Received: 18 July 2023 | Accepted: 16 October 2023

DOI: 10.1002/agm2.12273

REVIEW ARTICLE

Aging Medicine Open Access WILEY

A pathological convergence theory for non-communicable diseases

Alicia Padrón-Monedero

National School of Public Health, Institute of Health Carlos III, Madrid, Spain

Correspondence
Alicia Padrón-Monedero, National School of Public Health, Institute of Health Carlos III, C/ Monforte de Lemos 5, 28029, Madrid, Spain.
Email: a.padronm@isciii.es

Abstract

The current paradigm considers the study of non-communicable diseases (NCDs), which are the main causes of mortality, as individual disorders. Nevertheless, this conception is being solidly challenged by numerous remarkable studies. The clear fact that the mortality, by virtually all NCDs, tends to cluster at old ages (with the exception of congenital malformations and certain types of cancer, among a few others); makes us intuitive to assume that the common convergence mechanism that exponentially increases mortality by almost all NCDs in older ages is cell aging. Moreover, when we study NCDs, we are not analyzing which disorders cause the mortality of the populations, rather that which disorders kill us before others do, because the aging of the individuals causes inevitably their death by one cause or another. This is not a defeatist perspective, but a challenging and efficient one. These intuitive assumptions have been supported by studies from the pathophysiologic, epidemiologic, and genetic fields, leading to the affirmation that, as NCDs share genetic and pathophysiological mechanisms (derived from mostly the same risk factors), they should no longer be considered independently. Those studies should make us reconsider our current conceptions of studying NCDs as individual disorders, and to hypothesize about a paradigm that would consider most NCDs (cancer, neurological pathologies, cardiovascular diseases, type II diabetes mellitus, chronic respiratory diseases, osteoarthritis, and osteoporosis, among others) different manifestations of the same process: the cell aging.

KEYWORDS
age-related diseases, aging, inflammation, non-communicable diseases, radical oxidative species

1 | THE PATOPHYSIOLOGIC PERSPECTIVE

We commonly consider age as proxy of aging, but depending on our genetic background and the type and amount of risk factors at which we have been exposed throughout life, that finally determined our metabolic history, these two concepts could differ substantially.[1,2] In fact, some biomarkers could assess our biological age that may differ from our chronological one.[2,3]

This article presents independent research. The views expressed are those of the author(s) and not necessarily of the Instituto de Salud Carlos III.

Aging is considered a multifactorial process characterized by a loss of integrity and efficiency of physiological and biochemical processes that occur after the reproductive age,[4,5] leading to functional alterations and the development of diseases related to aging, that include most non-communicable diseases (NCDs),[5–7] and ultimately to cell death.[4]

Moreover, the fact that main risk factors are shared mostly by the main age-related NCDs[8,9]; could suggest the convergence of its pathogenesis on limited pathophysiological[2,7,10–12] and genetic[7,13] mechanisms that could be related to cell aging and be mediators between risk factors and NCDs (Figure 1). Specifically, it has been suggested that NCDs could be considered the consequence of the same molecular alterations, eventually oxidative stress (OS) and inflammation, that are additionally interconnected with each other[12,14,15] and determine aging in different tissues and organs.[2,3,14,16,17]

In this line, it has been described that inflammaging, (age-associated inflammation)[2,18,19] is one of the main pillars of aging[2] that additionally increases OS.[3,4,10,12,15,17,19–23] In turn, OS has proven to increase inflammation.[3,12,15,19,20,23–27] Thus, inflammation and OS maintain a vicious cycle and this media of inflammation/oxidation damages proteins, lipids, and DNA[10,12,20] and are related to most NCDs.[10,12,15,23]

Additionally, and conjoined to inflammaging, other sources, if sustained, may increase chronic inflammatory levels and thus accelerate the aging process. These factors include persistent microbial infections,[2,19,23] cell debris,[2] alterations in gut microbiota,[2] altered/misplaced proteins,[2] toxic chemicals,[23] radiation,[23] pollutants,[10,28–30] allergens,[23] alcohol consumption,[23] tobacco consumption,[18,23,31,32] stress,[18] depression,[18] sedentary lifestyle,[9] decrease of sex hormones,[18] unhealthy and/or high calorie diet,[9,18,23,32,33] and obesity.[10,21,23,24,32,34,35] Moreover, obesity is related to metaflammation and shares same mechanisms than inflammaging.[2] This could be explained by the fact that obesity produces inflammatory molecules and cytokines[24,32,35] and is related to adipose tissue macrophage infiltration.[18,24,35] Interestingly, the relation between obesity and inflammation is suggested to be due to visceral fat, that increases with aging, rather than to subcutaneous fat.[18,24,32,36] Additionally, the excess of energy could increase glucose and fatty acid metabolisms that in turn increase chronic low-grade inflammation, whereas caloric restriction reduces inflammatory levels.[10,24] Those aforementioned factors, by increasing chronic sterile inflammation that alters organ and tissues homeostasis,[2] are suggested to be among the main risk factors for age-related NCDs (Figure 1).[2,18,23]

On the other hand, the theory of aging based on free radical OS[3,4,17] describes the physiological basis of the aging process mainly related to the production of reactive species, which its most important representatives are the ones derived from oxygen, called reactive oxygen species (ROS).[4]

To survive, we need energy as ATP that is produced, in a greater extent, in a process called oxidative phosphorylation, carried out inside the mitochondria through the electron transport chain (ETC) with the fundamental participation of oxygen in the aerobic metabolism. Oxygen is acceptor of electrons at the end of the ETC, and mostly ends reacting with hydrogen to produce water. This process is basic for the survival of our cells; thus, its alteration affects all organs and systems. During aerobic metabolism, in normal circumstances, a small percentage of electrons (0.1–3% depending on the source) are inefficiently transported to oxygen and end up forming ROS.[3,4,26,29,37] ROS have an unpaired electron in their molecular outer orbit which makes them prone to react with adjacent molecules.[3,5] ROS can also be produced by numerous sources[5] like responses to: (a) external stimuli (air pollutants,[7,17,19,28,29,38] chemotherapeutics,[38]

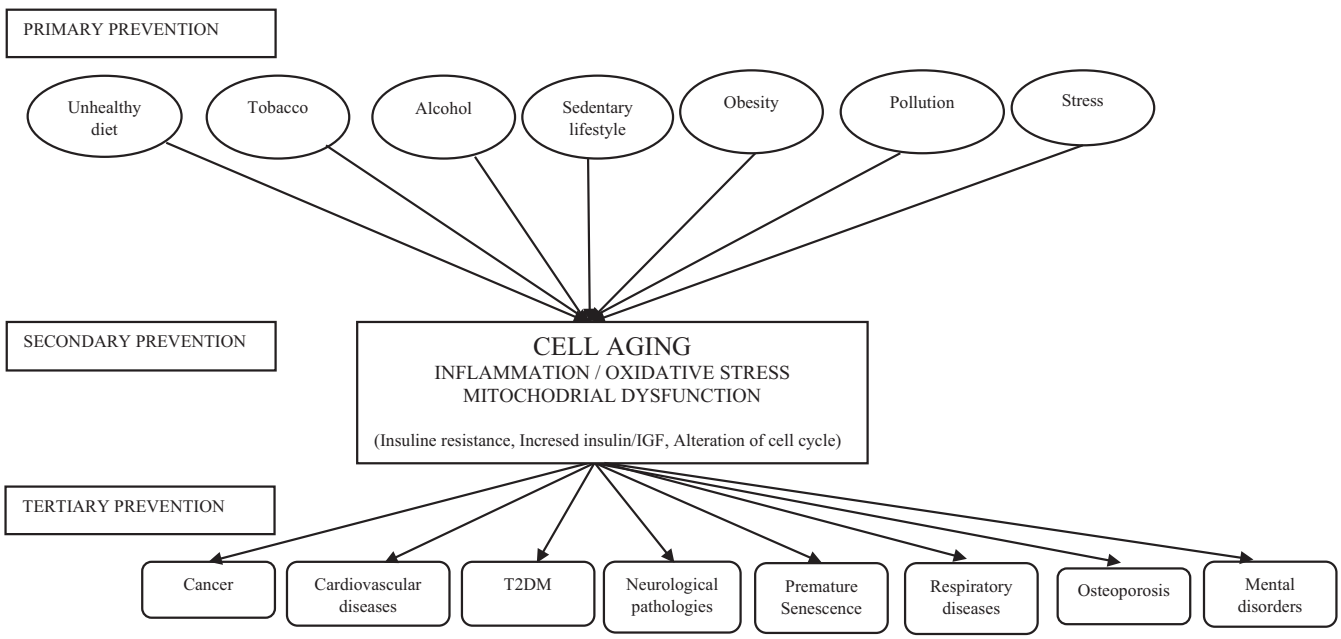

FIGURE 1 Convergence of non-communicable diseases pathogenesis on a summary of pathophysiological pathways related to cell aging. T2DM, type 2 diabetes mellitus.

ultraviolet light,[38] ionizing radiation,[7,17,38] cigarette smoke,[7,17,29,32] unhealthy/hyper caloric diet,[29,33,39] obesity[29,40] (that appears to increase OS independently of hypergycemia[41]), chronic infections,[10] (and in general by any stressor causing tissue damage[17]; Figure 1); (b) and by other endogenous sources (NADPH oxidases, cytochrome P450s,[38] xanthine oxidases, and nitric oxide synthases, among others[12,29]).

Anyhow, mitochondrial ETC is the major origin of ROS generation[5,17,29] by producing 92% of free radicals.[1]

Small levels of ROS are needed for processes related to energy metabolism, defense against infections, and cell signaling.[4,5,12,20,23,26,38] Although, the increase of ROS to levels that damage cell physiology and structure, is disruptive and it is called OS.[3,5,17,23,26,29] ROS lesions DNA, lipids, and proteins and accumulates over time.[3–5,17,37] Moreover, ROS formation in the mitochondria increases with age[37] until normal repair mechanisms are overwhelmed,[3,5] it induces cell senescence[4] and, altogether with chronic inflammation,[2,42] it becomes a main determinant of age-associated diseases.[4,5,15]

It is interesting to highlight that in humans, by measuring urinary markers, it has been quantified by the oxidative DNA damage, which is inversely associated to longevity.[4] Moreover, oxidative DNA damage does not only depend on the basal metabolic rate[4] but also on its repair mechanisms (that appear to decrease with age[1,4]). Additionally, decreased levels of oxidative markers are associated to some behavioral factors, like caloric restriction without malnutrition[4,10] and possibly to dietary antioxidants.[3,5] Nevertheless, antioxidant supplementation has not provided successful remarkable results in health outcomes,[29,43] what has been called the antioxidant paradox.[12] A possible hypothesis for the antioxidant paradox could be the entangled relation and coexistence between OS and chronic inflammation, that fuel each other and may require treatments that target both pathways simultaneously.[12]

Both nuclear and mitochondrial DNA control the ETC that is essential for energy matabolism.[37] The DNA most affected by ROS is the mitochondrial DNA[3,7,29] and the ROS related mitochondrial damages accumulate over time and they are associated to mitochondrial dysfunction (MD).[3,17,44] Thus, mitochondria is both a producer[42,45–47] and a target of ROS[3,20,29,43,46,48] and inflammation,[6,16,46,49] in a self-perpetuating vicious circle.[29,43,46,49,50] Additionally, obesity is associated to inflammation,[2,34–36] OS,[29,40,41,44] mitochondrial damage and dysfunction,[25,29,40] and premature aging.[40] Moreover, a hyper caloric diet overloads the mitochondria resulting in MD[25,29] and increases the accumulation of ROS[29,34] and chronic inflammation[2,36] that perpetuate MD.[20,29,46]

In turn, MD does not only increase ROS and inflammation levels,[42,45–47] but it is also associated to calcium and glucose homeostasis[37] and alterations in apoptosis.[40] Finally, MD is related to numerous NCDs (neurodegenerative pathologies, type II diabetes mellitus [T2DM] and cancer,[37] among others). Interestingly, T2DM is three times more frequently transmitted by the mother (the parent that transmits her mitochondria to the off springs) than by the father[51] and in centenarians longevity appears to be transmitted from the maternal branch of the family.[52]

It is important to highlight that MD is considered a major mechanism for insulin resistance (IR)[44,50] altogether with inflammation[24,34,36,44,50] and ROS.[41,50] The subsequent IR, and the following increased levels of insulin and insulin-like growth factor (IGF) are associated with numerous NCDs (T2DM, cardiovascular diseases, neurodegenerative disorders, cancer, and autoimmune diseases, among others)[53]; thus, they could be considered relevant mediators of the former physiological pathways.

As closure, there is physiological evidence of the role of ROS and chronic inflammation in the etiopathogenesis of NCDs, and both mechanisms usually coexist.[3,12,20,23,48] ROS (or related OS) is associated to the pathogenesis of: cancer,[4,5,17,22,23,26] cardiovascular diseases,[4,5,7,17,21,29] chronic pulmonary disorders,[7,23,54] T2DM,[4,7,17,50] increased aging,[4,17,23,26] osteoporosis,[38] neurodegenerative diseases,[4,5,7,17,46] certain mental disorders,[55] and eventually to cell death.[17]

On the other hand, chronic inflammation has also been associated to the pathogenesis of most NCDs,[18,42] including cancer,[18,23,32,56,57] cardiovascular diseases,[5,18,21,32,36,44,58–60] chronic pulmonary diseases,[61] T2DM,[24,32,34–36,44] neurological diseases,[18,19,32,46] certain mental disorders,[32,59,62] osteoporosis,[18,58] rheumatoid arthritis,[18] and also to frailty,[18] and an increased risk of mortality.[18]

In summary, inflammation and oxidative stress are mostly interconnected through a vicious self-perpetuating circle,[3,12,22,23] both are closely related to MD,[3,14,16,43,46,49,50] and contribute to the development of most NCDs (Figure 2).[11,15,33]

2 | THE GENETIC PERSPECTIVE

The pathological convergence theory is coherent with the following genetic data:

First, altogether with chronic inflammation and OS, the shortening of telomeres is considered a basic underlying mechanism of cell aging.[7,63,64] These factors are interdependent and synergistic.[42,64]

It has also been assessed that cell aging is determined by the modification of genes expression as we get older.[1] However, even though gene expression can be modified by numerous endogenous and exogenous factors, its major determinant is the telomere[1] that can modify the expression of nearby and distal genes.[65]

Telomeres maintain genomic integrity, but they decrease with each cell division that also alters proteins around them.[1] This decreased telomere length plays a critical role in aging[64,65] and it appears to be associated with age-related NCDs[7,65–67] (cancer,[65] cardiovascular diseases,[7,28,63,65,67] and neurodegeneration[7,65]), including mental disorders[68] and life expectancy.[65,66,69]

Nevertheless, telomere length has not always had a straight linear association with chronological age.[70] In fact, physical activity[9,65] and antioxidant diet[9,65] are associated with preserved telomere length. On the other hand, risk factors, such as obesity[40] and chronic stress,[42,64,71] among other environmental factors,[28,61,66] are associated to shorter telomere length. Moreover, pathologies that cause chronic inflammation, like periodontitis, are also associated

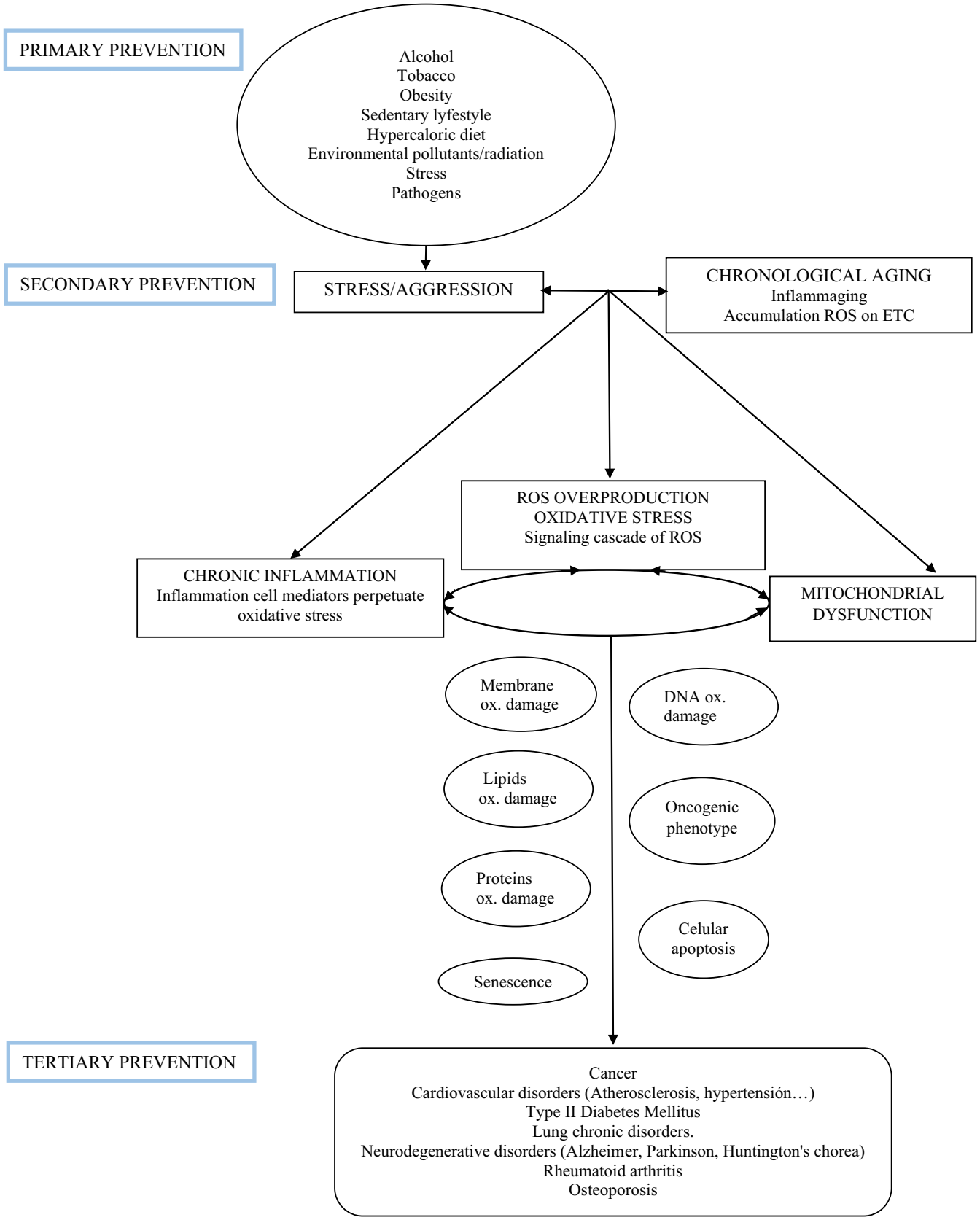

FIGURE 2 Summary of pathophysiological pathways between risk factors and NCDs. Prevention levels. ETC, electron transport chain; NCDs, non-communicable diseases; ROS, reactive oxygen species.

with shorter telomere length.[72] Likewise, inflammation markers and OS have been associated with a shortening of telomeres[19,42,64] and they appear to generate a vicious circle that leads to an increased aging and age-related NCDs.[42]

Second, low-grade inflammation through IGF1/insulin signaling could downregulate the expression of genes that appear to increase life expectancy and decrease age-related NCDs.[10] Additionally, it has been assessed that some genes related to inflammatory and OS responses and IGF1/insulin signaling, appear to present different polymorphisms in centenarians compared to younger individuals.[73] Interestingly, the genetic polymorphism of those genes may produce different health outcomes at younger than in older ages.[52,73,74]

Third, as epigenetic mechanisms may produce metabolic memory,[29,75,76] the long-term expression of genes can vary depending on our lifestyle[29] (including environmental exposures and diet, among other factors[22]). Specifically, hyperglycemia can activate the inflammatory and OS metabolic pathways in the long term[75] through epigenetic mechanisms. Interestingly, caloric restriction (30–50% reduction of normal amount of calories intake) inhibits GHRH-GH-IGF/insulin[77] (a possible inflammatory pathway[10]) and appears to reduce the incidence of age-related NCDs in mammals.[10] Moreover, Catalase-NAD^+–Sirtuin overexpression by caloric restriction could increase longevity in mammals[77] by regulating cell processes related to inflammation and ROS.[76] Additionally, the OS and a proinflammatory state can induce aberrant epigenetic regulation linked to NCDs.[22] Finally, as some detrimental epigenetic changes may be irreversible over time,[75] it would be interesting to assess the timing in which they become irreversible; which detrimental epigenetic modifications could be reversible, and to further analyze the external and modifiable factors that may increase the long-term expression of genes that benefit our survival and health.

Fourth, different diseases are highly connected genetically. Goh et al.[78] suggested that disease nodes are related with gene nodes and this network of NCDs tends to cluster in groups sharing the same pathophysiology.[78] In addition, Yang et al. assessed that nearly 80% of different disease pairs significantly share the same coexpression of genes, like T2DM with allergic asthma and chronic kidney disease,[13] and they suggested that the relation between different diseases could be explained by common dysfunctional regulation mechanisms that may determine a common etiology and pathophysiology.[13]

3 | THE PERSPECTIVE OF THE THEORY OF EVOLUTION

Human biology has always had an efficient purpose, because the evolution selected the best options for survival. Then, why do our bodies develop metaflammation, high ROS production, and IR if they accelerate cell aging and are associated to the pathogenesis of NCDs?

The *Homo Sapiens*, that we know as human being, exists since 315,000 years ago. All this time, it evolved to select those individuals more fitted to the environmental conditions they were living in. Those conditions included: high exposure to infectious diseases, limited food resources, high risk of mortality at delivery and by predators, and lack of proper medical assistance. For the survival of the species, the evolution focused on selecting those individuals more fitted to survive until they reached the reproductive stage (the one that matters in evolutionary terms). Thus, the physiology of our cells has prepared to face the almost always permanent exposure to infectious diseases and shortage of food.[2,34]

During the last century, in most of our planet, we changed abruptly the external conditions in which our cells learned to function. The protection from communicable diseases (CDs) and the more than sufficient access to food resources, have reduced our mortality by CDs and starvation, but have placed the physiology of our cells in conditions that they never faced before. Thus, they manage this situation poorly and, with the increase of life expectancy, their evolutionary learned physiologic behavior, make us more prone to die from NCDs.

The physiology of our cells, that has adapted to the external conditions present during 315,000 years, functions by: (1) increasing the immune response after the ingestion of any nourishment (postprandial inflammation)[2] because of the high prevalence of infectious microorganisms in food and water; as it has been assessed that gut inflammations can activate and imprint specific neurons that, when later stimulated, can trigger inflammatory responses[79,80]; (2) increasing the immune response to face any healing process and/or infection, even though it becomes chronic and leads to OS,[10,14] because a deficient healing process was a more urgent and hazardous health problem than a future NCD after the reproductive age (a life period not relevant in evolutionary terms); (3) increasing IR either after a sustained overstimulation of the insulin pathway, presumably by pathogens in its need to take up glucose,[34] or after any chronic inflammation,[2] with the possible objective of decreasing intracellular glucose levels, so the infectious microorganisms will not have energy resources for its replication[2,34]; (4) producing ROS that help our defense cells to kill pathogenic microorganisms[4,5,14]; and (5) and to increase energy storage (as adipose tissue) for the individual to be prepared for the, more than likely, periods of starvation,[2] probably in the same way that low birth weight newborns develop higher IGF-1 levels in adolescence to compensate and catch up with growth; however, the subsequent IGF-1 axis long-term programming leads to T2DM and hypertension.[53] If the fats stored are not used because of a sustained hypercaloric diet, the subsequent obesity might cause IR,[21,24,35,36,44] MD,[29,40] inflammation,[21,24,35,36,44] and OS[40,41,44]; that are related to cell aging and to most NCDs. One possible reason for the generation of metaflammation by adipose tissue could be that if the body has enough resources to prevent starvation to be an urgent hazard, it can afford to dedicate some resources to be prepared for the high risk of infections. This hypothesis is supported by the fact that malnourishment states are associated to immunosuppression[34] (possibly caused by a decreased production of leptin by adypocites[34]). Moreover, activation of acute phase

response (APR) against infections, depends on the mobilization of energy sources (mainly lipoid ones)[34] for an increased lipidic delivery to immune cells, and a direct neutralization of microorganisms by lipoproteins.[81] The APR may protect from acute injuries/infections but, if maintained, there is a suppression of the insulin signaling anabolic pathway[34] and an increase in atherogenesis,[81] inflammation,[34] and oxidation.[34] Additionally, the close relation between metabolic and immune pathways,[34] in line with our hypothesis, is also supported by the fact that adipocytes and immune cells, like macrophags,[35] share properties, functions,[2,34,35] genetic transcription factors,[34,35] and, in some cases, a same cellular origin (macrophages from white adipose tissue could derive from preadipocytes).[34,35] Moreover, macrophages can accumulate lipids and become foam cells in the atherosclerotic plaque.[34]

In summary, knowing the physiologic evolution of our cells may be relevant in NCDs research. It would be of interest to consider the field of human evolutionary biology[82]; within a Darwinian-evolutionary framework, for an evolutionary theory of aging in NCDs research.[73] Thus, by comprehending the past evolution of our cells, we could understand its current functioning and try to predict its future adaptation to the foreseeable changes in the environment.

4 | THE EPIDEMIOLOGIC PERSPECTIVE

The pathological convergence theory is coherent with the following epidemiological data:

First, as it is generally known, mortality increases exponentially with age until the point that all individuals die. According to the records, the person that lived longer was Jeanne Louise Calment that died at 122 years old.[14] The uneven distribution of mortality with the roughly asymptotic relation between age and mortality until an apparent age limit for the human race (in the current environmental circumstances), it is in line with our hypothesis that age (as a rough proxy of cell aging) is the main convergence mechanism that leads to most NCDs and ultimately and inevitably to death.

Second, NCDs aggregate in older people.[83–88] It has been described that roughly half of the population 50 years and older has between ≥ 2[89] and ≥ 5 NCDs[84] and the probability of NCDs multimorbidity increases remarkably with age[83–86] and obesity.[83,86] These data are consistent with the hypothesis that NCDs share pathophysiological mechanisms[85,87] that appear to be related to aging. Additionally, the aggregation of NCDs has been associated to an increased risk of mortality.[90]

Third, one risk factor is usually related to more than one NCD (stress,[91] unhealthy and/or hypercaloric diet,[8,9,53] obesity,[8,10,40,92] tobacco,[8,31,53] alcohol consumption,[93] environmental pollutants,[10,28,94] radiation,[95] and sedentary lifestyle[8,9]). Likewise, an NCD is usually related to more than one risk factor[8] (cancer,[8,31,92,93,96] cardiovascular diseases,[8,29,31,93] chronic pulmonary diseases,[9,31,92,96] neurological disorders,[93,97] T2DM,[8,53,92,96] arthritis,[92,98] and premature senescence,[9] among others). Moreover, usually there is a mid to long latency period between the exposure to risk factors and the development of NCDs (for example, the average lag time between smoking and the development of lung cancer is 30–40 years[96]). According to our hypothesis, this latency period corresponds to the increased cell aging caused by the risk factor that ends up with the development of NCDs at a younger chronological age than a person not exposed to the risk factor. This hypothesis is in line with the life course approach to chronic disease epidemiology.[96] The fact that some risk factors have higher impact in specific NCDs (for example, tobacco and lung cancer, and alcohol consumption and digestive diseases), it is reasonable to assume that it could be related to multiple factors, like the stage of life when they occurred (including intra utero exposures),[96] the sex,[96] the clustering of different risk factors,[96] the accumulation,[96] the lag time for the development of the disease,[96] and possibly to other factors like a direct exposure of the risk factor to the specific tissue, the dose, the bioavailability, the aggressivity, and the tissue specific susceptibility among others; in a similar way as a same pathophysiologic mechanism[60] and/or a same genetic alteration[99] may have different pathogenic responses depending on the organ in which they arise.[60,99]

Fourth, it has been assessed that the main NCDs are associated between them.[10,22,54,100,101] This fact is in line with our hypothesis that NCDs share common pathophysiologic pathways.[60] For example, it has been shown that there is an association between cardiovascular risk and osteoporosis even after adjusting for age.[58] Additionally, both share the same risk factors (tobacco, low physical activity, and vitamin D deficiency) and same pathophysiological mechanisms (OS, inflammation, and dyslipidemia).[58] Nevertheless, it has been suggested that the associations between some NCDs could be related to shared physiological pathways (like inflammatory changes and/or OS) independently of some of their shared risk factors.[54,58,101,102] There have also been assessed associations between cardiovascular and respiratory diseases,[100–102] rheumatoid arthritis and cardiovascular diseases,[103] chronic obstructive pulmonary disease (COPD) and lung cancer,[54] and T2DM and cancer,[22,104] among other NCDs.

Fifth, it has been assessed that primary prevention of risk factors is beneficial for improving health outcomes in studies in different age groups[6]; although it is recommended to initiate it at an early age.[6] For example, in the case of smoking, some health benefits could be most significant if quitting before 50 years old,[105] the impact of its amount on the risk of COPD appears to be higher at younger ages[106] and also the excess of risk for some NCDs appears to remain higher a long time after quiting,[107,108] although it is lower than for current smokers.[106] Thus, future studies should further analyze whether the clear benefit on health outcomes of the primary prevention of modifiable risk factors may have different impact depending on the age group, among other factors. Additionally, NCDs generally have mid to long latency periods[96] and a long prodromal stage (with changes in inflammatory and oxidative activity)[33]; moreover, some epigenetic modifications that contribute to the initiation of an NCD could be irreversible.[75]

Furthermore, in older populations, the association between inflammatory and/or oxidative markers and cardiovascular disease appears to be independent of some traditional risk factors.[18,109,110] Thus, for older people, it could be of interest to analyze the combination of necessary and effective primary and secondary classical prevention programs[6,8] with the development of additional prevention programs that could be beneficial on reducing or curbing the physiological decline related to aging[18,111] on an individual basis[33]; because it has been suggested that combining interventions targeting cell aging mechanisms with disease-specific approaches may result in more than additive health benefits.[112]

5 | CONCLUSIONS

Evidence obtained from the genetic, pathophysiologic, and epidemiologic approaches allow us to conceive and understand the nature of NCDs on an integral way as different facets of the same process: cell aging, and the convergence of the aggressions that represent the main risk factors in some limited pathophysiologic pathways (eventually related to inflammation and oxidative stress). Future studies should provide more evidence about the potential health benefits of combining the effective measures of addressing each risk factor and each NCD, with interventions targeting cell aging mechanisms, on an individual basis.

AUTHOR CONTRIBUTIONS

A.P.M. formulated the research question and conceived the study design, analyzed the data, wrote the manuscript, and critically reviewed and approved the final manuscript.

ACKNOWLEDGMENTS

I acknowledge Dr. I. Noguer Zambrano, Dr. P. Fantidis, Dr. E. Castellon Leal, and Frank J Arleth for their different contributions to this study.

FUNDING INFORMATION

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

The author declares no relevant financial or non-financial interests to disclose.

DATA AVAILABILITY STATEMENT

Not Applicable.

ETHICS STATEMENT AND PATIENT CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

ORCID

Alicia Padrón-Monedero https://orcid.org/0000-0002-0709-5757

REFERENCES

1. Anton B, Vitetta L, Cortizo F, Sali A. Can we delay aging? The biology and science of aging. *Ann N Y Acad Sci*. 2005;1057:525-535. doi:10.1196/annals.1356.040
2. Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. *Nat Rev Endocrinol*. 2018;14(10):576-590. doi:10.1038/s41574-018-0059-4
3. Martínez de Toda I, Ceprián N, Díaz-Del Cerro E, De la Fuente M. The role of immune cells in Oxi-Inflamm-aging. *Cell*. 2021;10(11):2974. doi:10.3390/cells10112974
4. Valko M, Leibfritz D, Moncol J, Cronin MTD, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. *Int J Biochem Cell Biol*. 2007;39(1):44-84. doi:10.1016/j.biocel.2006.07.001
5. Rahman K. Studies on free radicals, antioxidants, and co-factors. *Clin Interv Aging*. 2007;2(2):219-236.
6. Corina A, Abrudan MB, Nikolic D, et al. Effects of aging and diet on cardioprotection and cardiometabolic risk markers. *Curr Pharm des*. 2019;25(35):3704-3714. doi:10.2174/1381612825666191105111232
7. Milic M, Frustaci A, Del Bufalo A, et al. DNA damage in non-communicable diseases: a clinical and epidemiological perspective. *Mutat Res*. 2015;776:118-127. doi:10.1016/j.mrfmmm.2014.11.009
8. Eyre H, Kahn R, Robertson RM. ACS/ADA/AHA collaborative writing committee. Preventing cancer, cardiovascular disease, and diabetes: a common agenda for theAmerican cancer society, the American Diabetes Association, and the American Heart Association. *CA Cancer J Clin*. 2004;54(4):190-207. doi:10.3322/canjclin.54.4.190
9. Caprara G. Mediterranean-type dietary pattern and physical activity: the winning combination to counteract the rising burden of non-communicable diseases (NCDs). *Nutrients*. 2021;13(2):429. doi:10.3390/nu13020429
10. Probst-Hensch NM. Chronic age-related diseases share risk factors: do they share pathophysiological mechanisms and why does that matter? *Swiss Med Wkly*. 2010;140:w13072. doi:10.4414/smw.2010.13072
11. Camps J, García-Heredia A. Introduction: oxidation and inflammation, a molecular link between non-communicable diseases. In: Camps J, ed. *Oxidative Stress and Inflammation in Non-Communicable Diseases–Molecular Mechanisms and Perspectives in Therapeutics*. Vol 824. Advances in Experimental Medicine and Biology. Springer International Publishing; 2014:1-4. doi:10.1007/978-3-319-07320-0_1
12. Biswas SK. Does the interdependence between oxidative stress and inflammation explain the antioxidant paradox? *Oxid Med Cell Longev*. 2016;2016:5698931. doi:10.1155/2016/5698931
13. Yang J, Wu SJ, Dai WT, Li YX, Li YY. The human disease network in terms of dysfunctional regulatory mechanisms. *Biol Direct*. 2015;8:60. doi:10.1186/s13062-015-0088-z
14. De la Fuente M, Miquel J. An update of the oxidation-inflammation theory of aging: the involvement of the immune system in oxi-inflamm-aging. *Curr Pharm des*. 2009;15(26):3003. doi:10.2174/138161209789058110
15. Leyane TS, Jere SW, Houreld NN. Oxidative stress in ageing and chronic degenerative pathologies: molecular mechanisms involved in counteracting oxidative stress and chronic inflammation. *Int J Mol Sci*. 2022;23(13):7273. doi:10.3390/ijms23137273
16. Picca A, Lezza AMS, Leeuwenburgh C, et al. Fueling Inflamm-aging through mitochondrial dysfunction: mechanisms and

molecular targets. *Int J Mol Sci*. 2017;18(5):E933. doi:10.3390/ijms18050933
17. Willcox JK, Ash SL, Catignani GL. Antioxidants and prevention of chronic disease. *Crit Rev Food Sci Nutr*. 2004;44(4):275-295. doi:10.1080/10408690490468489
18. Singh T, Newman AB. Inflammatory markers in population studies of aging. *Ageing Res Rev*. 2011;10(3):319-329. doi:10.1016/j.arr.2010.11.002
19. Li X, Li C, Zhang W, Wang Y, Qian P, Huang H. Inflammation and aging: signaling pathways and intervention therapies. *Signal Transduct Target Ther*. 2023;8(1):239. doi:10.1038/s41392-023-01502-8
20. Federico A, Morgillo F, Tuccillo C, Ciardiello F, Loguercio C. Chronic inflammation and oxidative stress in human carcinogenesis. *Int J Cancer*. 2007;121(11):2381-2386. doi:10.1002/ijc.23192
21. Matsuda M, Shimomura I. Roles of oxidative stress, adiponectin, and nuclear hormone receptors in obesity-associated insulin resistance and cardiovascular risk. *Horm Mol Biol Clin Investig*. 2014;19(2):75-88. doi:10.1515/hmbci-2014-0001
22. Crujeiras AB, Díaz-Lagares A, Carreira MC, Amil M, Casanueva FF. Oxidative stress associated to dysfunctional adipose tissue: a potential link between obesity, type 2 diabetes mellitus and breast cancer. *Free Radic Res*. 2013;47(4):243-256. doi:10.3109/10715762.2013.772604
23. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: how are they linked? *Free Radic Biol Med*. 2010;49(11):1603-1616. doi:10.1016/j.freeradbiomed.2010.09.006
24. Ye J, Keller JN. Regulation of energy metabolism by inflammation: a feedback response in obesity and calorie restriction. *Aging (Albany NY)*. 2010;2(6):361-368. doi:10.18632/aging.100155
25. Camps J, García-Heredia A, Hernández-Aguilera A, Joven J. Paraoxonases, mitochondrial dysfunction and non-communicable diseases. *Chem Biol Interact*. 2016;259(Pt B):382-387. doi:10.1016/j.cbi.2016.04.005
26. Fang J, Seki T, Maeda H. Therapeutic strategies by modulating oxygen stress in cancer and inflammation. *Adv Drug Deliv Rev*. 2009;61(4):290-302. doi:10.1016/j.addr.2009.02.005
27. Kim JM, Lee EK, Park G, et al. Morin modulates the oxidative stress-induced NF-kappaB pathway through its anti-oxidant activity. *Free Radic Res*. 2010;44(4):454-461. doi:10.3109/10715761003610737
28. Martens DS, Nawrot TS. Air pollution stress and the aging phenotype: the telomere connection. *Curr Environ Health Rep*. 2016;3(3):258-269. doi:10.1007/s40572-016-0098-8
29. Niemann B, Rohrbach S, Miller MR, Newby DE, Fuster V, Kovacic JC. Oxidative stress and cardiovascular risk: obesity, diabetes, smoking, and pollution: part 3 of a 3-part series. *J Am Coll Cardiol*. 2017;70(2):230-251. doi:10.1016/j.jacc.2017.05.043
30. Elbarbary M, Oganesyan A, Honda T, et al. Systemic inflammation (C-reactive protein) in older Chinese adults is associated with long-term exposure to ambient air pollution. *Int J Environ Res Public Health*. 2021;18(6):3258. doi:10.3390/ijerph18063258
31. U.S. Department of Health and Human Services. Smoking Cessation: A Report of the Surgeon General— Executive Summary. 2020. Accessed October 6, 2023 https://www.hhs.gov/sites/default/files/2020-cessation-sgr-executive-summary.pdf
32. Shmerling R, Watson S, Underwood A, Netherton R, Crouse J, Dellenbaugh S. *Fighting Inflammation how to Stop the Damage before it Compromises your Health. Special Health Report*. Harvard Health Publishing; 2020.
33. Seyedsadjadi N, Grant R. The potential benefit of monitoring oxidative stress and inflammation in the prevention of non-communicable diseases (NCDs). *Antioxidants (Basel)*. 2020;10(1):E15. doi:10.3390/antiox10010015
34. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. *J Clin Invest*. 2005;115(5):1111-1119. doi:10.1172/JCI25102
35. Bastard JP, Maachi M, Lagathu C, et al. Recent advances in the relationship between obesity, inflammation, and insulin resistance. *Eur Cytokine Netw*. 2006;17(1):4-12.
36. Esposito K, Giugliano D. The metabolic syndrome and inflammation: association or causation? *Nutr Metab Cardiovasc Dis*. 2004;14(5):228-232. doi:10.1016/s0939-4753(04)80048-6
37. Enns GM. The contribution of mitochondria to common disorders. *Mol Genet Metab*. 2003;80(1–2):11-26. doi:10.1016/j.ymgme.2003.08.009
38. Filaire E, Toumi H. Reactive oxygen species and exercise on bone metabolism: friend or enemy? *Joint Bone Spine*. 2012;79(4):341-346. doi:10.1016/j.jbspin.2012.03.007
39. Saha SK, Lee SB, Won J, et al. Correlation between oxidative stress, nutrition, and cancer initiation. *Int J Mol Sci*. 2017;18(7):1544. doi:10.3390/ijms18071544
40. Niemann B, Chen Y, Teschner M, Li L, Silber RE, Rohrbach S. Obesity induces signs of premature cardiac aging in younger patients: the role of mitochondria. *J Am Coll Cardiol*. 2011;57(5):577-585. doi:10.1016/j.jacc.2010.09.040
41. Furukawa S, Fujita T, Shimabukuro M, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. *J Clin Invest*. 2004;114(12):1752-1761. doi:10.1172/JCI21625
42. Zhang J, Rane G, Dai X, et al. Ageing and the telomere connection: an intimate relationship with inflammation. *Ageing Res Rev*. 2016;25:55-69. doi:10.1016/j.arr.2015.11.006
43. Dias IHK, Milic I, Heiss C, et al. Inflammation, lipid (per)oxidation, and redox regulation. *Antioxid Redox Signal*. 2020;33(3):166-190. doi:10.1089/ars.2020.8022
44. Cipriani-Thorne E, Quintanilla A. Diabetes mellitus tipo 2 y resistencia a la insulina. *Rev Med Hered*. 2010;21(3):160-171.
45. Giuliani A, Prattichizzo F, Micolucci L, Ceriello A, Procopio AD, Rippo MR. Mitochondrial (Dys) function in inflammaging: Do MitomiRs influence the energetic, oxidative, and inflammatory status of senescent cells? *Mediators Inflamm*. 2017;2017:2309034. doi:10.1155/2017/2309034
46. Videira PAQ, Castro-Caldas M. Linking glycation and glycosylation with inflammation and mitochondrial dysfunction in Parkinson's disease. *Front Neurosci*. 2018;12:381. doi:10.3389/fnins.2018.00381
47. Shimada K, Crother TR, Karlin J, et al. Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. *Immunity*. 2012;36(3):401-414. doi:10.1016/j.immuni.2012.01.009
48. Yang L, Chen Y, Liu Y, et al. The role of oxidative stress and natural antioxidants in ovarian aging. *Front Pharmacol*. 2020;11:617843. doi:10.3389/fphar.2020.617843
49. Cicalese SM, da Silva JF, Priviero F, Webb RC, Eguchi S, Tostes RC. Vascular stress signaling in hypertension. *Circ Res*. 2021;128(7):969-992. doi:10.1161/CIRCRESAHA.121.318053
50. Kitada M, Ogura Y, Monno I, Koya D. Sirtuins and type 2 diabetes: role in inflammation, oxidative stress, and mitochondrial function. *Front Endocrinol (Lausanne)*. 2019;10:187. doi:10.3389/fendo.2019.00187
51. Ballinger SW, Shoffner JM, Hedaya EV, et al. Maternally transmitted diabetes and deafness associated with a 10.4 kb mitochondrial DNA deletion. *Nat Genet*. 1992;1(1):11-15. doi:10.1038/ng0492-11
52. Capri M, Salvioli S, Monti D, et al. Human longevity within an evolutionary perspective: the peculiar paradigm of a post-reproductive genetics. *Exp Gerontol*. 2008;43(2):53-60. doi:10.1016/j.exger.2007.06.004
53. Melnik BC. Permanent impairment of insulin resistance from pregnancy to adulthood: the primary basic risk factor of chronic Western diseases. *Med Hypotheses*. 2009;73(5):670-681. doi:10.1016/j.mehy.2009.04.047

54. Boots AW, Haenen GRMM, Bast A. Oxidant metabolism in chronic obstructive pulmonary disease. *Eur Respir J Suppl*. 2003;46:14s-27s. doi:10.1183/09031936.03.00000403a
55. Schiavone S, Colaianna M, Curtis L. Impact of early life stress on the pathogenesis of mental disorders: relation to brain oxidative stress. *Curr Pharm des*. 2015;21(11):1404-1412. doi:10.2174/1381612821666150105143358
56. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell*. 2010;140(6):883-899. doi:10.1016/j.cell.2010.01.025
57. Gonda TA, Tu S, Wang TC. Chronic inflammation, the tumor microenvironment and carcinogenesis. *Cell Cycle*. 2009;8(13):2005-2013. doi:10.4161/cc.8.13.8985
58. den Uyl D, Nurmohamed MT, van Tuyl LH, Raterman HG, Lems WF. (sub)clinical cardiovascular disease is associated with increased bone loss and fracture risk; a systematic review of the association between cardiovascular disease and osteoporosis. *Arthritis Res Ther*. 2011;13(1):R5. doi:10.1186/ar3224
59. Makkar H, Reynolds MA, Wadhawan A, Dagdag A, Merchant AT, Postolache TT. Periodontal, metabolic, and cardiovascular disease: exploring the role of inflammation and mental health. *Pteridines*. 2018;29(1):124-163. doi:10.1515/pteridines-2018-0013
60. Ross R. Atherosclerosis–an inflammatory disease. *N Engl J Med*. 1999;340(2):115-126. doi:10.1056/NEJM199901143400207
61. Barnes PJ. Mechanisms of development of multimorbidity in the elderly. *Eur Respir J*. 2015;45(3):790-806. doi:10.1183/09031936.00229714
62. Schrock JM, McDade TW, Carrico AW, D'Aquila RT, Mustanski B. Traumatic events and mental health: the amplifying effects of pretrauma systemic inflammation. *Brain Behav Immun*. 2021;98:173-184. doi:10.1016/j.bbi.2021.08.208
63. de Almeida AJPO, Ribeiro TP, de Medeiros IA. Aging: molecular pathways and implications on the cardiovascular system. *Oxid Med Cell Longev*. 2017;2017:7941563. doi:10.1155/2017/7941563
64. Lin J, Epel E. Stress and telomere shortening: insights from cellular mechanisms. *Ageing Res Rev*. 2022;73:101507. doi:10.1016/j.arr.2021.101507
65. Gruber HJ, Semeraro MD, Renner W, Herrmann M. Telomeres and age-related diseases. *Biomedicine*. 2021;9(10):1335. doi:10.3390/biomedicines9101335
66. Tedone E, Arosio B, Gussago C, et al. Leukocyte telomere length and prevalence of age-related diseases in semisupercentenarians, centenarians and centenarians' offspring. *Exp Gerontol*. 2014;58:90-95. doi:10.1016/j.exger.2014.06.018
67. Mehta SR, Iudicello JE, Lin J, et al. Telomere length is associated with HIV infection, methamphetamine use, inflammation, and comorbid disease risk. *Drug Alcohol Depend*. 2021;221:108639. doi:10.1016/j.drugalcdep.2021.108639
68. Pousa PA, Souza RM, Melo PHM, et al. Telomere shortening and psychiatric disorders: a systematic review. *Cell*. 2021;10(6):1423. doi:10.3390/cells10061423
69. Pavanello S, Campisi M, Grassi A, et al. Longer leukocytes telomere length predicts a significant survival advantage in the elderly TRELONG cohort, with short physical performance battery score and years of education as Main determinants for telomere elongation. *JCM*. 2021;10(16):3700. doi:10.3390/jcm10163700
70. Hodes RJ. Telomere length, aging, and somatic cell turnover. *J Exp Med*. 1999;190(2):153-156. doi:10.1084/jem.190.2.153
71. Weng NP. Telomere and adaptive immunity. *Mech Ageing Dev*. 2008;129(1–2):60-66. doi:10.1016/j.mad.2007.11.005
72. Nguyen LM, Chon JJ, Kim EE, Cheng JC, Ebersole JL. Biological aging and periodontal disease: analysis of NHANES (2001-2002). *JDR Clin Trans Res*. 2021;7:145-153. doi:10.1177/2380084421995812
73. Franceschi C, Olivieri F, Marchegiani F, et al. Genes involved in immune response/inflammation, IGF1/insulin pathway and response to oxidative stress play a major role in the genetics of human longevity: the lesson of centenarians. *Mech Ageing Dev*. 2005;126(2):351-361. doi:10.1016/j.mad.2004.08.028
74. DeVito LM, Barzilai N, Cuervo AM, et al. Extending human healthspan and longevity: a symposium report. *Ann N Y Acad Sci*. 2022;1507(1):70-83. doi:10.1111/nyas.14681
75. Wegner M, Neddermann D, Piorunska-Stolzmann M, Jagodzinski PP. Role of epigenetic mechanisms in the development of chronic complications of diabetes. *Diabetes Res Clin Pract*. 2014;105(2):164-175. doi:10.1016/j.diabres.2014.03.019
76. Intine RV, Sarras MP. Metabolic memory and chronic diabetes complications: potential role for epigenetic mechanisms. *Curr Diab Rep*. 2012;12(5):551-559. doi:10.1007/s11892-012-0302-7
77. Bao Q, Pan J, Qi H, et al. Aging and age-related diseases–from endocrine therapy to target therapy. *Mol Cell Endocrinol*. 2014;394(1–2):115-118. doi:10.1016/j.mce.2014.07.005
78. Goh KI, Choi IG. Exploring the human diseasome: the human disease network. *Brief Funct Genomics*. 2012;11(6):533-542. doi:10.1093/bfgp/els032
79. Brea D, Veiga-Fernandes H. Inflammation in the gut is encoded by neurons in the brain. *Nature*. 2022;10:217-218. doi:10.1038/d41586-021-03802-x
80. Koren T, Yifa R, Amer M, et al. Insular cortex neurons encode and retrieve specific immune responses. *Cell*. 2021;184(24):5902-5915.e17. doi:10.1016/j.cell.2021.10.013
81. Khovidhunkit W, Kim MS, Memon RA, et al. Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host. *J Lipid Res*. 2004;45(7):1169-1196. doi:10.1194/jlr.R300019-JLR200
82. Muehlenbein M. *Human Evolutionary Biology*. Cambridge Uniersity Press; 2010. doi:10.1017/CBO9780511781193
83. Kyprianidou M, Panagiotakos D, Faka A, Kambanaros M, Makris KC, Christophi CA. Prevalence of multimorbidity in the Cypriot population; a cross-sectional study (2018-2019). *PloS One*. 2020;15(10):e0239835. doi:10.1371/journal.pone.0239835
84. Fortin M, Bravo G, Hudon C, Vanasse A, Lapointe L. Prevalence of multimorbidity among adults seen in family practice. *Ann Fam Med*. 2005;3(3):223-228. doi:10.1370/afm.272
85. Chidumwa G, Maposa I, Corso B, et al. Identifying co-occurrence and clustering of chronic diseases using latent class analysis: cross-sectional findings from SAGE South Africa wave 2. *BMJ Open*. 2021;11(1):e041604. doi:10.1136/bmjopen-2020-041604
86. Arokiasamy P, Uttamacharya U, Jain K, et al. The impact of multimorbidity on adult physical and mental health in low- and middle-income countries: what does the study on global ageing and adult health (SAGE) reveal? *BMC Med*. 2015;13:178. doi:10.1186/s12916-015-0402-8
87. Garin N, Koyanagi A, Chatterji S, et al. Global multimorbidity patterns: a cross-sectional, population-based, multi-country study. *J Gerontol A Biol Sci Med Sci*. 2016;71(2):205-214. doi:10.1093/gerona/glv128
88. Britt HC, Harrison CM, Miller GC, Knox SA. Prevalence and patterns of multimorbidity in Australia. *Med J Aust*. 2008;189(2):72-77. doi:10.5694/j.1326-5377.2008.tb01919.x
89. Islam MM, Valderas JM, Yen L, Dawda P, Jowsey T, McRae IS. Multimorbidity and comorbidity of chronic diseases among the senior Australians: prevalence and patterns. *PloS One*. 2014;9(1):e83783. doi:10.1371/journal.pone.0083783
90. Gijsen R, Hoeymans N, Schellevis FG, Ruwaard D, Satariano WA, van den Bos GA. Causes and consequences of comorbidity: a review. *J Clin Epidemiol*. 2001;54(7):661-674. doi:10.1016/s0895-4356(00)00363-2
91. Sands LP, Do Q, Du P, Pruchno R. Peritraumatic stress from a disaster increases risk for onset of chronic diseases among older adults. *Innov. Aging*. 2022;6(1):igab052. doi:10.1093/geroni/igab052
92. Dizdar O, Alyamaç E. Obesity: an endocrine tumor? *Med Hypotheses*. 2004;63(5):790-792. doi:10.1016/j.mehy.2004.01.046

93. Schwarzinger M, Thiébaut SP, Baillot S, Mallet V, Rehm J. Alcohol use disorders and associated chronic disease – a national retrospective cohort study from France. *BMC Public Health*. 2018;18(1):43. doi:10.1186/s12889-017-4587-y
94. Campbell-Lendrum D, Prüss-Ustün A. Climate change, air pollution and noncommunicable diseases. *Bull World Health Organ*. 2019;97(2):160-161. doi:10.2471/BLT.18.224295
95. Abend M, Azizova T, Müller K, et al. Association of radiation-induced genes with noncancer chronic diseases in Mayak workers occupationally exposed to prolonged radiation. *Radiat Res*. 2015;183(3):249-261. doi:10.1667/RR13758.1
96. Lynch J, Smith GD. A life course approach to chronic disease epidemiology. *Annu Rev Public Health*. 2005;26:1-35. doi:10.1146/annurev.publhealth.26.021304.144505
97. World Health Organization. Dementia. Key facts. 2022. Accessed October 6, 2023. https://www.who.int/news-room/fact-sheets/detail/dementia
98. Romão VC, Fonseca JE. Etiology and risk factors for rheumatoid arthritis: a state-of-the-art review. *Front Med (Lausanne)*. 2021;8:689698. doi:10.3389/fmed.2021.689698
99. Cancer Genome Atlas Research Network, Weinstein JN, Collisson EA, et al. The cancer genome atlas Pan-cancer analysis project. *Nat Genet*. 2013;45(10):1113-1120. doi:10.1038/ng.2764
100. Barnes PJ. Senescence in COPD and its comorbidities. *Annu Rev Physiol*. 2017;79:517-539. doi:10.1146/annurev-physiol-022516-034314
101. Müllerova H, Agusti A, Erqou S, Mapel DW. Cardiovascular comorbidity in COPD: systematic literature review. *Chest*. 2013;144(4):1163-1178. doi:10.1378/chest.12-2847
102. Iribarren C, Tolstykh IV, Eisner MD. Are patients with asthma at increased risk of coronary heart disease? *Int J Epidemiol*. 2004;33(4):743-748. doi:10.1093/ije/dyh081
103. Sattar N, McCarey DW, Capell H, McInnes IB. Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. *Circulation*. 2003;108(24):2957-2963. doi:10.1161/01.CIR.0000099844.31524.05
104. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. *Int J Cancer*. 2007;121(4):856-862. doi:10.1002/ijc.22717
105. Liu Y, Pleasants RA, Croft JB, et al. Smoking duration, respiratory symptoms, and COPD in adults aged ≥45 years with a smoking history. *Int J Chron Obstruct Pulmon Dis*. 2015;10:1409-1416. doi:10.2147/COPD.S82259
106. Chang JT, Meza R, Levy DT, Arenberg D, Jeon J. Prediction of COPD risk accounting for time-varying smoking exposures. *PloS One*. 2021;16(3):e0248535. doi:10.1371/journal.pone.0248535
107. Lee PN, Fry JS, Forey BA. Estimating the decline in excess risk of chronic obstructive pulmonary disease following quitting smoking–a systematic review based on the negative exponential model. *Regul Toxicol Pharmacol*. 2014;68(2):231-239. doi:10.1016/j.yrtph.2013.12.006
108. Huang R, Wei Y, Hung RJ, et al. Associated links among smoking, chronic obstructive pulmonary disease, and small cell lung cancer: a pooled analysis in the international lung cancer consortium. *EBioMedicine*. 2015;2(11):1677-1685. doi:10.1016/j.ebiom.2015.09.031
109. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med*. 2000;342(12):836-843. doi:10.1056/NEJM200003233421202
110. Shishehbor MH, Zhang R, Medina H, et al. Systemic elevations of free radical oxidation products of arachidonic acid are associated with angiographic evidence of coronary artery disease. *Free Radic Biol Med*. 2006;41(11):1678-1683. doi:10.1016/j.freeradbiomed.2006.09.001
111. Seals DR, Justice JN, LaRocca TJ. Physiological geroscience: targeting function to increase healthspan and achieve optimal longevity. *J Physiol*. 2016;594(8):2001-2024. doi:10.1113/jphysiol.2014.282665
112. Tchkonia T, Palmer AK, Kirkland JL. New horizons: novel approaches to enhance Healthspan through targeting cellular senescence and related aging mechanisms. *J Clin Endocrinol Metab*. 2021;106(3):e1481-e1487. doi:10.1210/clinem/dgaa728

How to cite this article: Padrón-Monedero A. A pathological convergence theory for non-communicable diseases. *Aging Med*. 2023;6:328-337. doi:10.1002/agm2.12273