recent study highlight the existence of inflammation-senescence-related genes that have an age-related expression shared between tissues and different animal species [111]. Related-lifestyle data analysis showed that the ageing process could be accelerated by risk factors (such as smoking, sedentary lifestyle, and diet), underlining the role of lifestyle in the inflammaging [39].

## 3. MODERN LIFESTYLE, GUT MICROBIOTA, AND CSLGI: A PATHOLOGIC TRIAD

3.1. The "Changing Modern Gut Microbiota" and the "Dismetabolomic Gut"

Since the industrial revolution in the 18th century, society has experienced several changes in the lifestyle and habits of people [112]. These shifts happened too speedily in the human evolutionary scenario, leaving humans with no time to fully adapt. This hypothesis was confirmed by the spread of chronic diseases in modern societies, in contrast to other populations living in non-industrialized contexts [108]. How GM can modulate the health effects of modern lifestyle is currently a debate object. It is known that people living in industrialized countries have significant differences in GM composition compared to rural populations. Specifically, there is a conspicuous loss of microbial diversity and richness in the intestinal content of high-income societies [113]. In addition, a lower gut microbiota diversity is associated with inflammatory biomarkers (high level of CRP and white cells count). A recent study finds a depletion of GM richness due to antibiotic use in five clusters of chronic diseases [114]. Notably, all modern chronic pathologies display some kind of gut dysbiosis (Fig. **3**).

Conversely, high microbiome biodiversity appears essential to good health status. In fact, GM richness can contribute to the host's well-being through several pathways, as a prompt and better adaptation to the external environment [115], involving a plethora of metabolites produced by the different microbial strains [116].

The production of GM metabolites (amino acids, vitamins, polyphenols, polyamines, neurotransmitters, and short-chain fatty acids) is influenced by three elements: the availability of primary sources (primary form diet), the bacterial composition, and host-related factors [117].

These products (identified with the term "metabolome") exert their action not only in the local environment but also in blood circulation, directly or indirectly acting on all human cells through genetic or
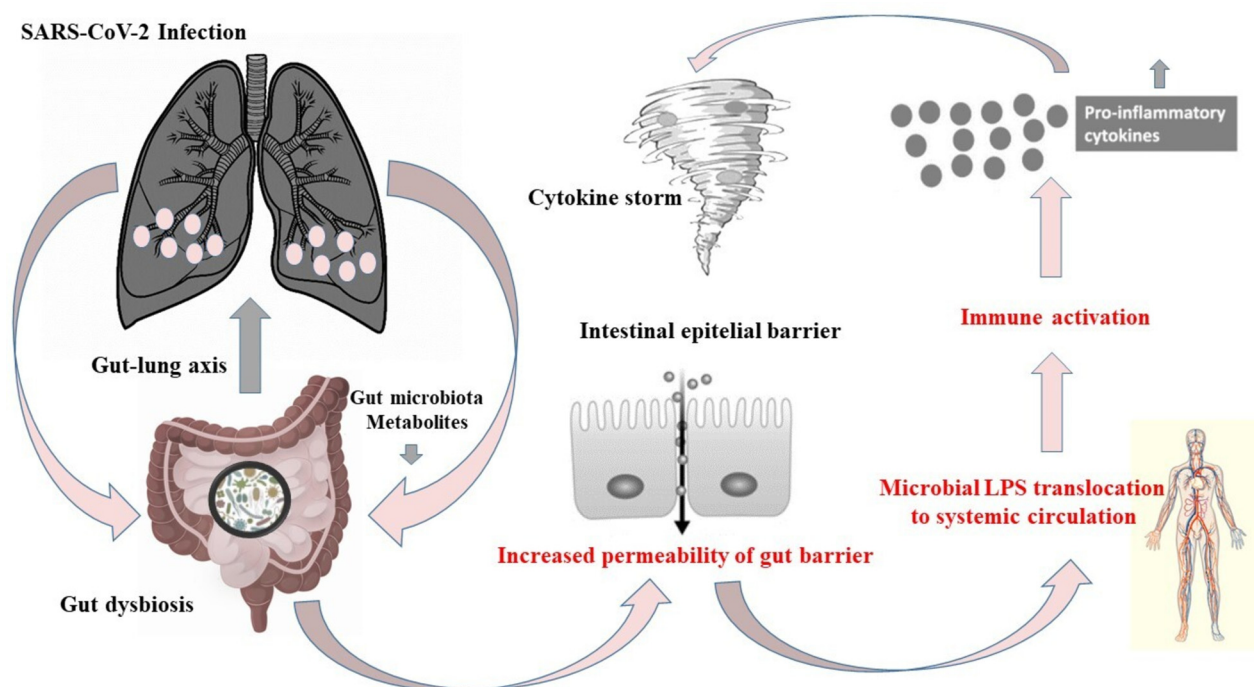
Fig. (3). The perturbation of the gut microbiota-inflammation axis leading to severe COVID-19 by a cytokine storm. This figure is adapted from the paper : Russo, E., Curini L., Fabbrizzi, A., Amedei, A. (2022). SARS-CoV-2 and Microbiota. In: Gupta, G., Oliver, B.G., Dua, K., Singh, A., MacLoughlin, R. (eds) Microbiome in Inflammatory Lung Diseases. Springer, Singapore. DOI: https://doi.org/10.1007/978-981-16-8957-4_14. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

epigenetic mechanisms [118, 119]. There are more studies focusing on gut metabolites pathways, but the investigation of the complex interaction between these signals and the host genome is still in infancy [117].

In the CSLGI scenario, the investigation of metabolome represents a future and attractive challenge to discover potential new biomarkers in order to predict the risk or the progression of inflammatory diseases and to define the relationship between lifestyle and gut immune response.

If some gut metabolites can have positive effects on the human host and can be protective against inflammation (such as SCFA, some vitamins, and amino acids), some others can have detrimental effects (urea, indoxyl sulfate (IS), and p-cresyl sulfate (PCS), trimethylamine N-oxide (TMAO)) [120]. In addition, some of these microbiota-derived substances regulate the gut epithelial barrier [121], which represents the interface between the content of the gut lumen and the inner body.

Its integrity is preserved by different signals that act on receptors' sites, principally on the surface of tight junctions, adherens junctions, and desmosomes [122]. A deficit or an excess of microbiota-derived metabolites leads to barrier dysfunction, hence causing an increase in gut permeability.

The lipopolysaccharide-LPS (the most representative PAMPs - Pathogen-Associated Molecular Patterns), a component of gram-negative gut bacteria, is normally confined in the gut lumen but in the presence of intestinal barrier damage, it can reach the bloodstream eliciting an inflammatory response at distant sites [123]. So, in this situation, the GM can be an additional direct source of CSLGI through the passage of the LPS on peripheral blood [124].

From this perspective, we can speculate that, in addition to GM shift, changes in metabolome secretion (a "dismetabolomic gut") due to lifestyle can have serious consequences for the host functionalities.

3.2. The Influence of Western Dietary Habits on Gut and CSLGI

A cornerstone of a healthy lifestyle is represented by nutrition. According to WHO, a healthy diet is the most effective approach for the prevention of chronic diseases [125]. Multiple studies have emphasized that dietary patterns are the major contributing factors in GM shaping, and dietary changes can have profound ef-

fects on health and protection against several diseases [126-128]. However, modern civilization has promoted a shift in dietary habits. Notably, the "Western diet" is marked by high total calories, saturated fats, salt, refined sugars, alcohol, low fibers, and omega 3 intake. In addition, a large number of consumed foods are not organic but preserved and/or processed, added with chemical agents. Recent evidence highlights that this nutrition pattern is pro-inflammatory and has deleterious consequences for the human body, increasing the risk of chronic illness [129]. Current reports suggest that Western diets promote a fertility decrease, inflammatory bowel diseases, metabolic syndrome, and cancer through various mechanisms (such as intestinal permeability, endotoxiemia, dysregulate IR, and inflammation) [130-133].

Finally, alterations in the microbiota composition and function seem to be the link between the modern diet and its detrimental effect on human health [134, 135].

3.2.1. The High-fat Diet

The fats introduced by the diet are divided into two main groups: saturated and unsaturated lipids.

Notably, the type and proportion of dietary lipids are more important than the total amount.

A high-fat diet (HFD), especially rich in saturated fatty acids (SFAs), impacts gastric and GM and induces crucial dysbiotic changes in the gut ecosystem [136], promoting the growth of noxious bacteria such as *Escherichia*, *Shigella*, *Klebsiella* Alistipes spp*., all gram-negative bacteria, releasing high LPS amount [137]. The increase of LPS content in the gut lumen is responsible for the massive activation of the Toll-like receptor 4 (TLR4) pathway, a stronger component of primary inflammatory response. Hence, the subsequent production of inflammatory cytokines exerts a toxic action on the small intestine and colon, leading to atrophy, impaired mucus production, and reduction of tight junction proteins. Indeed, a high amount of dietary lipids induced the synthesis and secretion of bile acids, increasing the epithelial gut permeability [138]. These collections of events finally lead to endotoxemia and contribute to CSLGI.

Another class of dietary lipids is unsaturated fatty acids. Between polyunsaturated fatty acids (PUFA), omega 3 and omega 6 are precursors of eicosanoids, a family of lipids with biologic effects on inflammation. While omega 3 displays a protective effect on endotoxemia and systemic inflammation with a more pronounced production of anti-inflammatory cytokines,

omega 6 seems to show an opposite action [139].

Likewise, an excessive level of omega 6 PUFA intake has adverse effects, unbalancing the omega-6/omega-3 ratio [140]. A high omega 6/omega 3 ratio, typically in the western diet, is associated with dyslipidemia, obesity, mood disorders, and many other chronic diseases [140-142].

The level of FFAs (free fatty acids) not only depends on the diet but is also influenced by GM composition. Recent evidence suggests that GM may have a role in the metabolism of PUFA.

PUFA are transformed into fatty acids (FAs) by the microbiota, such as Linoleic Acid (omega-6 lipid)-derived metabolites and α-Linoleic Acid (omega-3 lipid)-derived metabolites [143]. A specific microbiota profile, abundant in some *Lactobacillus* strains (*i.e. Lactobacillus salivarius Lactobacillus gasseri* and *Lactobacillus plantarum*), is able to suppress the inflammatory response, converting the excess of Linoleic Acid (an omega-6 fat) into 10-hydroxy-cis-12-octadecenoic acid (HYA) [143, 144]. HYA is a pleiotropic molecule promoting the intestinal epithelial barrier, which inhibits intestinal inflammation and *Helicobacter* infection and has an interesting neuroprotective effect through inhibition of microglial cells in the brain [144-146].

In conclusion, in an HFD, LA-derived metabolites are predominant compared with those associated with αLA, predisposing to obesity, but in the presence of a favourable gut signature, these effects are attenuated by the action of specific strains and HYA-producers. Another enlightening example of the role of gut lipid metabolism is that the total serum FFAs are negatively correlated to the abundance of *Akkermansia* species and some *Lactobacillus* strains [147].

For a specific strain, the *Lactobacillus plantarum* Q180, a recent study has demonstrated its involvement in reducing the dietary lipidic absorption through the release of a peptide that has a direct pancreatic lipase inhibitory effect [148].

3.2.2. Food Additives

Another distinctive feature of modern nutrition is the presence of a large number of additives used to preserve, colour, or sweeten the food.

The consumption of artificial non-nutrient sweeteners (NNS), used as an alternative to sugar, is increasing in the eating pattern with the introduction of the so--called "dietetic foods" to reduce the intake of the total amount of simple sugars. Despite the available literature linking the NNS consumption to metabolic syn-

drome, the fine mechanism is not yet fully elucidated, and the evidence is not conclusive due to the limits of clinical studies and controversial results [149, 150]. However, regular NNS use can modify the GM composition [151]. Based on animal studies, particularly chronic saccharine consumption seems to produce an enrichment of some pathogenic bacteria belonging to *Bacteroides* spp. and *Clostridiales* phylum producing proinflammatory bacterial metabolites, such as LPS, which causes liver inflammation [152]. Other sweeteners cause a microbiota shift related to glucose impairment [152, 153]. In addition, emulsifiers are agents used as thickeners in processed foods such as dairy products, soups, desserts, and ice creams [154]. The researchers focused on carboxymethylcellulose, polysorbate 80, and glycerol monolaurate, demonstrating that these substances can promote massive bacterial proinflammatory overgrowth, the release of LPS and flagellin in the gut, upregulation of the circulating levels of serum LPS, IL-1β, IL-6, and TNF-α, thus promoting CSLGI metabolic syndrome in genetic-predispose mice [155]. Surprisingly, in HFD, glycerol monolaurate attenuated the detrimental effect on lipids and metabolism. Furthermore, the Western diet is also rich in foodborne nanosized particles (1-100 nm) derived from food additives, food supplements, drugs, and packaging, representing a threat to human health thinking of the long-term exposure and their cumulative, synergistic effects [156]. However, the impact of these nanoparticles on GM remains elusive. The chronic exposure to these additives (such as titanium dioxide, iron oxides and hydroxides, silver, gold, and silicon dioxide) in rats induces an increase of inflammatory cytokines in the bloodstream, with serious injury to kidney and heart and also a neurotoxic, gastro-toxic, hepato-toxic effect, thus decreasing antioxidant enzymes activities and increasing oxidative stress and ROS production [157, 158]. In rodent models, nanoparticles elicit the release of gut inflammatory cytokines such as TNF-α, IL-12, IL-4, and IFN-γ. Relevant studies support the idea that they have a high impact on GM activity, composition, and production of microbial metabolites, inducing a selection of pathobionts and a depletion of beneficial bacteria as a result of their antimicrobic activity [156].

3.2.3. Excessive Salt Intake

Excessive salt intake is a key feature of the Western diet. WHO suggests that adults consume less than 5 g of salt per day while the average consumption is two times higher. The excess sodium comes principally from processed foods, while only a small amount comes from home-cooked meals [159]. A high salt diet (HSD) is associated with an elevated risk of hypertension and heart and renal diseases [160].

At the intestinal level, HSD increases *Firmicutes/ Bacteroidetes* ratio and *Lachnospiraceae* and *Ruminococcus* genera and decreases the abundance of *Akkermansia muciniphila*, *Bifidobacterium* (such as *B. longum and B. adolescentis),* and *Lactobacillus* (in particular, of the subtype *L. murinus*), which has a role in modulating the T cells differentiation, promoting an inflammatory environment with an elevation of activated T cells. Indeed, salt decreased butyrate production and increased TMAO, a specific gut-bacteria metabolite found in blood [161, 162]. TMAO is a product by GM from dietary amino acids choline, betaine, and carnitine. It is defined as a pro-atherogenic metabolite, and its accumulation in the blood is related to cardiometabolic diseases [163, 164].

3.2.4. Alcohol Abuse

Alcohol abuse is one of the most important risks in several diseases (cardiovascular, cancer, autoimmunity) [165-167], and chronic alcoholism is mainly associated with liver diseases and primary cirrhosis but also with consistent damage to gastric and intestinal mucosa [168]. Moreover, heavy alcohol consumers display a dysbiotic status with i) decrease of both *Bacteriodetes* and *Firmicutes* and increase of *Actinobacteria* and *Proteobacteria*, ii) increased intestinal permeability, gut inflammation, and translocation of bacterial products in the bloodstream, iii) endotoxemia and low-grade inflammation [169-172].

The alcohol detoxification process in human beings is mediated by liver and GM enzymes. Many bacteria show alcohol dehydrogenase activity that transforms ethanol into a toxic and carcinogenic compound called acetaldehyde, which can be converted into acetate by another enzyme, the aldehyde dehydrogenase [173]. The acetaldehyde level in the gut and its negative effects may depend on the balance between these two mentioned enzymes that can reflect the bacterial gut metabolism. Surprisingly, the alcohol intake exhibits a dual opposite effect in a dose-dependent manner on the health of consumers. A high dose exacerbates a low-grade inflammation; on the other hand, a low dose has a protective role in reducing the inflammatory biomarkers (specifically red wine) [174]. The reason for this phenomenon, probably microbiota-related, is not completely known and requires further investigation. This dual-action can be explained since, at a low dose, alcohol can stimulate a hormesis response. Moreover, alcoholic beverages have antioxidant proprieties due to large flavonoid content, which are invalidated by the toxic alcoholic metabolites [175].

3.2.5. Low Fiber Intake

Data from epidemiological studies report that a low fiber intake represents a great risk factor for the development of stroke, coronary disease, hypertension, diabetes, cancer, and obesity, and conversely, a high fiber intake is protective against chronic diseases [176, 177]. The European guidelines recommended a daily intake of 25-35 gr for adults, but national dietary statistics demonstrated that most people do not reach the recommended intake [178]. Dietary fibers are a nutrient source for gut anaerobic bacteria; indeed, in the case of fiber deprivation, they use the host-secreted mucus glycoproteins as an alternative source, leading to damage of the mucus layer in the intestinal barrier, exacerbating a colitis state [179]. The main product of dietary fibers fermentation by GM is represented by SCFAs as acetate, propionate, and butyrate, which are also the main energy source of intestinal epithelial cells, contributing to intestinal homeostasis and gut barrier function [180]. Despite their complex role currently under investigation, SCFAs represent metabolic signals involved in several physiological pathways such as lipogenesis, gluconeogenesis, appetite control, energy intake, systemic bone mass, skeletal muscle metabolism and function, immune regulation, and microbiota-gut-brain crosstalk [181-184]. In addition, new evidence shows that a high soluble fibers diet mitigates the noxious influence on the health due to excessive red meat intake [185]. Furthermore, a high soluble fiber diet (derived from wheat bran) considerably decreases the metabolism of TMAO by inducing the growth of beneficial gut bacteria and the production of SCFAs [185]. A recent scientific report highlights that specific SCFAs profiles are characteristic of different gut diseases, and this points out the role of the SCFAs signature in health and disease. SCFAs are key regulators in the inflammatory process through the modulation of cytokine production and T cells' proliferation/differentiation, and their administration shows a therapeutic effect in gut inflammatory disease; however, they can also act as pro-inflammatory in some cases depending on phenotypes [186-188]. The growth of SCFAs- producers is stimulated in different ways. In particular, one of these is through the diet, with the intake of dietary fibers, such as inulin and galactomannan [189]. Therefore, the specific role of different dietary fibers on GM is still under investigation, and the effect of dietary intervention requires accurate microbiome analysis of follow-up [190]. However, it appears clear that a high fiber diet can protect against a systemic chronic low-grade inflammation, enhancing the expression of genes coding anti-inflammatory cytokines such as IL-10 and IL-22 and downregulating inflammatory interleukins such as IL- 8 through a microbiota-dependent route [191, 192].

3.3. Indoor Living and Working

Modern people's spending most of their day in closed environments has a wide range of consequences: inhalation of indoor air rich in pollutants and particulates, exposure to artificial light with a breakdown of circadian rhythms and reduction of sun exposure, with decreasing of D vitamin production [193, 194]. The closed environment exposes the human body to various contaminants present in the air and in the dust. Indoor semi-volatile organic compounds (SVOCs), for example, include a long list of chemicals (phthalates, Polychlorinated biphenyls (PCBs), Polycyclic aromatic hydrocarbons (PAHs), Polyfluorinated alkyl substances (PFASs), parabens, organochlorine pesticides, pyrethroids, and others) used as plasticizers, flame retardant products, repellents, and released by building materials and consumer products [195]. Regarding the effect on GM, in a recent study, Gardner *et al.* examined the effect of SVOCs on children. Notably, blood, urine, and fecal samples were tested for 44 SVOCs, and 29 substances were present in >95% of the analysis. In addition, the PFOS presence was associated with a decline in several bacterial and fungi taxa, and halogenated SVOCs increased the abundance of dehalogenating bacteria, demonstrating a pressure of SVOCs on the microbiome [196].

The toxicity of phthalate seems to depend on dose and time, but it can be improved by a dysbiotic state [197]. In general, the VOC toxicity can be mediated by the microbiota, and the bacteria play a fundamental role in detoxification processes. These substances exacerbate gut inflammation, impair the gut barrier, increase LPS in blood, and release cytokines, thus contributing to CSLGI [198]. In addition, the GM can activate some of these compounds, such as polycyclic aromatic hydrocarbons in estrogenic metabolites, with an effect on development and fertility [199].

Another trait of modern life is exposure to artificial light and light pollution that can alter circadian rhythm, suppress melatonin secretion, and modify intestinal microbiota [200]. The constant light exposure in HFD rats induced changes at the colonic level, increasing *Christensenella* and *Dehalobacterium genus* and decreasing *Butyricicoccus, Clostridium, Turicibacter* genus, and class *Bacilli*. Besides, the animals showed a reduction in butyrate acid and consequently gut barrier dysfunction with LPS translocation and endotoxemia. These findings can exacerbate a CSLGI condition and pose a greater risk for cancer [201, 202].

Today, in our daily lives, we are constantly exposed to blue light emitted by different sources of illumination and electronic devices (TV, smartphone, PC). However, assessing the human risk derived from this exposure is very difficult due to the lack of long-term data [203]. Nevertheless, we can speculate that a modified melatonin secretion alters circadian phases, inducing pathological consequences for various motives. The first reason is that melatonin is a hormone produced by the pineal gland at night, acting in various organs of the body. It is implicated in fertility, immunity, and neurological functions [204]. In addition, melatonin is also a powerful antioxidant, immunomodulator, and an up regulator of Sirtuin-1 genes [205]. There is increasing evidence of melatonin use in a plethora of pathologies related to aging and inflammation [206]. The oral melatonin administration counteracts dysbiosis in HFD mice improving the acetic acid production and reducing lipid accumulation; in addition, it decreases the *Firmicutes*-to-*Bacteroidetes* ratio and increases the *Akkermansia muciniphyla* levels, preventing the onset of obesity [207, 208]. The role of melatonin on GM and CSLGI is supported by the evidence that a sleep deprivation causes dysbiosis-related intestinal damage and barrier dysfunction, through the activation of NF-κB pathway by oxidative stress [209]. Another undesirable consequence of life in indoor environment is a low blood level of vitamin D, a prohormone mostly produced from the 7-dehydrocholesterol in the skin through the UVB exposure or introduced with the diet. It undergoes biotransformation reactions in the liver and kidneys to be transformed into the active form (1α, 25-dihydroxyvitamin D3), exerting endocrine, autocrine, and paracrine effects. It has long been known that vitamin D is crucial in calcium-phosphate homeostasis and bones development and the turnover and this deficit is related to rickets and osteomalacia. New emerging roles are now rising as regulators of apoptosis mechanisms, cells differentiation, and IR and nervous system control [210, 211].

in vitro and *in vivo* studies have revealed an immunoregulatory action of vitamin D. The vitamin D receptors (VDRs) are present in different cells, such as adipose and immune cells, inhibiting the release of inflammatory cytokines such as TNF-alfa, IL-6, and IL 8 and eliciting the secretion of IL-10 by dendric cells. However, the clinical supplementation of vitamin D not always induces the desired effect on inflammation [212]. A deficiency of vitamin D is reported in various inflammatory conditions such as autoimmunity, cancer, and IBD [213]. Finally, vitamin D activates genes essential for gut homeostasis as those involved in the gut epithelial barrier functions, secretion of intestinal mucus, and immune balance [214]. In addition, a VDRs downregulation is observed in IBD and can be related to impaired integrity of gut barrier and to a reduction of antimicrobial protection. Furthermore, the lack of an active form of vitamin D or downregulation of VDRs is linked to a decrease in gut *Lactobacillus* and an increase in *Proteobacteria*. In this scenario, it is documented that an optimal level of vitamin D ensures an appropriate VDRs function with a beneficial effect on microbiota and on the related CSLGI [215].

3.4. Stress

Stress refers to a condition characterized by an excess of environmental pressure that overcomes the capacity of host adaptation [216]. Psychological stressors come from a set of elements related to work as well as social and emotional contexts. During the COVID-19 pandemic, we have an emerging stressor in our lives due to the limitations of freedom resulting from lockdowns and quarantine periods [217, 218]. Cross-sectional studies on mental health have highlighted that there was a positive correlation between depressive disorders and lockdowns [219, 220]. Interesting research compared inflammatory markers in blood samples of 241 subjects before and during the lockdown, evidencing an elevation in CRP and platelet counts, with an emerging CSLGI that the authors linked to stressors such as isolation, chronic stress, and physical inactivity [221].

The management of these stressors is a milestone in well-being, and a reduction of the resilience process increases the susceptibility not only to psychological disorders (anxiety, depression, insomnia) but also to inflammatory and degenerative diseases [222, 223].

In recent years, the relationship between chronic stress, GM, and CSLGI has been clear. The impact of stressful situations on bacterial composition has been studied in several models, but the clinical evidence is limited [224]. Chronic stress promoted colitis in DSS-exposed mice through changes in intestinal inflammatory species, such as *Helicobacter, Peptostreptococcaceae, Streptococcus*, and *E. faecalis* and *Akkermansia*, a mucolytic bacterium that contributes to degrading mucus layer with barrier dysfunction and inflammation development [225].

In support of this theory, a fecal transplant from animal donors, affected by stress, exacerbates anxiety and depression in recipients causing neuroinflammation in the hippocampus [226]. Recent evidence suggests the existence of comorbidity between stress, gut dysbiosis, hyperpermeability, endotoxemia, and neurological diseases such as Parkinson's and Alzheimer's [227]. It is

established that there is a complex network of signals that cooperate in the gut-brain axis to mediate the effects of psychological stress. These signals are also involved in the dysregulation of immunity, CSLGI, and related diseases [228].

3.5. Physical Inactivity

Regular physical activity represents a primary defense against chronic diseases and premature mortality. Despite various studies reporting an association between inactivity and low-grade systemic inflammation and an inverse correlation between sport and inflammatory markers, some trials exploring the effect of training on CRP levels display contradictory results [229-231]. What appears clear is that during exercise, the balanced release of specific cytokines named "myokines" (IL-6, irisin, IGF-1, FGF-2, IL-10, IL-1ra) are responsible not only for the muscular function, growth, and strength but also for the systemic anti-inflammatory action [232, 233].

Growing evidence in preclinical studies indicates that exercise-induced structural and functional changes in GM increase the biodiversity of a community, have a good beneficial bacterial load, and reverse gut dysbiosis [234, 235]. An increase of SCFAs-producers such as *Faecalibacterium praunizii, Akkermansia muciniphila,* and *Roseburia hominis* was observed when comparing trained women with sedentary, showing that these anti-inflammatory species and their metabolites exert a beneficial effect on the gut barrier and reduce the activation of the immune system [236]. However, if a moderate exercise can reduce chronic systemic low-grade inflammation, conversely, a strenuous workout can be deleterious inducing gut hyperpermeability, immunodepression, and inflammation through excessive ROS production [237, 238].

3.6. Cigarette Smoking

Cigarette smoking is associated with the incidence of many diseases, such as cardiovascular, respiratory, intestinal, and autoimmune pathologies, as well as the augmented risk of various cancer types [239]. At the same time, tobacco addiction seems to be protective against ulcerative colitis and Parkinson's disease [240].

Focusing on the relationship between smoke and low-grade inflammation, it has been proven that smokers have more elevated inflammatory markers (blood leukocytes, platelets, CRP, and fibrinogen) compared to non-smokers [241, 242]. The studies on the effects of smoking habits on GM communities are scarce and not conclusive. A very recent pilot study in a human co-

hort has explored the action of smoke on bacterial composition with a higher relative abundance of *Prevotella* and lower relative abundance of *Bacteroides* [243]. In agreement with these data, a previous analysis of smokers' GM affected by Crohn's disease shows a higher *Bacteroides-Prevotella* ratio and a low count of *F. prausnitzii* [244]. Interestingly, smoking cessation induces only a minor change in microbiota after 12 weeks in ex-smokers, while other research shows a shift after 9 weeks with an increase of *Firmicutes* and *Actinobacteria* and a decrease in *Bacteroidetes* and *Proteobacteria* [245]. The reduction of anti-inflammatory bacteria such as *F. prausnitzii* and *Akkermansia muciniphila* with a higher abundance of pro-inflammatory bacteria such as *Ruminococcus gnavus* and *Bacteroides vulgatus,* as revealed by a metagenomic sequencing, can explain the systemic pro-inflammatory action of smoke [246].

3.7. Drugs

In the last decades, GM has been recognized as an essential actor of therapeutic drug metabolism and, consequently, an essential modulator of their efficacy and toxicity [247]. New science has appeared in the microbiome scenario, the "pharmacomicrobiomics," which studies the interaction between drugs and microbes [248]. Moreover, several drugs have a deep impact on gut composition with a profound change in the abundance of the single microbial taxon. A recent metagenomics cohort-based study revealed that the drugs such as antibiotics, metformin, proton-pump inhibitors, and laxatives could induce important changes in microbiota profile. However, the interplay between drugs and GM is poorly understood. In addition, the effect of drugs on low-grade inflammation through reshaping the microbiota profile are unclear [249]. Among all the drugs, we will describe only some of them which are suspected of playing a role in CSLGI. Historically, the most investigated field is antibiotic treatment. The antibiotic courses alter the equilibrium and reduce the microbiota diversity for several months or, in some cases, years [250]. According to scientific evidence, antibiotics can have a contradictory effect on low-grade inflammation. First of all, some antibiotics not only have an antimicrobial but also an intrinsic anti-inflammatory action (*i.e.*, tetracyclines) [251]. Secondly, they reduce a load of some pathogenic bacteria, alleviating the gut and related systemic inflammation [252]. Hence, in a dysbiotic state with predominant species, an antibiotic cycle can be beneficial to the host, shifting to a eubiosis condition [253]. Finally, because the interaction between antibiotics and the host physiology depends on several factors and also on individual GM

features, it is difficult to predict microbiome stability and resilience toward the treatment [254]. However, it is universally accepted that antibiotic intake, especially in early life, can alter the regular development of GM and immunity [255]. Moreover, increasing evidence indicates that "infant" microbiota educates the immune system and dysregulation of this training process induces long-term consequences with an altered immune and inflammatory response later in life [256].

Another drug class that shows a dualistic effect on CSLGI, probably mediated by GM, is represented by the nonsteroidal anti-inflammatory drugs (NSAIDs). The NSAIDs are used for a wide range of pathologies because of their anti-inflammatory, analgesic, and antipyretic properties that induce gastrointestinal, renal, hepatic, and cardiovascular side effects [257]. To date, no extensive review analysed their effect on CSLGI, but there is mounting evidence highlighting that the damage to gastrointestinal mucosa induced by NSAIDs can exacerbate inflammatory bowel disease-inducing CSLGI [258]. On the contrary, NSAIDs can be beneficial in some related low-grade inflammatory diseases like depression or cancer [259]. In other words, there are no conclusive data and the role of NSAIDs in CSLGI needs to be more deeply investigated.

Finally, the proton pump inhibitors (PPIs) are a group of drugs used globally to treat gastroesophageal reflux disease, gastritis, or gastric-duodenal ulcers. This class has been used for a long time and frequently without a medical control or diagnosis as they also exist in over-the-counter (OTC) formulation [260]. Based on the available literature, PPIs can have some side effects, especially increased risk of enteric infections, such as *Clostrium difficile* bacteria [261]. Deep analysis has revealed that PPI users have a modified microbiota with less diversity and richness and an elevated percentage of pathogenic bacteria compared to the non-users, superior to antibiotic users. Furthermore, several studies highlight an association between an increase in faecal calprotectin (FC), a marker for gut inflammation, and PPI therapy [262]. This fact can explain the side effect on the gut, especially in case of inappropriate use. Based on this data, the PPI can be a factor that can induce microbiota modifications to promote a CSLGI, especially in long therapies.

4. DISCUSSION

The rapid and wide changes in the modern urbanized society have an enormous impact on human health, with a growing burden of chronic diseases, disabilities, and premature deaths [108, 112, 113]. As previously reported, many of these chronic diseases show common pathogenetic aspects, especially in sharing a chronic systemic low-grade inflammation [15-17]. Moreover, it has recently emerged that COVID-19 and long-COVID prognosis may depend on CSLGI level, pointing out the crucial need to deepen the relation between modern habits and low-grade inflammation.

Additionally, compelling evidence supports the primary role of GM in host well-being, as its activity is not only confined to its local environment but to the entire organism [22]. As discussed in this review, a fascinating scenario is emerging, where the GM is a "trait d'union" between lifestyle - CSLGI and related pathologies. Indeed, the microbiota uses, metabolizes, detoxifies, and activates various xenobiotics. As an output, the intestinal microbiota sends out a myriad of signals implicated in the modulation of various metabolic pathways in host systems and organs [118, 119]. Each lifestyle factor discussed here is able to modulate the GM composition and its metabolism, leading to crucial consequences on individual health status. In particular, the modern lifestyle can elicit a shift in the microbiome composition and in the production of gut metabolites, with an overgrowth of an inflammatory microbial community [232] and an overload of noxious signals.

These signals promote a gut local inflammatory milieu, leading to gut epithelial barrier dysfunction and consequent LPS passage in the blood (endotoxemia). Microbial signals can also reach distal organs and exert an epigenetic regulation of inflammatory genes. Together, these mechanisms promote the CSLGI.

Conversely, the GM can modulate the detrimental effect of unhealthy lifestyles by its resilience, which depends on specific host factors (*e.g.*, genetics), and consequentially, its response to external changes is driven by individual microbiota signature.

The deleterious effects of the western diet can be counteracted by a eubiotic GM, which is rich in lactobacilli and is able to metabolize the excess lipids, thus preventing obesity. Moreover, excessive consumption of red meat and salt with an elevation of TMAO can be neutralized by a reduction of TMAO-bacteria producers with an administration of specific antibiotics [263].

Unravelling GM composition and the pathways of its metabolites will help explain the effect of a single lifestyle on CSLGI as well as evaluate GM resilience.

In the future, the design of new randomized clinical trials and the development of sophisticated and integrated "multi-omics" approaches for GM profiling will better define the intricate network of GM adaptations to modern lifestyle changes and its consequences in host physiopathology.

Moreover, as there is a mutual interplay between the microbiome and immune response, it is also important to deepen the study of an "anti-inflammatory" GM community and bacterial metabolome able to counteract the widespread pro-inflammatory environment, which is characteristic of the CSLGI condition [261].

In this context, the exploration of GM shaping appears critical to preventing and decreasing CSLGI, considering both consolidated and emerging approaches, such as the use of bacteriophage or engineered microorganisms. The use of selected probiotics, prebiotics, nutraceuticals, and gut metabolites, as well as a personalized diet or a faecal transplant, can replenish microbiota balance, induce a healthier gut metabolome production, ensure the gut barrier integrity, prevent endotoxemia, and finally inhibit CSLGI and its chronic related diseases [264].

The choice of the clinical approach (*i.e.*, the selection of the probiotics species) needs to be appropriated and not based on empiric methods, thus avoiding a worsening of the dysbiosis and correlated CSLGI.

CONCLUSION

In the future, a multi-integrated investigation on CSLGI-related diseases through a multi-omics approach, including microbiota analysis, and a deep lifestyle investigation with clinical tests on detrimental unhealthy environmental and dietetic markers, appears to be essential in order to identify optimal treatment in a vision of a personalized and precision medicine.

LIST OF ABBREVIATIONS

CSLGI	=	Chronic Systemic Low-Grade Inflammation
GM	=	Gut Microbiota
SCFA	=	Short Chain Fatty Acids
IR	=	Immune Response
CRP	=	C Reactive Protein
TNF-α	=	Tumor Necrosis Factor-Alpha
IL-6	=	Interleukin -6
PCS	=	P-Cresyl Sulfate
LPS	=	Lipopolysaccharide
TMAO	=	Trimethylamine N-Oxide
PCBs	=	Polychlorinated Biphenyls
PAHs	=	Polycyclic Aromatic Hydrocarbons
PPI	=	World Health Organization

AUTHORS' CONTRIBUTION

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

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