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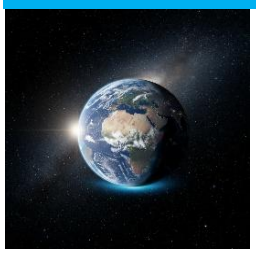

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Chronic low-grade inflammation as a key mechanism in the development of civilization diseases - a narrative review

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Abstract

Background

Chronic low-grade inflammation (CLGI) is a persistent activation of the immune system that typically does not produce any signs of acute inflammation, chronically affects metabolism, endothelial function, and homeostasis. Contemporary evidence suggests that CLGI constitutes a biological “common background” for many civilization diseases including visceral obesity and insulin resistance, type 2 diabetes, atherosclerosis and cardiovascular diseases, metabolically associated steatotic liver disease as well as selected neuropsychiatric and neurodegenerative disorders, cancers, and chronic respiratory and kidney diseases. This mechanism is further amplified by immune ageing (inflammaging) which may help explain the increasing burden of multimorbidity in the population.

Aim

The aim of this article is to present CLGI as a pathogenetic mechanism in the development of civilization diseases and to discuss: (1) the main axes (immunometabolism, the gut–microbiota–barrier axis, endothelial dysfunction, oxidative stress, and ageing-related processes), (2) clinically useful biomarkers, and (3) the prevention and treatment.

Material and methods

A narrative review of the literature was conducted. The scope included publications addressing CLGI and its associations with selected civilization diseases. Searches were performed in databases e.g., PubMed/MEDLINE using keywords such as including, among others, “low-

grade inflammation", "metainflammation/metaflammation", "inflammaging", "hs-CRP", "NLRP3", "gut microbiota", "atherosclerosis", "MASLD/NAFLD", "CKD inflammation", and "COPD systemic inflammation". The selection was purposive and problem-oriented: meta-analyses, systematic reviews, large cohort studies, and randomized clinical trials were prioritized and findings were synthesized thematically (mechanisms → biomarkers → disease entities → modulation strategies).

Results

The literature synthesis indicates that CLGI is sustained by the overlap of metabolic and environmental stimuli. Key contributors include dysfunction of visceral adipose tissue, disturbances of the intestinal axis (dysbiosis, increased intestinal barrier permeability), persistent activation of innate immunity (including inflammasome pathways) and endothelial and microcirculatory dysfunction. Biomarkers such as hs-CRP are clinically practical. However, the interpretation requires consideration of confounders (infections, comorbidity burden, obesity, and exacerbations of chronic diseases). CLGI supports the development and progression of metabolic disorders, atherosclerosis, metabolically driven liver disease, selected brain–immune axis disorders, and it increases the risk of complications and multimorbidity in CKD and COPD.

Conclusions

CLGI constitutes a coherent, biologically plausible mechanism linking lifestyle factors and ageing to the development of civilization diseases. Clinically, strategies that reduce the stimuli driving CLGI such as reduction of visceral obesity, physical activity, dietary modification, sleep improvement and stress reduction and the identification of individuals with an elevated inflammatory-risk phenotype are of particular importance. In selected populations, interventions with documented anti-inflammatory effects may be considered as an adjunct to standard management.

Key words: chronic low-grade inflammation; metainflammation; inflammaging; hs-CRP; atherosclerosis; MASLD; chronic kidney disease; COPD

1. Introduction

Civilization diseases are currently the dominant source of health burden in most populations. This group includes, among others, visceral obesity and metabolic syndrome, type 2 diabetes, atherosclerosis and cardiovascular diseases, metabolically associated steatotic liver disease, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), as well as selected neuropsychiatric and neurodegenerative disorders and cancers [1–8,11,12,30–39]. Despite different target organs, these conditions share convergent risk backgrounds (lifestyle, environment, ageing) and similar pathophysiological axes, including persistent activation of innate immunity, oxidative stress, endothelial dysfunction and disturbed metabolic signaling [1–6,17–20]. In this context, chronic low-grade inflammation (CLGI) is increasingly indicated as a key biological "link" between civilization-related exposures and the development of organ damage [1–4,20].

In contrast to acute inflammation, which plays a defensive role and usually resolves after removal of the causative factor, CLGI is long-lasting, low-intensity, and often clinically silent, yet it can consistently "reset" the homeostasis toward a phenotype of high metabolic and vascular risk [1–4,5,6]. This phenomenon is particularly well captured by the concept of immunometabolism which assumes a tight coupling between immune function and energy homeostasis: metabolic signals can activate inflammatory responses even in the absence of infection and chronic inflammatory activation can secondarily worsen metabolic disturbances creating a vicious cycle [1–4].

Research Objective

The aim of the article is to present chronic low-grade inflammation (CLGI) as a key mechanism underlying the development of civilization diseases and to discuss the main sources and pathophysiological axes of CLGI, its biomarkers, and the clinical implications for prevention and potential therapeutic strategies.

Research Problems

The following research problems were addressed: how CLGI should be defined and which features distinguish it from acute inflammation and classical chronic inflammation, which immunometabolic mechanisms explain why a "low-grade" inflammatory state can lead to major clinical consequences, what the most important population-level sources of CLGI are and how they initiate persistent immune activation, how CLGI contributes to the pathogenesis of major

civilization diseases and which biomarkers best reflect CLGI and what the limitations of their interpretation are in clinical practice.

Research Hypotheses

It was assumed that CLGI integrates metabolic and environmental stimuli with persistent activation of innate immunity and endothelial and metabolic dysfunctio thereby promoting the development and progression of civilization diseases [1–6,17–20]. It was also assumed that the main population sources of CLGI—particularly visceral obesity, adverse dietary patterns, disturbances of the gut–microbiota axis, chronic stress, and sleep deprivation—may act synergistically, increasing inflammatory "tone" and raising the risk of multimorbidity, especially in the context of immune ageing (inflammaging) [13–20,43,44]. Furthermore, it was assumed that in some patients the elevated inflammatory-risk phenotype is modifiable and that targeting selected inflammatory axes may translate into measurable clinical benefits in selected diseases, particularly in secondary prevention of cardiovascular disease [21–23].

1.1. Definition and characteristics of chronic low-grade inflammation (CLGI)

CLGI can be described as a chronic, low-intensity activation of inflammatory responses, usually without a clear infectious trigger, characterized by a long-term, moderate increase in inflammatory mediators e.g. CRP, IL-6) and activation of pro-inflammatory pathways in metabolic tissues and the vasculature [1–6,22,33]. In the literature, CLGI is often linked to metainflammation/metaflammation—a concept emphasizing that chronic inflammation can be initiated and maintained by metabolic stress related to an excess of energy substrates, lipotoxicity and cellular dysfunction [1–4]. A parallel concept is inflammaging-age-related sterile low-grade inflammation associated with immunosenescence and accumulation of damage-associated signals [17–20].

An attribute of CLGI is its "silent" course—biochemical changes are typically subtle and their significance becomes evident over years through the accumulation of organ damage and increased clinical risk. Unlike classical chronic inflammation (e.g. autoimmune), CLGI more often has a metabolic–environmental background, is strongly linked to visceral obesity and metabolic disturbances and can coexist with multiple disease entities simultaneously [1–4,24–26].

1.2. Immunometabolism: why “low-grade inflammation” has major consequences

The key to understanding the clinical significance of CLGI is immunometabolism—a field describing how cellular metabolism shapes inflammatory responses and how inflammatory mediators in turn alter systemic energy homeostasis [1–4]. In visceral obesity and metabolic syndrome adipose tissue is remodeled through adipocyte hypertrophy, local hypoxia, cellular stress, and recruitment of immune cells (especially macrophages). These processes promote the secretion of pro-inflammatory cytokines and impair insulin signaling, providing a mechanistic bridge between CLGI and insulin resistance [24–26].

A crucial component is persistent activation of innate immunity. Metabolic and damage-associated stimuli (DAMPs) can activate inflammatory pathways in antigen-presenting cells and phagocytes as well as in organ cells. In this context, the NLRP3 inflammasome is described as an important “node” linking metabolic stress to IL-1β maturation and persistence of inflammatory responses [27,28]. In atherosclerosis cholesterol crystals have been shown to activate NLRP3 in macrophages, strengthening local inflammation within the vascular wall [27,28]. Consequences of chronic activation of these axes include endothelial dysfunction, microcirculatory impairment and enhancement of atherogenic processes [5,6,21].

Moreover, CLGI does not act solely locally. Chronic exposure to inflammatory mediators can modulate liver, skeletal muscle and adipose tissue function promoting insulin resistance, atherogenic dyslipidemia, and progression of organ disease [1–4,30]. A “low-grade” inflammatory state sustained for years may generate substantial clinical consequences including increased cardiovascular event risk, progression of liver fibrosis, declining kidney function and intensified multimorbidity [5,6,21,30,35].

1.3. Sources of CLGI in the population

Visceral obesity and sedentary lifestyle.

Obesity (especially visceral) is one of the most important population-level sources of CLGI as adipose tissue remodeling promotes persistent pro-inflammatory responses and metabolic disturbances [24–26]. Physical inactivity supports the maintenance of visceral fat mass and limits the beneficial anti-inflammatory effects of exercise (including cytokine profile modulation and improved insulin sensitivity) [40].

Diet and nutritional quality.

Not only caloric excess but also dietary composition can modulate inflammatory "tone". Dietary patterns high in saturated fats and ultra-processed foods are mechanistically linked to metabolic stress, whereas a Mediterranean dietary pattern is associated with favorable effects on inflammatory markers and reduced cardiovascular risk [41,42]. At the population level diet also acts indirectly via its impact on gut microbiota and bacterial metabolites [13,29].

Dysbiosis and the gut–microbiota–barrier axis.

The concept of metabolic endotoxemia suggests that chronic low-level exposure to LPS may initiate and sustain inflammation and insulin resistance, particularly under high-fat dietary conditions [15]. In parallel, reviews emphasize that the gut microbiota and innate immunity form a coupled system in which changes in microbiome composition and function can modulate the risk of metabolic and organ diseases [13,14]. The gut–liver axis is particularly important in MASLD/MASH, where gut-derived signals can promote inflammation and fibrosis [30–32].

Sleep and psychosocial stress.

Sleep disturbances and insomnia are associated with neuroendocrine axis activation and increased inflammatory markers and the relationship between sleep and inflammation may be bidirectional [43]. Chronic stress, including psychosocial stress, may enhance inflammatory responses through neuroimmune mechanisms. Theoretical models describe how social threat signals can activate inflammatory pathways and increase chronic disease risk [44].

Environmental factors.

Environmental exposures may contribute to the maintenance of CLGI, including tobacco smoking (especially relevant to COPD and cardiovascular risk) and air pollution, both linked to chronic inflammatory activation and endothelial dysfunction [37–39]. In clinical reality, these factors rarely occur in isolation and often overlap with obesity, sleep disturbances and stress amplifying the inflammatory phenotype.

1.4. Review thesis: CLGI as a common mechanism of civilization diseases

The thesis of this review is that CLGI constitutes a common, biologically plausible mechanism linking civilization-related exposures with the development and progression of chronic diseases. This mechanism operates through several recurring axes: (1) persistent activation of innate immunity and cytokine pathways, (2) metabolic dysfunction, (3) disturbances of the gut–

microbiota axis, (4) endothelial and microcirculatory dysfunction, and (5) amplification of immune ageing processes (inflammaging) [1–6,13–20]. Consequently, CLGI may contribute to pathogenesis and multimorbidity in T2D and CVD [5,6,21–23,24–26], influence the progression of MASLD/MASH [30–32], participate in mechanisms of depression and neurodegeneration through neuroimmune axes [9–12], support carcinogenesis via modulation of the tumor microenvironment [7,8] and worsen prognosis and complications in CKD and COPD where systemic inflammation is clinically significant [34–39]. The following sections present the mechanisms of CLGI, biomarkers and a map of CLGI links to major civilization diseases as well as preventive and therapeutic implications, focusing on interventions with the highest biological and clinical plausibility.

2. Survey methodology / Materials and methods (narrative review)

2.1. Design: narrative review

This article is a narrative review aimed at a synthetic presentation of the mechanisms of chronic low-grade inflammation (CLGI) and their translation into the development and progression of civilization diseases. The thematic scope comprised: (1) definitions and key pathophysiological axes of CLGI (immunometabolism, the gut–microbiota–barrier axis, inflammasome and cytokines, endothelial dysfunction, oxidative stress, inflammaging), (2) CLGI biomarkers and their clinical utility, (3) the role of CLGI in high-population-impact disease entities (visceral obesity/T2D, atherosclerosis and CVD, MASLD/MASH, neuropsychiatric/neurodegenerative disorders, carcinogenesis, CKD, COPD), and (4) preventive and therapeutic implications.
Publications were considered primarily in English (reflecting the dominance of English-language literature in immunometabolism and translational research), and in justified cases also in Polish.

2.2. Sources and search strategy

The literature search was conducted in leading medical and interdisciplinary databases: PubMed/MEDLINE and, additionally, Scopus and Web of Science. A strategy of combining

keywords (AND/OR operators) was used, alongside cascade searching ("snowballing"), i.e., screening the reference lists of key publications to identify additional relevant sources.
Search terms and their variants included, among others: "chronic low-grade inflammation", "low-grade inflammation", "metainflammation"/"metaflammation", "inflammaging", "hs-CRP", "IL-6", "TNF-α", "NLRP3 inflammasome", "insulin resistance", "type 2 diabetes", "atherosclerosis", "cardiovascular disease", "NAFLD", "MASLD", "MASH", "gut microbiota", "intestinal permeability", "metabolic endotoxemia", "neuroinflammation", "depression", "Alzheimer", "cancer-related inflammation", "chronic kidney disease", and "COPD systemic inflammation". The search strategy was iteratively refined based on results and emerging mechanistic themes.

2.3. Eligibility / Selection approach

Study selection was purposive and problem-oriented. Priority was given to publications with high credibility and translational relevance: meta-analyses and systematic reviews (when available for a given topic), large cohort studies, randomized clinical trials (especially those with hard clinical endpoints), and leading mechanistic papers explaining key CLGI pathways. In addition, terminology consensus statements and definition-focused documents (e.g., in the MASLD/MASH field) were included when relevant for clinical interpretation.
Publications of clearly limited methodological quality (e.g., without clear methods, extremely small samples without mechanistic value), papers not addressing CLGI or not related to disease entities covered by this review, and reports with conclusions inconsistent with the presented data or based purely on speculation without literature support were excluded.

2.4. Data extraction

From each included publication, information was collected to build a coherent interpretative pathway: (1) the mechanism/hypothesis (e.g., the role of visceral adipose tissue, inflammasome, intestinal barrier), (2) related biomarkers and clinico-laboratory indices (e.g., hs-CRP, IL-6, metabolic markers), (3) the disease entity or clinical phenotype (e.g., T2D, CVD, MASLD/MASH, CKD, COPD), (4) clinical consequences (risk, progression, complications, multimorbidity), and (5) practical implications (prevention, modifiable factors, potential

therapeutic targets). Extraction was performed to enable comparison of shared mechanisms across diseases and identification of disease-specific elements.

2.5. Synthesis method

A thematic synthesis approach was used mapping identified CLGI mechanisms to individual civilization diseases. First, evidence was organized by pathophysiological axes (immunometabolism, gut–microbiota, inflammasome/cytokines, inflammaging, endothelium), and then aligned with clinical evidence concerning specific disease entities. This approach allowed identification of "shared mechanisms" (e.g., persistent innate immune activation and endothelial dysfunction) as well as "dominant mechanisms" in particular clinical phenotypes (e.g. metabolic inflammation in MASLD/MASH or systemic components in COPD and CKD).

2.6. Quality appraisal

A formal quality assessment (as used in systematic reviews) was not the goal of this narrative review. However, descriptive credibility rules were applied: greater weight was assigned to meta-analyses, large cohorts, and RCTs than to small observational studies at higher risk of bias; studies with clear methods and reproducible findings were preferred; and in areas of ambiguity, publications presenting divergent conclusions were included with an indication of possible reasons for discrepancies (population heterogeneity, definitional differences, confounders).

2.7. AI statement

In line with editorial requirements, artificial intelligence tools may have been used as supportive instruments for language editing and structuring the manuscript; however, literature selection, data interpretation, and formulation of conclusions remain the authors' responsibility.

3. Results

3.1. CLGI pathophysiology – main mechanistic axes

Visceral adipose tissue and metainflammation

One of the best-documented CLGI models is visceral obesity, in which adipose tissue ceases to be solely an energy depot and becomes an active immunometabolic organ [2–4]. Obesity is associated with adipocyte hypertrophy, local hypoxia, cellular stress and recruitment of immune cells (especially macrophages) shifting the adipose microenvironment toward a pro-inflammatory state [24–26]. Classic studies demonstrated increased macrophage accumulation in adipose tissue in obesity and its association with insulin resistance [24,25]. Mechanistically, chronic production of pro-inflammatory mediators (e.g., IL-6, TNF-α) and activation of metabolic stress pathways impair insulin signaling and simultaneously enhance lipotoxicity and secondary organ damage [2–4,25,26]. This mechanism—termed metainflammation/metaflammation—acts as a key "engine" of CLGI in populations with high prevalence of overweight and obesity [1–4].

Importantly, metainflammation is not merely "local." Visceral adipose tissue, through its secretory profile (cytokines, adipokines, lipid mediators), affects the liver, muscles, and vasculature, promoting insulin resistance, atherogenic dyslipidemia, and endothelial dysfunction [1–6]. Clinically, this means that obesity-associated low-grade inflammation becomes a starting point for a cascade leading to T2D, CVD, and liver disorders [1–6,30].

The gut–microbiota–barrier axis and metabolic endotoxemia

A second key CLGI concept is disturbed intestinal homeostasis. The gut microbiota and innate immunity form a coupled signaling system in which changes in microbiome composition and function can affect inflammatory responses and host metabolism [13,14]. The metabolic endotoxemia model proposes that under high-fat dietary conditions there may be a chronic, slight increase in LPS exposure, which initiates and sustains inflammation and promotes insulin resistance [15]. This is clinically relevant because it links everyday lifestyle factors to persistent innate immune activation even in the absence of overt infection [13–16].

The microbiota's influence on CLGI extends beyond LPS. Bacterial metabolites (e.g. short-chain fatty acids) can modulate metabolic and immune functions, and diet quality influences the "direction" of this modulation [29]. Clinically, the gut–liver axis is particularly important

in metabolic disorders and liver diseases, where gut-derived signals can promote inflammation and fibrosis [30–32]. The gut–brain axis is also considered a pathway through which peripheral inflammation and immune signals may affect central nervous system function [9–12].

Inflammasome, cytokines, NF-κB signaling, oxidative stress and mitochondria

A central feature of CLGI is persistent innate immune activation. Damage-associated signals (DAMPs) and microbiota-derived signals (MAMPs) activate pro-inflammatory pathways, including transcriptional response programs (e.g., via NF-κB), leading to long-term production of cytokines and inflammatory mediators [1–4,13–16]. Particular attention is given to the IL-1β axis and the NLRP3 inflammasome viewed as a "node" integrating metabolic stimuli with inflammatory responses [27,28]. In atherosclerosis cholesterol crystals can activate NLRP3 in macrophages, strengthening local inflammation in the vascular wall [27,28]. This is relevant because it links a molecular mechanism to a clinical consequence (increased cardiovascular event risk) and to a potential intervention target (IL-1β axis) [21].

In chronic organ disease the coupling of inflammation with oxidative stress and mitochondrial dysfunction is also important. Chronic inflammatory activation increases oxidative burden and worsens cellular function, while oxidative stress can feed back to intensify inflammatory signaling, thereby maintaining CLGI [1–4,17–20]. Consequently, CLGI acts as a "damage amplifier": it is not always the primary cause of disease, but it accelerates progression and increases susceptibility to complications.

Endothelial and microcirculatory dysfunction

The endothelium is a key "distributed organ" sensitive to chronic inflammatory and metabolic stimuli. In atherosclerosis, inflammation regulates plaque development and destabilization, and chronic exposure to inflammatory mediators promotes endothelial activation, impaired vascular function and lesion progression [5,6]. Endothelial and microcirculatory dysfunction can be seen as a shared downstream endpoint of many CLGI axes—linking metainflammation, lipid abnormalities and immune signaling into a pathway leading to clinically overt vascular events [5,6,21–23]. Clinical validation of inflammation's role in vascular disease comes from trials where modulating inflammatory axes reduced cardiovascular event risk [21,23].

Immunosenescence and inflammaging

At the population level, CLGI is amplified by immune ageing (inflammaging), i.e., increasing chronic inflammatory activity with age [17–20]. This phenomenon is associated with immunosenescence, accumulation of damage signals, altered regulation of innate responses,

and higher inflammatory “tone” [17–20]. Inflammaging may explain why the risk of many civilization diseases rises with age even under similar exposures and why multimorbidity is often associated with elevated inflammatory markers [17–20]. Clinically, this implies that CLGI is not only a lifestyle-related issue but also part of the biology of ageing—although lifestyle can substantially modulate it.

3.2. Biomarkers and the “clinical face” of CLGI

hs-CRP, IL-6, TNF-α, and indirect indices

In clinical practice, the most accessible CLGI marker is hs-CRP. Its prognostic significance in cardiovascular disease is well described, and the JUPITER trial showed that a population with elevated hs-CRP may benefit from intensified prevention (including interventions affecting both lipids and inflammation) [22]. In terms of “inflammatory phenotyping,” hs-CRP therefore serves as a pragmatic proxy for inflammatory axis activity, particularly regarding vascular risk [22,33].

IL-6 is mechanistically closer to CLGI because it contributes to acute-phase regulation (including CRP induction) and is often elevated in chronic inflammatory states. TNF-α is strongly linked to adipose tissue inflammation and insulin resistance, although it is less commonly measured routinely [2–4,25,26]. Clinically useful are also indirect indices reflecting CLGI consequences and immunometabolic “reprogramming”: increasing insulin resistance, atherogenic dyslipidemia (e.g., high TG and low HDL), and features of metabolic syndrome [1–6,26].

Interpretation limitations and confounders

Interpreting CLGI biomarkers requires caution. hs-CRP is non-specific, influenced by biological variability and by acute infections, trauma, exacerbations of chronic diseases, smoking, and obesity. In conditions such as CKD and COPD, inflammatory markers may be chronically elevated for many reasons, making it difficult to distinguish “pure” CLGI from inflammation driven by active organ disease [34–39]. Practically, biomarkers should be interpreted in clinical context: symptoms, comorbidities, recent infections and exacerbations, and alongside assessment of metabolic and vascular risk [22,33–39].

3.3. CLGI as a mechanism of civilization diseases

Visceral obesity / insulin resistance / T2D

In visceral obesity, CLGI is a driving component of insulin resistance. Adipose tissue remodeling (hypoxia, metabolic stress, macrophage infiltration) promotes chronic production of cytokines and mediators that impair insulin signaling in target tissues [2–4,24–26]. As this phenotype becomes established, the risk of T2D increases, while vascular and hepatic consequences intensify, fostering multimorbidity [1–6,26]. In this model, CLGI is not an "add-on" to metabolic disturbances but a mechanism that deepens their pathogenesis and maintains a vicious cycle: insulin resistance → lipotoxicity → cellular stress → inflammation [1–4,26].

Atherosclerosis and CVD

Atherosclerosis is now viewed as an inflammatory disease of the vascular wall, where innate responses regulate both lesion initiation and plaque destabilization [5,6]. Mechanistically, lipid and inflammation are tightly coupled: lipid factors initiate the reaction, while inflammatory mediators sustain and amplify it [5,6]. Incorporating the inflammasome axis (NLRP3) explains how stimuli such as cholesterol crystals can strengthen inflammatory responses [27,28]. The strongest clinical argument for inflammation's role in CVD comes from RCTs: CANTOS showed that IL-1β inhibition with canakinumab reduced cardiovascular events in post-myocardial infarction patients [21], and COLCOT demonstrated benefits of low-dose colchicine in secondary prevention [23]. These findings support the concept that in high-risk patients with an active inflammatory component, modulating CLGI may yield measurable clinical benefits [21–23].

MAFLD/NAFLD (MASLD/MASH) and metabolic syndrome

Metabolic liver disease is strongly linked to CLGI. Mechanistically, progression from steatosis to inflammation and fibrosis results from overlapping insulin resistance, lipotoxicity, oxidative stress, and immune signaling (including gut-derived signals) [30–32]. Changes in nomenclature toward MASLD/MASH emphasize the central metabolic background of the disease, consistent with the metaflammation model [31,32]. Clinically, this means MASLD/MASH should be viewed as part of a broader immunometabolic phenotype: the liver is a "nodal" organ where CLGI becomes particularly evident and may determine prognosis through fibrosis progression [30–32].

Neuropsychiatric disorders and neurodegeneration (the brain–gut–immune axis)

In psychiatry and neurology, interest in inflammation is growing. Reviews indicate that a subset of patients with depression displays an inflammatory phenotype, and mechanisms may include cytokine effects on neurotransmission, neuronal plasticity, and mood-related circuits [9,10]. In neurodegeneration, especially Alzheimer's disease, neuroinflammation and microglial activation are recognized as important elements of pathophysiology, and peripheral chronic inflammation may modulate CNS processes [11,12]. In this context, the brain–gut–immune axis is interpreted as a multidirectional communication pathway: microbiota and gut signals can influence inflammatory tone, and inflammation can alter neuroendocrine and behavioral functions, which in turn affects lifestyle (e.g., sleep, activity) [9–14,29,43,44].

Carcinogenesis (inflammatory microenvironment)

In oncology, inflammation is regarded as an important component of the tumor microenvironment. The "cancer-related inflammation" concept describes how inflammatory states can promote proliferation, angiogenesis, invasion, tumor cell survival, and modulate anti-tumor immune responses [7,8]. Regarding CLGI, this implies that a chronic pro-inflammatory milieu (e.g., associated with obesity and inflammaging) may create conditions favoring initiation or progression of certain cancers, although the strength and specificity of these relationships depend on cancer type and biological context [7,8,17–20].

CKD and COPD as chronic diseases with an inflammatory component

In CKD chronic inflammation is common and multifactorial, associated with disease progression, cardiovascular complications, oxidative stress, and metabolic disturbances [34–36]. CLGI in CKD may be both a consequence of the disease (e.g., uremic toxins and oxidative stress) and a factor accelerating damage and multimorbidity, particularly vascular comorbidity [34–36].

In COPD, many syntheses indicate the presence of a systemic component with elevated inflammatory markers, which may explain part of the comorbidity burden (especially CVD) and poorer prognosis [37–39]. Tobacco smoke and chronic environmental exposure act both as initiating and sustaining factors, while COPD exacerbations further "boost" inflammatory tone [37–39]. In these two disease entities, biomarker interpretation requires particular caution because chronic organ disease itself may maintain elevated inflammatory activity [34–39].

3.4. Implications: modulating CLGI

Lifestyle (diet, exercise, sleep, stress)

The greatest potential for CLGI modification at the population level lies in lifestyle interventions because they target the main stimuli driving metainflammation and immunometabolic dysfunction [1–4]. Physical activity has anti-inflammatory effects and can reduce CLGI by decreasing visceral fat mass, improving insulin sensitivity, and modulating cytokine profiles [40]. In nutrition, the Mediterranean dietary pattern is associated with improved cardiovascular risk profiles and reduced events in primary prevention, as well as favorable effects on inflammatory markers [41,42]. Sleep and stress are often underestimated regulators: reviews indicate associations between sleep disturbances and inflammatory activation [43], and neuroimmune models describe how psychosocial stress may raise inflammatory "tone" and chronic disease risk [44]. Clinically, effective CLGI lowering requires a multi-component approach integrating diet and physical activity with sleep hygiene and chronic stress reduction.

Treatment and prevention – anti-inflammatory mechanisms (general)

From a translational perspective evidence from CVD is particularly important, showing that targeting inflammatory axes can reduce clinical event risk in selected patients. CANTOS (IL-1β inhibition) and COLCOT (colchicine) provide proof that modulating inflammation can be beneficial in secondary prevention [21,23]. These findings suggest CLGI can be not only a risk marker but also a modifiable intervention target in appropriately selected individuals. At the same time, pharmacologic anti-inflammatory strategies must consider safety profiles, infection risk, comorbidities, and the need for patient selection (e.g., inflammatory phenotype) [21,23]. In routine practice, the "anti-inflammatory" effects of standard preventive strategies (weight reduction, improved diet quality, physical activity) remain foundational, with pharmacology serving as an adjunct in selected situations [40–42].

Future directions: inflammatory phenotyping, personalization, microbiota-targeted interventions

A key development direction is moving from general CLGI concepts toward inflammatory phenotyping, i.e., identifying patient subgroups in which inflammation plays a decisive role in risk and disease progression. Practically, this may involve combining biomarkers (e.g., hs-CRP) with metabolic and clinical profiles to guide more precise interventions [22,33]. Another area is microbiota-targeted approaches, because the microbiome is a potentially modifiable regulator

of immunometabolic signaling [13,14,29]. Finally, the growing importance of inflammaging indicates that strategies reducing CLGI may matter not only for single-disease prevention but also for reducing age-related multimorbidity risk [17–20]. Clinically, the most promising perspective is combining population-level approaches (lifestyle) with personalized strategies (inflammatory phenotype identification and response monitoring).4. Discussion

A coherent model: why CLGI is a shared mechanism and where diseases differ

The evidence synthesized in the Results section supports a coherent model in which CLGI acts as an integrating mechanism linking civilization-related factors (energy surplus, sedentary lifestyle, adverse dietary patterns, chronic stress and sleep disturbances, environmental exposures) with long-term organ consequences [1–4,17–20,43,44]. In this framework, CLGI is shared across many diseases because it relies on recurring biological axes: persistent innate immune activation, immunometabolic disturbances, endothelial dysfunction, and gut–microbiota–barrier interactions [1–6,13–16]. These mechanisms create a "risk platform" upon which different disease phenotypes develop depending on the dominant target organ, exposure duration, and individual predispositions.

At the same time, civilization diseases differ in the primary site of initiation and the relative dominance of specific CLGI axes. In visceral obesity and T2D, metainflammation in adipose tissue predominates, along with insulin signaling impairment and lipotoxicity [2–4,24–26]. In atherosclerosis, inflammatory axes are tightly coupled to vascular wall pathology, with innate mechanisms (including inflammasome activation) particularly important for plaque development and destabilization [5,6,27,28]. In MASLD/MASH, hepatocyte lipid overload and the interaction between gut-derived signals and hepatic immune responses drive the transition from steatosis to inflammation and fibrosis [30–32]. In neuropsychiatric and neurodegenerative conditions, neuroinflammation and brain–immune axes become more prominent, but causal relationships are more complex and phenotypically heterogeneous [9–12]. In carcinogenesis, inflammation operates largely through the tumor microenvironment and immune response modulation, and CLGI may provide a permissive background depending on tumor type [7,8]. In CKD and COPD, inflammation is often both a consequence of organ disease and a factor worsening prognosis through increased comorbidity (especially cardiovascular), making it difficult to clearly separate "primary" CLGI from inflammation secondary to active disease [34–39]. These differences indicate that CLGI is a shared mechanism, but its dominant sources and effector pathways are disease-specific.

Clinical significance: primary and secondary prevention and early risk identification

Clinically, the value of the CLGI concept lies in the possibility of identifying risk earlier than when overt organ disease becomes established. In primary prevention, this implies shifting focus from late complication treatment to identifying an immunometabolic high-risk phenotype: visceral obesity, rising insulin resistance, dyslipidemia, and persistently elevated inflammatory markers such as hs-CRP [2–6,22,33]. In practice, hs-CRP can support risk stratification, especially in the vascular context, but its interpretation must incorporate confounders and situations where elevation is secondary to other processes [22,33–39].

In secondary prevention, the clearest clinical relevance is in CVD, where evidence indicates that inflammatory axis modulation can reduce recurrent cardiovascular event risk in selected patients. Trials such as CANTOS and COLCOT demonstrate that inflammation is not merely a marker but may be a modifiable therapeutic target in specific high-risk populations [21,23]. At the population level, however, lifestyle interventions have the greatest potential for CLGI reduction: decreasing visceral adiposity, increasing physical activity, and improving diet quality—actions that affect both inflammatory drivers and metabolic consequences [40–42]. Sleep hygiene and chronic stress reduction are additional important elements, since sleep disruption and stress can increase inflammatory "tone" and limit the effectiveness of other interventions [43,44]. Overall, CLGI encourages an integrated clinical approach: prevention and treatment should not be viewed solely as organ-specific tasks but as modulation of a shared immunometabolic axis.

Limitations of the narrative review

This paper is a narrative review and therefore has methodological limitations. First, compared with systematic reviews, narrative selection may be more susceptible to selection bias, as it does not include a formal search protocol, full selection pathway reporting, or study-by-study risk-of-bias assessment. Second, the absence of a meta-analysis limits quantitative effect summary and comparability of association magnitudes across populations and endpoints. Third, some conclusions rely on synthesis of mechanistic and observational data, which—despite biological coherence—do not always permit definitive causal inference. Finally, in areas such as neuropsychiatry, microbiota research, or inflammation in CKD/COPD, heterogeneity of definitions, populations, and biomarker measurement methods further limits generalizability [9–16,34–39].

Research gaps and future directions

Despite growing evidence, several research gaps remain. First, improved CLGI phenotyping is needed, including biomarker panels (rather than single markers) that can differentiate dominant inflammatory axes (e.g., gut vs adipose vs vascular) and predict intervention response [22,33]. Second, many promising hypotheses—particularly regarding the gut–microbiota–barrier axis and microbiota-targeted interventions—require more definitive clinical studies with well-defined endpoints and robust control of confounders (diet, medications, lifestyle) [13–16,29]. Third, in CKD and COPD, studies are needed that better separate inflammation as a consequence of active organ disease from CLGI as an independent amplifier of vascular risk and multimorbidity, and that identify which interventions truly reduce clinical risk in these populations [34–39].

Another direction is the development of precision strategies: identifying patients with "residual inflammatory risk" (e.g., persistently elevated hs-CRP despite control of classical risk factors) and selecting targeted therapies. Evidence from CVD suggests targeted anti-inflammatory approaches can be beneficial in selected groups, but selection criteria are needed to minimize adverse effects and maximize benefit [21,23]. Finally, the growing relevance of inflammaging indicates that CLGI should be considered part of ageing biology; future studies should determine the extent to which long-term CLGI modulation affects multimorbidity, functional capacity, and healthy ageing [17–20]. Clinically, combining population-level approaches (lifestyle) with personalization (phenotyping and response monitoring) appears most promising for improving prevention and treatment of civilization diseases.

5. Conclusions

CLGI (chronic low-grade inflammation) represents a common pathophysiological axis across many civilization diseases because it links lifestyle factors and ageing with persistent innate immune activation and metabolic and vascular dysfunction and its main population sources include visceral obesity and insulin resistance, disturbances of the gut–microbiota–barrier axis, adverse dietary patterns, sleep deprivation, chronic stress, and environmental exposures (including tobacco smoking), which clinically translates into the possibility of earlier risk identification (most often using hs-CRP interpreted in the context of confounders, particularly

in CKD and COPD) and into the practical conclusion that the foundation for CLGI reduction is intensive lifestyle-based prevention (reduction of visceral adiposity, regular physical activity, an anti-inflammatory dietary pattern, sleep hygiene, and stress reduction), while the strongest evidence supporting targeted modulation of inflammatory axes concerns secondary prevention of cardiovascular disease in selected patients, and future directions include inflammatory phenotyping and personalized interventions, including microbiota-targeted approaches and other targeted anti-inflammatory strategies [1–6,13–16,17–23,22,33–44].

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Conceptualization: MKP and NG; methodology: MKP; software: EC and MKP; validation: MKP, NG and EC; formal analysi:, MKP; investigation: NG and PD; resources: EC and MA; data curation: MKP; writing: all authors, original draft preparation: MKP, NG and PD; writing—review and editing: MKP and EC; supervision: MKP; project administration: EC and MA. All authors have read and agreed to the published version of the manuscript.

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