

Telomere Length in Metabolic Syndrome: Mechanisms, Epidemiology and Clinical Implications: A Narrative Review

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Abstract: Metabolic syndrome (MetS) is a major and growing global public health challenge, affecting a substantial proportion of adults worldwide and contributing markedly to the rising burden of type 2 diabetes, cardiovascular disease, metabolic dysfunction-associated steatotic liver disease, and premature mortality. Despite its high prevalence and systemic consequences, the biological mechanisms linking chronic metabolic stress to cellular ageing remain incompletely resolved. Telomere length (TL), particularly leukocyte telomere length (LTL), has emerged as a candidate integrative biomarker of biological ageing, cumulative metabolic injury, and disease risk; however, the field remains limited by heterogeneous study designs, inconsistent measurement approaches, conflicting genetic data, and uncertainty regarding whether TL is merely a correlate of metabolic dysfunction or a clinically informative biomarker and mechanistic mediator. This narrative review synthesizes evidence on the epidemiology, mechanistic basis, and clinical implications of TL variation in obesity and MetS, with emphasis on human population studies. It specifically addresses the current gap between observational associations and biological interpretation by integrating epidemiological, longitudinal, mechanistic, and Mendelian randomization data within a unified framework. Across large cohorts and meta-analyses, MetS and several of its component traits are generally associated with shorter LTL. Shorter LTL in MetS appears to identify individuals at higher risk of adverse outcomes, including all-cause and cardiovascular mortality. Mechanistically, oxidative stress, chronic low-grade inflammation, mitochondrial dysfunction, hormonal perturbation, and genetic and epigenetic regulation of telomere-maintenance pathways emerge as interconnected drivers of accelerated telomere attrition and cellular senescence. Mendelian randomization studies indicate a more complex architecture, in which adiposity-related traits may causally shorten LTL, whereas genetically longer LTL may associate with selected adverse metabolic phenotypes, consistent with pleiotropy, tissue specificity, and pathway-dependent effects. This review collates the current evidence, highlights major research gaps, and outlines the methodological and biological advances needed to determine whether TL can serve as a clinically actionable biomarker or therapeutic target in MetS.

Keywords: oxidative stress, chronic inflammation, insulin resistance, telomerase

Introduction

The prevalence of metabolic syndrome (MetS) has risen in parallel with the global obesity epidemic, contributing substantially to the burden of type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD) and premature mortality.¹ Recent Global Burden of Disease analyses underscore the scale of this problem, showing rising exposure to all major metabolic risk factors with particularly concerning increases in the burden attributable to high fasting plasma glucose and high body-mass index.² Traditionally, obesity has been defined by body mass index (BMI), yet this metric fails to account for variations in fat distribution and metabolic health status, thereby limiting its utility for precise cardiometabolic risk assessment.^{3,4}

In recent years, TL has gained attention as a biomarker of biological aging and a potential link between metabolic health and cellular senescence. Telomeres, repetitive deoxyribonucleic acid (DNA) protein complexes at chromosome ends, progressively shorten with each cell division, and their attrition is accelerated by oxidative stress, chronic low-

grade inflammation and metabolic dysregulation. Observational and meta-analytic studies increasingly suggest that both obesity and MetS are associated with shorter LTL, although some genetic and longitudinal evidence indicates more complex, possibly bidirectional, relationships.⁴

Despite growing interest, the mechanistic pathways connecting adiposity, insulin resistance, dyslipidaemia, hypertension and hyperglycaemia to telomere dynamics remain incompletely understood. This narrative review collates current evidence on the interplay between telomere biology and MetS, integrating epidemiological findings with insights into oxidative, inflammatory, hormonal, and mitochondrial mechanisms. Additionally, it explores how lifestyle and pharmacological interventions may preserve telomere integrity, with implications for cardiometabolic risk stratification and targeted therapeutic strategies.

A comprehensive literature search of PubMed and Google Scholar was conducted, encompassing original research, meta-analyses and systematic reviews.

Obesity and Metabolic Syndrome

Body mass index (BMI) remains the most widely applied metric for defining obesity. Although useful as a population-scale measure, BMI is an imperfect surrogate of cardiometabolic risk because it does not distinguish fat from lean mass or capture fat distribution patterns. The limitations of BMI, the concept of obesity phenotyping, and definitions of metabolic health across weight categories (including metabolically healthy obesity and metabolically unhealthy normal weight) have been reviewed previously.³

These considerations are directly relevant to metabolic syndrome (MetS) - a cluster of interrelated cardiometabolic abnormalities commonly defined by NCEP-ATP III as the presence of at least three of the following: central obesity, hypertriglyceridaemia, low HDL cholesterol, elevated blood pressure, and impaired fasting glucose. MetS substantially increases the risk of type 2 diabetes, cardiovascular disease, metabolic dysfunction-associated steatotic liver disease (MASLD), and premature mortality.⁴ Its pathobiology is driven by excess visceral adiposity and insulin resistance, which promote chronic low-grade inflammation, oxidative stress, endothelial dysfunction, and atherogenic dyslipidaemia.⁵ Additional contributors include ectopic fat deposition, neurohormonal activation and vascular remodelling further amplify metabolic and cardiovascular risk. Thus, MetS is best understood as a systemic metabolic derangement rather than a set of isolated abnormalities.

Importantly, the inflammatory and oxidative stress pathways that underpin MetS are also implicated in accelerated biological ageing, including telomere attrition. Against this background, this narrative review aims to synthesise current mechanistic, epidemiologic, and clinical evidence linking telomere biology to MetS, and to evaluate the potential utility and limitations of telomere length as a biomarker in cardiometabolic disease. These issues are clinically applicable as they impact on risk stratification, disease progression, and the development of biologically informed preventive and therapeutic strategies.

Telomere Biology

Structure and Function of Telomeres

Telomeres are repetitive DNA-protein complexes located at the ends of chromosomes, consisting of more than 2000 tandem repeats of the non-coding double-stranded DNA sequence “TTAGGG” and a single-stranded guanine-rich overhang.^{6–8} They preserve genomic stability by preventing recognition of chromosome ends as DNA damage and by protecting against end-to-end fusions.⁹ Telomeres also participate in signalling pathways that regulate cellular proliferation, effectively acting as a “biological clock” that limits the replicative potential of somatic cells.^{10–12}

Telomere structure is maintained by specialized protein assemblies, primarily the shelterin complex and the CTC1-STN1-TEN1 (CST) complex.^{12–15} A six-protein shelterin complex (TRF1, TRF2, POT1, TIN2, TPP1, RAP1) binds telomeres and regulates telomerase, thereby preserving telomere stability.¹⁰

TRF1 negatively regulates TL by inhibiting telomerase activity,^{12–15} whereas TRF2 prevents end-to-end fusions and supports cell cycle progression. POT1 binds the single-stranded overhang, protecting it from degradation and inappropriate DNA repair.^{16–20} RAP1, in association with TRF2, contributes both to telomere protection and transcriptional

regulation.^{21,22} TIN2 links double-stranded and single-stranded telomeric DNA-binding proteins, coordinating complex stability.¹⁶ TPP1 interacts with POT1 and TIN2, enhancing telomerase recruitment and processivity.^{23–25}

The CST complex, composed of 3 subunits: conserved telomere protection component 1 (CTC1), suppressor of cdc thirteen 1 (STN1), and telomeric pathway with STN1 (TEN1), facilitates replication of telomeric DNA and complements telomerase function by ensuring proper synthesis of the complementary C-rich strand.^{15,26–28} CTC1 and STN1 can limit telomerase-mediated overextension, acting as a length-regulation checkpoint, while TEN1 supports replication restart and telomere stability.^{29–31}

Without these protective complexes, chromosome ends may be misidentified as DNA breaks, triggering inappropriate repair processes and genomic instability. TL is thus a key determinant of cellular senescence, aging and age-related disease susceptibility. Shortened TL has been associated with cancer, cardiovascular disease, and metabolic disorders, including obesity and MetS. Advances in TL measurement, particularly quantitative polymerase chain reaction (qPCR), have enabled large-scale epidemiological studies to explore these associations with high reproducibility and sensitivity.^{32,33}

In summary, telomere maintenance relies on the intricate interplay between telomerase, shelterin and CST complexes, which collectively safeguard chromosomal stability and cellular longevity. This delicate equilibrium is highly vulnerable to systemic metabolic disturbances. Persistent exposure to metabolic stressors common in MetS and obesity, such as chronic inflammation, oxidative stress, hormonal dysregulation and mitochondrial impairment, can perturb telomere homeostasis by amplifying oxidative damage, suppressing telomerase activity and altering the expression of telomere-protective proteins. These cumulative insults may precipitate premature telomere shortening and genomic instability, forming a mechanistic bridge between molecular telomere biology and the clinical manifestations of metabolic syndrome explored in the subsequent section.

Telomeres, Metabolic Syndrome and Its Components

Evidence from large cohorts, meta-analyses and genetic studies consistently links telomere shortening with metabolic syndrome (MetS). A summary of the principal epidemiological and longitudinal studies linking telomere length with metabolic syndrome and related cardiometabolic traits is provided in [Table 1](#). In a 17-year NHANES cohort limited to individuals with MetS, Xiong et al reported that participants with the shortest leukocyte telomere length (LTL) had significantly higher all-cause and cardiovascular mortality compared with those in the longest LTL tertile, suggesting telomere shortening within MetS may reflect adverse prognosis rather than being an incidental finding.³⁴ Prospective data from Révész et al supported a temporal link, showing that shorter baseline LTL was associated with less favourable metabolic profiles and that worsening MetS components over six years correlated with accelerated telomere attrition.³⁵ A 2024 meta-analysis by Al-Hawary et al confirmed that MetS is generally associated with shorter LTL, while acknowledging heterogeneity across studies due to varying measurement techniques, populations and MetS definitions.³⁶

Phenotype-level analyses emphasize that metabolic dysfunction rather than obesity itself drives telomere shortening. Molli et al showed that metabolically healthy obese women had longer telomeres compared to obese women with MetS and LTL declined in parallel with the number of metabolic abnormalities.³⁹

In the LIPIDOGEN2015 cohort, Banach et al observed shorter LTL in metabolically unhealthy participants, obese or non-obese, but these associations were attenuated when adjusted for age, sex, lifestyle, and comorbidities.⁴¹ Cheng et al reported that increasing numbers of MetS components were more strongly associated with shorter LTL in women than men, suggesting sex-specific telomere-metabolic dynamics.⁴⁰

Mendelian randomization (MR) adds complexity to the picture, reflecting a shift from purely observational associations toward a more nuanced understanding of causality in telomere - metabolic interactions. Over the past decade, evidence has evolved from cross-sectional correlations to genetic approaches that infer directionality and pleiotropy. Paradoxically, MR studies have revealed that genetically longer LTL can sometimes associate with adverse metabolic traits such as higher blood pressure or central adiposity, suggesting that telomere-lengthening mechanisms may exert tissue-specific or compensatory effects rather than universal protection.

Loh et al showed that genetically longer LTL was associated with higher waist-to-hip ratio (adjusted for BMI), elevated blood pressure and increased odds of MetS, suggesting pleiotropy in telomere-lengthening pathways that may elevate cardiometabolic risk.⁴⁵ Similarly, Codd et al reported that longer genetically predicted LTL was linked to higher

Table 1 Key Epidemiological and Longitudinal Studies Linking Telomere Length with Metabolic Syndrome and Related Cardiometabolic Phenotypes

Study	Population/Cohort	Main Exposure/Comparison	Main Outcome	Key Finding	Main Interpretation
Cross-sectional studies					
Demissie et al, 2006 ³⁷	Framingham Heart Study men	Insulin resistance, oxidative stress and hypertension	LTL	Shorter LTL was associated with insulin resistance and oxidative stress-related cardiometabolic burden	Early evidence linking adverse metabolic phenotype to shorter telomeres
Nordfjäll et al, 2008 ³⁸	MONICA Northern Sweden Study	Abdominal obesity and adverse psychosocial/metabolic factors	LTL	Increased abdominal obesity was associated with shorter telomere length	Central adiposity appears more relevant than body size alone
Iglesias Molli et al, 2017 ³⁹	Women grouped by metabolic phenotype	Metabolically healthy obesity (MHO) vs obesity with metabolic syndrome (MSO)	LTL	Women with MHO had longer telomeres than obese women with metabolic syndrome	Metabolic health may be a stronger determinant of telomere biology than obesity alone
Cheng et al, 2017 ⁴⁰	Adult population sample in the NHANES	Metabolic syndrome and sex-specific analyses	LTL	An increase in the number of MetS components was strongly associated with shorter telomere length, especially in female participants	Suggests possible gender-specific telomere-MetS relationships
Banach et al, 2024 ⁴¹	Adults from the LIPIDOGEN2015 study	Metabolic syndrome components	TL	Metabolically unhealthy obese (MUO) and non-obese with MetS (NOMS) phenotypes contribute to the shortening of telomere length	Telomere length varied across metabolic health categories rather than obesity alone
Cherkas et al, 2008 ⁴²	AdultsTwin cohort	Physical activity	LTL	Higher physical activity associated with longer telomere length	Lifestyle factors may mitigate telomere shortening and indirectly influence metabolic risk
Longitudinal studies					
Révész et al, 2015 ³⁵	Adult population from The Netherlands Study of Depression and Anxiety	Metabolic syndrome components	LTL	Metabolic dysregulations are associated with shorter telomeres over two time points	Supports a temporal link between metabolic dysfunction and telomere attrition
Verhulst et al, 2016 ⁴³	Adult twin cohort from the national Danish Twin Registry.	Baseline LT	Development of insulin resistance	Short LTL was associated with development of insulin resistance.	Suggests telomere shortening may precede metabolic deterioration
Gardner et al, 2005 ⁴⁴	Young adults from the Bogalusa Heart Study	Insulin resistance and BMI	LTL	Increasing insulin resistance and body weight were associated with accelerated telomere attrition	Reinforces insulin resistance and obesity as key drivers of biological ageing
Xiong et al, 2023 ³⁴	NHANES participants with MetS	Baseline telomere length in individuals with MetS	All-cause and cardiovascular mortality	Telomere length was associated with long-term mortality outcomes in MetS	TL may have prognostic significance beyond MetS diagnosis itself

Notes: This table summarizes representative human studies discussed in the review that examined the relationship between telomere length, particularly leukocyte telomere length (LTL), and metabolic syndrome (MetS) or related cardiometabolic traits. Studies are grouped by design to distinguish cross-sectional from longitudinal evidence and are presented with their population or cohort, principal exposure or comparison, main outcome, key finding, and overall interpretation.

blood pressure,⁴⁶ reinforcing the notion that the relationship between LTL and cardiometabolic traits is complex and may differ according to underlying genetic pathways or tissue context. In contrast, Li et al showed that higher genetically predicted BMI causally shortens LTL and accelerates epigenetic aging, supporting adiposity's causal role in telomere attrition.⁴⁷ Yang et al reported complex relations: longer telomeres associated with higher triglycerides, while higher LDL-C and apolipoprotein B predicted longer LTL, likely reflecting mediation via adiposity or inflammation.⁴⁸

These MR findings highlight the importance of investigating cell-type specificity in telomere-metabolic pathways, particularly within metabolically active tissues such as adipose, hepatic, and pancreatic cells, rather than relying solely on leukocyte measurements. Furthermore, future research should include long-term randomized controlled trials with LTL as a predefined endpoint of lifestyle or pharmacological interventions to determine whether telomere preservation directly mediates metabolic improvement and to clarify the contradictory results arising from genetic pleiotropy.

Multiple components of metabolic syndrome, particularly central adiposity, hyperglycaemia/insulin resistance and hypertension, demonstrate consistent inverse associations with LTL across observational studies^{35,37,38,40,49}. Evidence from MR analyses further supports a potential causal role for blood pressure regulation in LTL variation.^{37,46} In contrast, associations between dyslipidaemia and LTL remain inconsistent, with discordant findings reported across both observational and genetic studies.^{41,48,50}

Notably, lifestyle factors also intersect with telomere dynamics. Cherkas et al showed that in over 2400 adult twins, greater leisure-time physical activity was associated with longer LTL by approximately 200 nucleotides (equivalent to ~10 years of biological age), independent of BMI, smoking, socioeconomic status and activity at work. Even among twin pairs discordant for activity level, the more active twin had longer telomeres.⁴² This highlights that behaviour and fitness level may influence or offset the telomere-shortening effects of metabolic syndrome.

From Association to Mechanism – Linking Telomere Shortening, MetS and Obesity

The mechanistic pathways linking MetS and obesity to telomere shortening are multifactorial, interdependent and biologically complex, involving chronic systemic inflammation, oxidative stress, mitochondrial dysfunction, hormonal imbalances and genetic as well as epigenetic regulatory mechanisms. These factors act both independently and synergistically to promote telomere attrition, accelerate biological aging, and drive metabolic deterioration (Figure 1).

Importantly, these processes are not discrete but form a tightly interconnected network of mutual reinforcement. Inflammation stimulates reactive oxygen species (ROS) generation through cytokine-driven activation of NADPH oxidase, while oxidative stress in turn amplifies inflammatory signaling via redox-sensitive transcription factors such as NF-κB. Both oxidative and inflammatory stress impair mitochondrial function, leading to reduced ATP production and further ROS leakage from the electron transport chain. This establishes a self-perpetuating feedback loop in which mitochondrial dysfunction, oxidative stress and inflammation continuously amplify one another, collectively accelerating telomere attrition and cellular senescence in MetS.

MetS is characterized by a pro-inflammatory and pro-thrombotic state and is associated with increased risk of cognitive decline, frailty, type 2 diabetes (T2DM), cardiovascular disease and certain cancers, with oxidative stress (OxS) playing a central role in its pathophysiology.^{51,52} While both aging and MetS increase OxS, the imbalance induced by MetS is often more pronounced, as each component; central obesity, dyslipidemia, hypertension, and hyperglycemia, contributes to a pro-oxidative milieu.^{53–55} A cumulative association between the number of MetS components and OxS levels has been reported, suggesting a dose-response relationship.⁵⁶ The causal relationship between OxS and MetS remains debated, but it is hypothesized that a bidirectional interaction exists.⁵⁶

Oxidative Stress and Telomere Damage

Oxidative stress (OxS) in MetS arises from impaired antioxidant defenses and increased pro-oxidant activity. Elevated hydrogen peroxide (H₂O₂) downregulates superoxide dismutase (SOD) expression while stimulating interleukin-1β (IL-1β) production in peripheral mononuclear cells.⁵⁷ Excess transition metals such as iron and copper exacerbate oxidative injury and are linked to obesity, hypertriglyceridemia, low HDL, hypertension and hyperglycemia.^{58,59}

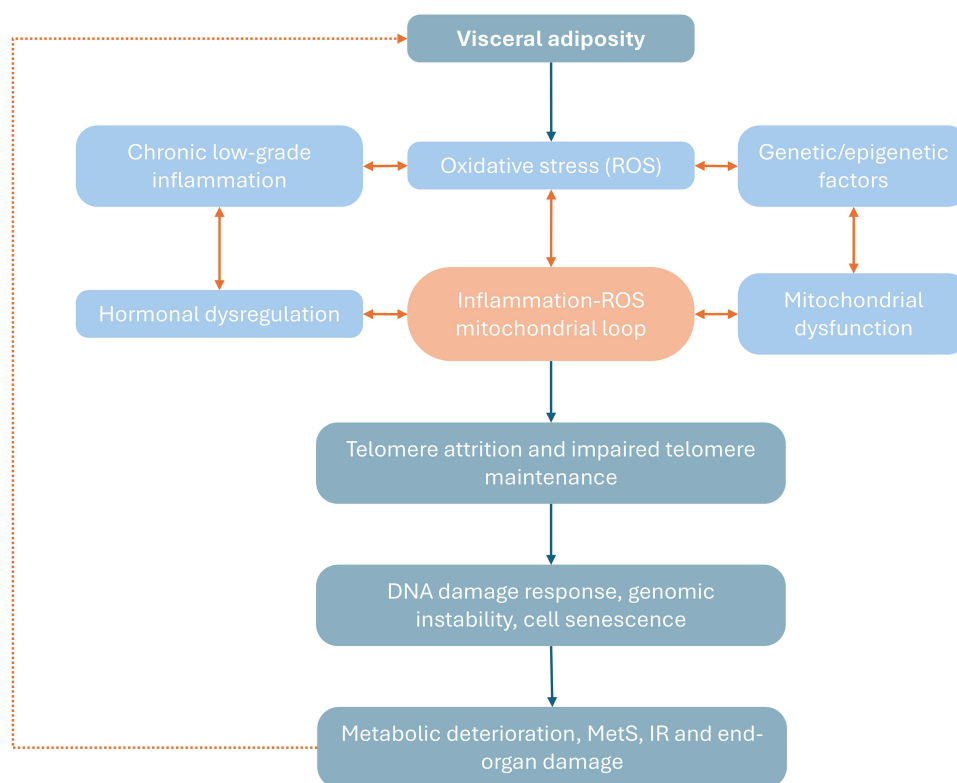


Figure 1 Pathophysiological Drivers of Telomere Attrition in Obesity and MetS. This diagram illustrates the complex bidirectional interplay between obesity and its pathophysiological drivers - chronic systemic inflammation, oxidative stress, mitochondrial dysfunction, hormonal imbalances, and genetic/epigenetic factors. These processes do not act independently but form a self-reinforcing feedback loop: inflammation stimulates reactive oxygen species (ROS) generation; oxidative stress amplifies inflammatory signalling and damages mitochondrial function; and dysfunctional mitochondria further increase ROS production, sustaining a cycle of cellular injury. This continuous interplay accelerates telomere attrition, genomic instability, and cellular senescence, thereby promoting metabolic deterioration and the development of MetS.

MetS is associated with elevated free radical production, mitochondrial dysfunction, and oxidative damage to DNA (8-oxodG), lipids (prostaglandin F_{2α}, malondialdehyde, 4-hydroxynonenal), proteins (carbonylated proteins), LDL and carbohydrates (glyoxal, methylglyoxal).^{60–65} This is compounded by reduced levels of vitamins C, E, carotenoids,^{66,67} glutathione (GSH) and diminished activities of SOD, glutathione peroxidase (GPx) and catalase (CAT).^{68,69} Telomeres, due to their guanine-rich sequences, are particularly susceptible to ROS-mediated damage and repeated oxidative insults impair telomerase activity, accelerating attrition.^{43,44}

Adipose tissue dysfunction enhances mitochondrial ROS production, driven partly by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation.^{6,70} Increased adiposity elevates lipid peroxidation markers such as 8-epi-prostaglandin F_{2α} (8-epi-PGF_{2α}), which contribute to insulin resistance. Transcriptional repression of shelterin complex components further disrupts telomere stability.⁷¹

The effects of MetS may extend across generations. In a 10-year follow-up, McAninch et al reported shorter telomeres in offspring of mothers with MetS, potentially predisposing them to chronic disease and higher mortality.^{72,73}

Some studies have paradoxically observed elevated telomerase activity in MetS,^{74,75} possibly as a compensatory response to oxidative injury, although this may still promote senescence. MetS has also been linked to increased cancer mortality in women (colorectal, breast) and higher incidence of pancreatic cancer and Hodgkin's lymphoma in men,^{76,77} suggesting shared oxidative and telomere-related pathways.

Chronic Inflammation

Chronic low-grade inflammation in obesity is a key driver of telomere attrition. Visceral adipose tissue functions as an active endocrine and immune organ, secreting pro-inflammatory cytokines such as TNF- α , IL-6 and C-reactive protein (CRP), which accelerate telomere shortening via increased immune cell turnover and direct DNA damage.⁷⁸

Chronic inflammation may both cause and be exacerbated by telomere dysfunction. For instance, inflammatory cytokines activate nuclear factor kappa B (NF- κ B), which can alter telomerase reverse transcriptase (TERT) gene⁷⁹ activity; conversely, telomere-binding proteins like RAP1 influence NF- κ B signaling, creating a feedback loop between telomere integrity and inflammatory pathways.^{80–83}

Insulin Resistance, Hormonal Imbalance and Metabolic Dysregulation

MetS is characterised by interconnected metabolic and hormonal perturbations that converge on shared pathways driving telomere attrition. Central to this process is insulin resistance, a core feature of obesity and MetS, which promotes sustained hyperglycaemia, hyperinsulinaemia, endothelial dysfunction, and mitochondrial stress, thereby accelerating telomere erosion.⁷⁸

Chronic dysglycaemia is associated with increased oxidative stress, reflected by elevated triglycerides, LDL-C, malondialdehyde, and oxidative DNA damage markers such as 8-hydroxy-2'-deoxyguanosine, alongside reduced anti-oxidant enzyme activity.⁸⁴ Telomeric DNA, enriched in guanine residues, is particularly vulnerable to oxidative damage.

Oxidative stress also mechanistically links metabolic dysregulation with hypertension, acting through redox-sensitive vascular signalling, increased superoxide ($O_2^{\bullet-}$) production, angiotensin II activation, and endothelin-mediated vasoconstriction.^{85,86} These shared pathways reinforce the overlap between cardiometabolic dysfunction and telomere shortening.

Hormonal abnormalities further modulate telomere biology. Reduced growth hormone secretion in obesity impairs lipolysis, antioxidant capacity, and telomere maintenance, contributing to increased cardiometabolic risk.^{87,88} Insulin-like growth factor-1 exhibits context-dependent effects, with chronic elevation potentially promoting telomere attrition, while reduced levels in advanced obesity may impair tissue repair.⁸⁹ Elevated fibroblast growth factor-21 reflects target-tissue resistance, attenuating its mitochondrial-protective and telomerase-supporting actions.^{90,91}

Together, these data support a unifying model in which insulin resistance, oxidative stress, vascular dysfunction, and hormonal dysregulation act synergistically to accelerate telomere shortening in MetS.

Genetic and Epigenetic Regulation

TL is influenced by genetic loci identified in genome-wide association studies (GWAS), including telomerase RNA component (TERC), TERT and Oligonucleotide/Oligosaccharide-Binding Fold Containing 1 (OBFC), which encode components of the telomerase complex and telomere-stabilising proteins.⁹² Epigenetic mechanisms, such as subtelomeric DNA methylation, histone modifications, and non-coding RNA regulation further modulate telomerase accessibility and shelterin function. Dysregulation of these processes may link environmental and metabolic stress to premature telomere shortening.⁹³

Importantly, genetic predisposition may confound observed associations between LTL and metabolic syndrome, while metabolically driven epigenetic alterations provide a plausible mechanism through which environmental exposures characteristic of MetS accelerate telomere attrition, reinforcing the interaction between inherited susceptibility and metabolic stress.

Mitochondrial Dysfunction and Cellular Senescence

Mitochondria are essential for cell survival, primarily through ATP production via the electron transport chain, during which reactive oxygen species (ROS), including superoxide radicals ($O_2^{\bullet-}$) are inevitably generated. This ROS production predominantly occurs at complexes I (NADH ubiquinone oxidoreductase) and III (ubiquinol-cytochrome c oxidoreductase) of the mitochondrial inner membrane.⁹⁴

Under normal physiological conditions, ROS function as secondary messengers in various signaling pathways that regulate homeostasis, growth and development in aerobic organisms. However, oxidative stress (OxS) arises when there is an imbalance between ROS production and antioxidant defenses, with ROS levels exceeding the capacity of antioxidant systems.⁶

During electron transport, $O_2^{\bullet-}$ generated by the mitochondria can react with transition metals such as Fe^{3+} to form hydrogen peroxide (H_2O_2). Together, $O_2^{\bullet-}$ and H_2O_2 can produce hydroxyl radicals ($\bullet OH$) through Fenton and Haber-Weiss reactions.⁹⁵

Highly reactive species such as $\bullet\text{OH}$ and singlet oxygen ($^1\text{O}_2$) can damage DNA, forming adducts like thymine glycol and 8-hydroxy-2'-deoxyguanosine (8-OHdG). The $\bullet\text{OH}$ radical reacts with the C8 position of guanine to form 8-OHdG, which can further undergo keto-enol tautomerism to form 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG), which is considered the most abundant oxidative injury^{96,97} (Figure 2).

Beyond inflammation and oxidative stress, mitochondrial dysfunction, often observed in obese and insulin-resistant individuals, also contributes to telomere damage. Damaged mitochondria release excessive ROS and activate pro-apoptotic and senescence pathways, which in turn impair telomerase function and cellular repair capacity. Telomere shortening itself may trigger DNA damage responses (DDR), leading to cell cycle arrest, senescence or apoptosis, especially in metabolically active tissues such as liver, adipose and muscle. This may contribute to organ-level metabolic dysfunction and the progression of MetS.^{74,98}

Dietary Effects on Telomere Length and Interacting Metabolic Pathways

Nutritional patterns play a pivotal role in modulating TL through their influence on oxidative stress, inflammation, metabolic regulation and adiposity. Emerging evidence indicates that certain dietary profiles, particularly those rich in antioxidants, anti-inflammatory nutrients and phytochemicals, are associated with longer telomeres and delayed cellular aging.

Mediterranean Diet and Telomere Maintenance

The Mediterranean diet (MedDiet), characterized by high consumption of fruits, vegetables, legumes, whole grains, olive oil and fish, has been consistently associated with reduced telomere attrition.⁹⁹ This dietary pattern provides omega-3 fatty acids, polyphenols and vitamins C and E, which mitigate reactive oxygen species (ROS) production and systemic inflammation, both key mediators of telomere shortening.

A systematic review and meta-analysis by Canudas et al (2020) pooled data from eight cross-sectional studies (n≈13,733) across five countries and found that MedDiet adherence correlates with lower insulin resistance and improved

Evidence linking leukocyte telomere length with metabolic syndrome and cardiometabolic traits

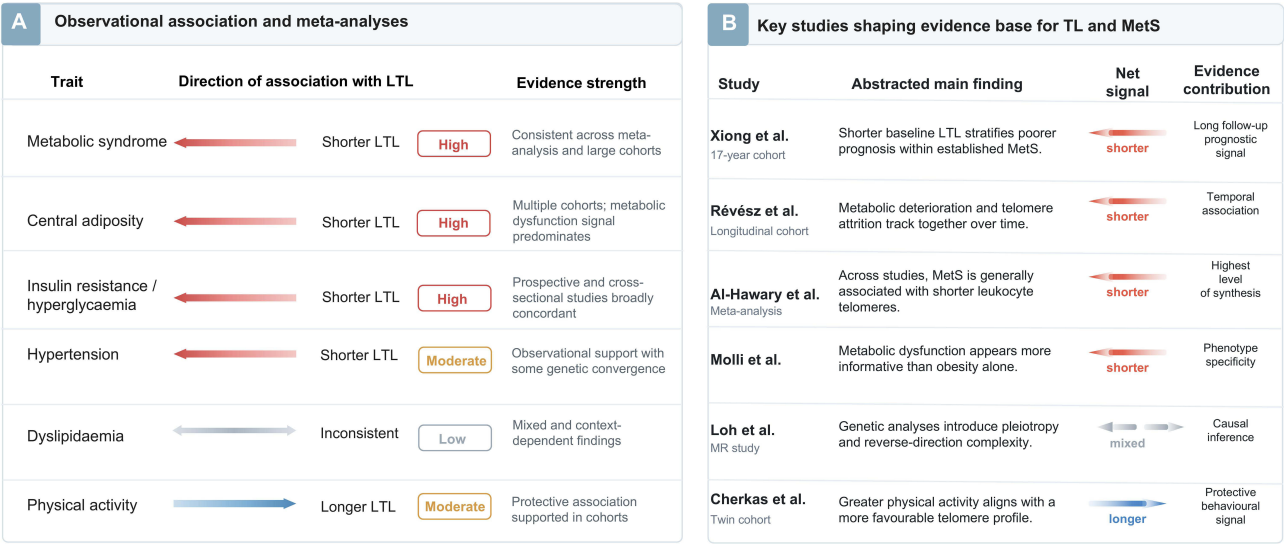


Figure 2 Evidence linking leukocyte telomere length with metabolic syndrome and cardiometabolic traits. **(A)** summarizes the overall direction and strength of association between leukocyte telomere length (LTL) and major metabolic syndrome (MetS)-related traits based on the reviewed literature. MetS, central adiposity, insulin resistance or hyperglycemia, and hypertension are predominantly associated with shorter LTL, whereas dyslipidemia shows inconsistent or context-dependent associations, and physical activity is associated with longer LTL. Arrow color and direction indicate the prevailing direction of association, and the adjacent evidence labels summarize the overall strength and consistency of the supporting literature. **(B)** highlights key studies that shape the evidence base for the LTL-MetS relationship and abstracts their principal contribution. Longitudinal and prognostic studies support the view that shorter baseline LTL tracks with metabolic deterioration and poorer outcomes within established MetS, meta-analytic synthesis supports an overall association between MetS and shorter LTL, phenotype-stratified studies suggest that metabolic dysfunction may be more informative than obesity alone, Mendelian randomization studies introduce genetic complexity including pleiotropy and possible reverse-direction effects, and twin data support a protective association between physical activity and a more favorable telomere profile. Together, these findings indicate that shorter LTL is most consistently linked to adverse metabolic dysfunction and prognosis, while genetic and lipid-related associations remain more heterogeneous and mechanistically complex.

lipid profiles, which may further preserve LTL by reducing metabolic stress.⁹⁹ This suggests that anti-inflammatory and antioxidant components of the diet may mediate telomere protection.

Plant-Based Diets, Micronutrients and Telomere Health

Crous-Bou et al (2019) compiled evidence that plant-rich dietary patterns, rich in antioxidants like carotenoids, flavonoids and vitamins, are plausibly linked to longer telomeres via reduced oxidative stress and inflammation.¹⁰⁰

Micronutrients such as magnesium, selenium, folate and zinc, along with vitamin D, contribute to genomic stability and DNA repair, potentially safeguarding telomeres from accelerated erosion.¹⁰⁰

Importantly, plant-rich diets are also associated with lower BMI and visceral fat, both of which are independent predictors of telomere attrition. Visceral adiposity, through its pro-inflammatory and lipotoxic effects, enhances immune cell turnover and telomere damage, underscoring the importance of maintaining a healthy weight through dietary means.¹⁰⁰

Oxidative Balance, Diet and Telomere Length

The Oxidative Balance Score (OBS), a composite index reflecting dietary and lifestyle factors that influence oxidative stress, has been proposed as a valuable measure for evaluating redox status. Higher OBS, reflecting greater antioxidant intake and lower pro-oxidant exposure (eg, saturated fats, processed meats).¹⁰¹

Zhang et al used the Oxidative Balance Score (OBS) and found that higher OBS was positively associated with longer LTL in women in the NHANES 1999–2002 cohort.¹⁰¹ This supports the hypothesis that diets rich in natural antioxidants can offset oxidative telomeric damage and promote genomic stability.

Furthermore, it was demonstrated that individuals with both poor oxidative balance and metabolic dysfunction, including dysglycemia and obesity, had the shortest telomeres, suggesting that the interplay between diet quality and metabolic status is critical in telomere biology.¹⁰¹

Dietary Patterns, Metabolism and Inflammation: A Vicious Cycle

Paul (2011) emphasized that diets high in refined carbohydrates, saturated fats and ultra-processed foods can accelerate telomere shortening through mechanisms involving insulin resistance, inflammation and oxidative stress; conversely, dietary restriction and low-glycaemic diets may enhance telomerase activity and slow telomere attrition.¹⁰² Moreover, exercise synergizes with diet in modulating telomere biology. Physical activity enhances mitochondrial function, reduces adipose inflammation and improves insulin sensitivity, all factors that mitigate oxidative and inflammatory stress. Thus, diet and exercise together exert compounding benefits, especially when targeting central obesity and dysglycemia.^{101,102}

Overall, dietary composition modulates oxidative stress and inflammation, both of which are shaped by, and in turn influence, adiposity and glucose homeostasis. Poor diet combined with sedentary behavior facilitates visceral fat accumulation, insulin resistance and increased oxidative burden, accelerating LTL loss. In contrast, antioxidant-rich, plant-based dietary patterns, particularly when coupled with regular physical activity, support LTL preservation and may delay the onset of metabolic diseases and age-related decline^{99–102} (Figure 3).

Clinical Implications and Therapeutic Strategies

The recognition that telomere shortening is intricately linked to the pathophysiology of metabolic syndrome (MetS) and obesity carries important clinical implications. Telomere attrition not only reflects cumulative metabolic and oxidative stress but may also serve as an early biomarker for biological aging, cardiometabolic risk stratification and therapeutic response monitoring. While routine LTL testing in clinical care remains limited by assay variability and the need for longitudinal validation, LTL may serve as an adjunct biomarker for identifying individuals at higher risk of MetS-related complications and for monitoring intervention responses.

Lifestyle interventions have the strongest evidence for modulating telomere biology. Beyond the metabolic benefits already discussed, adherence to antioxidant-rich dietary patterns such as the Mediterranean diet is positively associated with LTL, as shown in a meta-analysis of ~13,700 participants by Canudas et al, where higher MedDiet adherence correlated with longer telomeres, particularly in women.⁹⁹ Plant-forward diets rich in anti-inflammatory nutrients show similar associations,¹⁰⁰ while higher Oxidative Balance Scores (OBS) are linked to longer LTL in population cohorts, with the shortest telomeres observed in those with poor oxidative balance and metabolic dysfunction.¹⁰¹

Dietary patterns, metabolic dysregulation and inflammatory pathways influencing telomere dynamics

Diet, inflammation and metabolic pathways relevant to telomere shortening

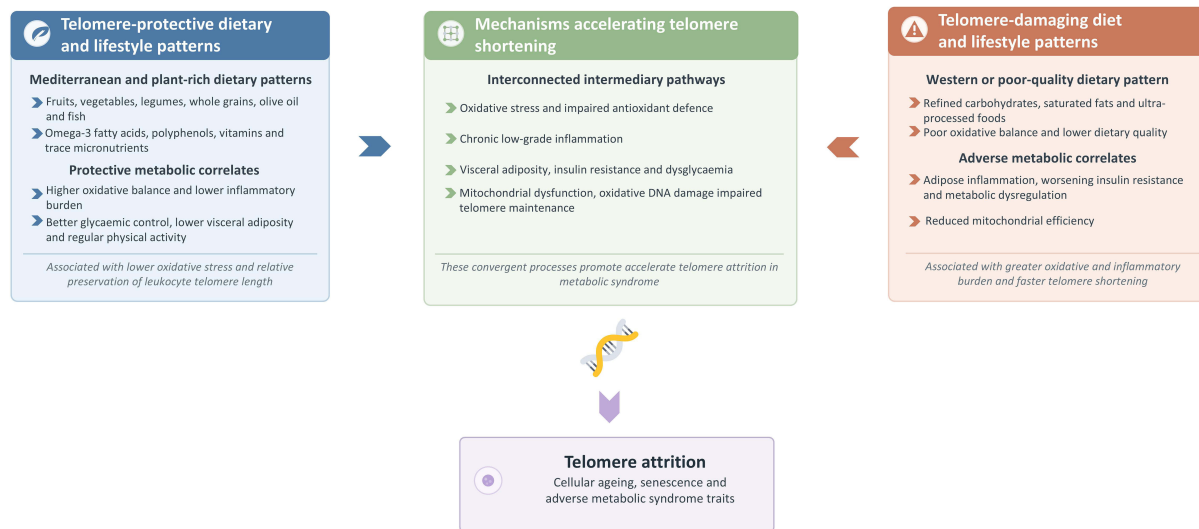


Figure 3 Dietary patterns, metabolic dysregulation and mechanistic pathways influencing telomere dynamics in metabolic syndrome. This figure summarizes how diet and lifestyle may modulate leukocyte telomere length through interconnected metabolic and inflammatory pathways. Telomere-protective patterns, including Mediterranean and plant-rich diets, favorable oxidative balance, regular physical activity, improved glycemic control, and lower visceral adiposity, are associated with reduced oxidative stress and chronic inflammation, improved metabolic homeostasis, and relative preservation of telomere length. In contrast, telomere-damaging exposures, including Western or poor-quality dietary patterns rich in refined carbohydrates, saturated fats, and ultra-processed foods, together with sedentary behavior and metabolic dysregulation, promote oxidative stress, chronic low-grade inflammation, visceral adiposity, insulin resistance, impaired mitochondrial function, and reduced antioxidant defense. These interacting processes converge on oxidative DNA damage, impaired telomere maintenance, and accelerated telomere attrition, thereby contributing to cellular senescence, biological ageing, and adverse metabolic syndrome traits. The figure reflects the integrated evidence reviewed linking dietary quality, inflammation, metabolic dysfunction, and telomere biology.

Physical activity exerts synergistic effects with diet on telomere protection. In a large twin cohort, by Cherkas et al, greater leisure-time activity was linked to longer LTL.⁴² Comprehensive programs combining diet, exercise, stress management and social support increased telomerase activity at 3 months and were associated with relative telomere lengthening at 5 years.^{103,104} A 3-year lifestyle trial using an energy-reduced Mediterranean diet plus physical activity slowed telomere shortening in older adults.¹⁰⁵

Weight-loss interventions, including bariatric surgery, have also shown LTL increases in prospective cohorts¹⁰⁶ and modest gains in randomized trials.¹⁰⁷

Pharmacologic strategies that improve metabolic health may have indirect benefits on telomere dynamics. Statins have been linked to changes in telomerase activity and telomere damage markers in cardiometabolic risk groups.^{108,109} Metformin shows telomere-stabilizing effects in preclinical vascular aging models.¹¹⁰ Mitochondria-targeted antioxidants such as MitoQ have counteracted telomere shortening and extended fibroblast lifespan under oxidative stress in vitro,¹¹¹ though human evidence is lacking.

Although direct human data are limited, preclinical and cellular evidence indicates that glucagon-like peptide-1 receptor agonists (GLP-1 RAs) may indirectly protect telomeres by mitigating oxidative stress, suppressing inflammation, and delaying cellular senescence. As reviewed by Peng et al, GLP-1 RAs enhance antioxidant capacity, down-regulate pro-inflammatory cytokines and activate DNA-repair pathways, collectively supporting genomic stability and potentially slowing telomere attrition.¹¹² In a non-human primate model, adolescent plasma GLP-1 levels positively predicted adult LTL, suggesting an adaptive mechanism during development.¹¹³ In human retinal endothelial cells exposed to hyperglycemia, liraglutide increased telomerase activity, upregulated SIRT1 and reduced the expression of senescence markers p53 and p21.¹¹⁴ Experimentally, GLP-1 RA exenatide enhanced DNA base-excision repair via upregulation of APE1 and improved cellular resilience through Sirtuin-1, PPAR γ and PGC-1 α pathways.¹¹⁵

While these findings are biologically compelling, they remain scientifically plausible rather than clinically actionable. The available evidence for a direct telomere-preserving effect of GLP-1 RAs or other pharmacologic agents, including metformin, statins, and mitochondria-targeted antioxidants, is confined to experimental and animal studies. Robust human trials confirming causality or clinical benefit are still lacking. Thus, these agents should be viewed as potential modulators of telomere biology rather than established therapeutic tools.

In contrast, lifestyle modification remains the only strategy with consistent, direct human evidence for influencing LTL. Adherence to antioxidant-rich dietary patterns such as the Mediterranean diet, regular physical activity, sustained weight reduction and stress-management practices have been reproducibly associated with slower telomere attrition or even length maintenance across prospective cohorts and randomized lifestyle interventions.^{42,103–105} Beyond telomere effects, these behaviours confer well-validated cardiometabolic benefits, underscoring their primacy in prevention and treatment of MetS.

From a translational perspective, significant barriers prevent routine clinical use of LTL measurement. Common assays, including quantitative PCR, flow-FISH, and Southern blot, show inter-laboratory variability and lack harmonized reference standards. The absence of population-specific cut-offs defining “short” telomeres, together with assay cost and limited availability, restricts clinical feasibility. Moreover, LTL is not yet a validated therapeutic target; interventions cannot presently be titrated or monitored based on telomere dynamics. Accordingly, LTL should be regarded as a promising research biomarker reflecting cumulative metabolic and oxidative stress, rather than a diagnostic or treatment endpoint.

Continued methodological standardization, inclusion of telomere metrics as prespecified outcomes in long-term randomized trials and deeper exploration of tissue-specific telomere biology will be essential to clarify whether telomere preservation directly mediates cardiometabolic benefit and to determine when, if ever, LTL assessment will become clinically actionable.

Conclusions, Implications for Practice, and Directions for Future Research

MetS is increasingly recognized not only as a cluster of cardiometabolic risk factors but also as a state of accelerated biological ageing. The evidence reviewed here indicates that shorter LTL is broadly associated with MetS and several of its major components. These associations are supported by substantial observational and meta-analytic evidence, while mechanistic studies provide biological plausibility through convergent roles for oxidative stress, chronic low-grade inflammation, mitochondrial dysfunction, hormonal perturbation, and dysregulation of telomere-maintenance pathways. MR studies also indicate that the relationship is not uniformly linear and may be influenced by pleiotropy, pathway-specific effects, and tissue context, underscoring that telomere biology in MetS is more complex than a simple model of progressive shortening alone.

This synthesis has important implications for current understanding of the field. First, it supports the view that telomere dynamics may reflect the cumulative burden of metabolic and inflammatory stress rather than serving merely as a passive marker of chronological ageing. Second, it suggests that metabolic dysfunction, rather than obesity in isolation, may be the more biologically relevant determinant of telomere attrition, helping to refine interpretation of heterogeneous findings across obesity and MetS phenotypes. Third, it places telomere biology within a broader pathophysiological framework linking adiposity, dysglycaemia, vascular dysfunction, oxidative injury, and cellular senescence. In this sense, telomere length may be better conceptualized at present as an integrative biomarker of systemic metabolic stress than as a standalone mechanistic endpoint.

From a clinical perspective, however, the current evidence does not support routine use of LTL measurement in the diagnosis, prognostication, or treatment monitoring of MetS. Major barriers remain, including inter-assay variability, lack of harmonized methodology, uncertain comparability across laboratories, absence of validated population-specific thresholds, and limited understanding of how leukocyte-based measurements relate to telomere dynamics in metabolically active tissues. Furthermore, although shorter LTL has been associated with adverse outcomes within MetS, it has not yet been established that measuring telomere length adds clinically meaningful predictive value beyond conventional risk factors or that modifying telomere dynamics directly improves patient outcomes. Accordingly, LTL should currently be regarded as a promising research biomarker rather than a clinically actionable test.

Nonetheless, the reviewed evidence is relevant to practice in a broader translational sense. The literature consistently indicates that adverse telomere profiles cluster with central adiposity, insulin resistance, chronic inflammation, oxidative stress, and sedentary behaviour, reinforcing the concept that chronic metabolic dysfunction exerts cumulative biological damage extending beyond traditional biochemical endpoints. In contrast, lifestyle modification remains the intervention domain with the strongest human evidence for favourable telomere associations. Mediterranean and plant-rich dietary patterns, improved oxidative balance, regular physical activity, sustained weight reduction, and multidomain lifestyle interventions have all been associated with longer LTL or slower telomere attrition. While these findings do not justify telomere-guided clinical decision-making, they strengthen the rationale for intensive lifestyle-based prevention and management of MetS and support the broader principle that interventions targeting metabolic health may also mitigate cellular ageing processes.

The review also highlights several priorities for future research. Standardization of telomere length measurement and reporting should be a major methodological priority, including improved assay harmonization, quality control, and clearer guidance on interpretation of effect sizes across platforms. Large prospective studies with repeated telomere measurements are needed to clarify temporality and to determine whether telomere shortening precedes metabolic deterioration, accompanies it, or reflects its cumulative consequences. Future work should also move beyond leukocyte-based analyses wherever feasible and investigate telomere dynamics in adipose tissue, liver, skeletal muscle, pancreas, and vascular tissues, where metabolic dysfunction is biologically expressed more directly. Better phenotypic resolution will be equally important, particularly in distinguishing metabolically healthy from metabolically unhealthy obesity, characterizing visceral and ectopic adiposity more precisely, and integrating inflammatory and endocrine profiles into analyses of telomere dynamics.

Randomized controlled trials should prospectively incorporate telomere endpoints when evaluating lifestyle and pharmacological interventions relevant to MetS. Although several agents, including metformin, statins, glucagon-like peptide-1 receptor agonists, and mitochondria-targeted antioxidants, show biologically plausible telomere-related effects in experimental systems, robust human evidence remains insufficient. Prospective trials are therefore needed not only to assess whether such interventions influence telomere dynamics, but also to establish whether any telomere-related changes correspond to meaningful metabolic or vascular benefit. Finally, integrative studies combining deep phenotyping with genomics, epigenomics, transcriptomics, and functional experimentation will be required to resolve the apparent contradictions in MR findings and to determine whether telomere biology can improve causal inference, risk stratification, or therapeutic target discovery in MetS.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Author Contributions

Kyle Cilia: Conceptualization, Methodology, Writing – original draft. Zachary Gauci: Conceptualization, Methodology, Writing – original draft. Rachel Agius: Conceptualization, Writing - review and editing, Supervision. Stephen Fava: Conceptualization, Writing - review and editing, Supervision. Nikolai P Pace: Writing - review and editing, Visualization, Supervision, Project administration. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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