Evolutionary, Social, and Environmental Causes of Aging and Non-Communicable Diseases

by

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A dissertation accepted and approved in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

in Anthropology

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Spring 2025

DISSERTATION ABSTRACT

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Doctor of Philosophy in Anthropology

Title: Evolutionary, Social, and Environmental Causes of Aging and Non-Communicable Diseases

This dissertation applies theory and methods from Human Biology to the study of aging and Non-Communicable Diseases (NCDs). It evaluates and considers evolutionary theories of aging, and how they can help us understand the physiological basis of aging. Further, it uses a global perspective, with data from Mexico, China, Tunisia, Cambodia, and Ecuador, to separate the effects of contemporary environments from aging-related decline and disease. Results from the Tunisian Health Examination Survey indicate that, controlling for age, menopause is associated with higher levels of triglycerides, HbA1c, total cholesterol, LDL cholesterol, and glucose. Results from the Study on global AGEing and adult health (SAGE) showed that women living in China had no association between age and inflammation, and women living in Mexico had a negative association between age and inflammation. Results from the Shuar Health and Life History Project indicate that inflammation is not due to intrinsic aging and instead appears driven by metabolic factors. Finally, data from the World Health Survey Plus (WHS+) in Cambodia highlights the improvements that are needed in the measurement of market integration and shows that market diet, sedentary behavior, and chronic psychosocial stress do not mediate the relationship between market integration and cardiometabolic health, which has been a common assumption in the literature. The findings highlight that there is a need to re-evaluate the Disposable Soma Theory and develop new evolutionary approaches that integrate the evolutionary causes of aging with the physiological causes of aging. Further, one of the most

agreed upon mechanisms of aging, an increase in chronic low-grade inflammation with age, seems to be entirely due to cumulative metabolic dysregulation from an evolutionary mismatch with current environments. Finally, this research highlights that the transition to market economies that is often associated with worse cardiometabolic health is complex, and that more research is still needed to understand how it shapes health and contributes (or not) to aging. Human biologists have rarely specialized in aging research; however, this dissertation highlights that these perspectives and methods can help us untangle the centuries-old mystery: What is aging and why does it occur?

ACKNOWLEDGMENTS

First and foremost, I would like to acknowledge that I have had the best advisor, Josh Snodgrass. Thanks for providing me with opportunities, showing me how to be a great academic, and pouring countless hours into providing feedback on this work and others. Thanks to Larry Sugiyama, for the creation and leadership you have provided to the Shuar Health and Life History Project, and for bringing your high-level insights into the world of cells to collaborate on my work. I appreciate Kirstin Sterner for expanding my insight with her thoughtful feedback and contributions, and Clare Evans for teaching me many of the statistical methods contained in this dissertation. Thank you to Paul Kowal, Nirmala Naidoo, and Nawi Ng for providing me with opportunities, guidance, and feedback.

Several of the works contained within this dissertation are part of large-scale collaborative research efforts led by the World Health Organization (WHO), and I am grateful to many people for their involvement. This includes the leaders and data collection team for the Study on global AGEing and adult health in China and Mexico (SAGE; including Somnath Chatterji, Wu Fan, Zheng Yang, Ye Lu, Aaron Salinas Rodriguez, Betty Manrique-Espinoza, Ricardo Robledo, Salvador Villalpando) with special thanks to Yanfei Guo for continued involvement in my work, the team that performed the Tunisiain Health Examination survey (including Olfa Saidi and Hajer Aounallah-Skhiri), and to everyone who administered the World Health Survey Plus (WHS+) in Cambodia (including, Srean Chimm, Savuth Chin, and Heng Sopheab). Finally, to the tens of thousands of participants across these studies, thank you so much for letting us take so much of your time and a little bit of your blood. I am grateful.

My favorite chapter is the one done in collaboration with the Shuar Health and Life History Project and lots of people have put blood, sweat, and tears into collecting the data

contained herein. This includes Felicia Madimenos, Mellissa Leibert, Sam Urlacher, Tara Cepon-Robins, Aaron Blackwell, Josh Shrock, and Dorsa Amir. To the *Federacion Interprovincial de Centros Shuar* (FICSH), thank you so much for your long-term collaboration. To our friends in Ecuador, we appreciate your kindness, hospitality, and help with research (including Luzmilla Jempeket, Estella Jempeket, Cesar Kayap, Oswaldo Mankash, Medardo Tunki, and Don and Doña Guimo). Finally, to all of the Shuar community members I appreciate you for welcoming us, spending time hanging out with us, and for participating in our research.

This work was financially supported by a US National Institute of Health & National Institute of Aging Interagency Agreement, the Ministry of Health in Mexico, the Shanghai CDC in China, the Tunisian Ministry of Health, the WHO, Germany, the US National Science Foundation, Wenner Gren, and the University of Oregon.

I have a large group of amazing friends, many of whom are also academics, that provided the most critical support needed for a PhD, emotional support. Thanks to the Pact, Alejandra Rivera, Joanna Mathias, and Cortney Griffin, for being my rocks for the past 18 years. To the Accountabilibudies, Erin Winters, Laura Meinzen-Dick, Arian Seifoddini, Komal Choudhary-Hart, and Charlotte Ambrozek for not only keeping me accountable but for your friendship and support. Finally, to Tian Walker for going on this crazy journey with me.

To my mom, Betty Davis, and siblings, Nicole Bowers and Dylan Davis, thanks for your unwavering support. To my in-laws, Madelyn and Rod Gartner, thank you for welcoming me into your family and supporting me like one your own. To Erin and Amber Gartner, thanks for watching my son so that I could sleep and work, in that order. To my son, Lucas DeLouize-Gartner, who arrived during this experience, thank you. Not for helping or inspiring me, you did quite the opposite, but for enriching my life and being my favorite human.

To my husband, Bryce, for the sacrifices, support, and care that made this journey possible.

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CHAPTER I

Introduction

Aging, or a decline in organismal function over time, is nearly ubiquitous in multicellular organisms. However, a recent survey of researchers who study aging revealed a striking lack of consensus on how or why aging occurs (Cohen et al., 2020). The only agreement was that aging is heterogeneous and there is a need for a unified paradigm. Meanwhile, every country in the world is experiencing an increase in its older adult population (WHO, 2024). Globally, it is estimated that 1 in 6 people in the world will be over the age of 60 in 2030, and 2.1 billion people will be over the age of 60 in 2050 (double the size of this population today; WHO, 2024). Currently, most of the additional years of life are spent in poor health (Kyu et al., 2018). In addition to the negative effects on quality of life, aging-related decline and disorders put financial and personal strain on families and/or caregivers (Olfson et al., 2018; Sciubba, 2020). It also leads to financial and workforce strain in the healthcare field (Kallestrup-Lamb et al., 2024). Combating aging and the diseases it is associated with is a major priority globally, and a better understanding of the proximate and ultimate causes of aging and non-communicable diseases is needed to further public health goals (WHO, 2023).

One reason understanding the physiological cause of aging has been difficult is the close overlap between aging and metabolism. Non-communicable diseases (NCDs) have long been termed aging-related diseases, although now they are occurring at younger ages, making the term a misnomer (Cohen et al., 2020). All of these aging-related disorders are rooted in metabolism and associated with increased low-grade chronic inflammation (Furman et al., 2019). Even the pathways that are implicated in aging are the same as those that are implicated in metabolic dysregulation (Franceschi et al., 2018). This is especially concerning because low- and middle-

income countries (LMICs) are still undergoing an epidemiological transition by which increasing market integration (i.e., a transition to a market-based economy) leads to worsening cardiometabolic health (Zuckerman et al., 2014). Evolutionarily, there is a mismatch where recent changes to environment and culture in humans have led to different selective pressures than those that have previously affected the genome. This manifests as an increase in NCDs from environmentally novel calorie-dense diets, sedentary behavior, and psychosocial stress. Given the ubiquity of this metabolic environment in high-income countries (HICs), where research is normally conducted, it has been difficult to distinguish between metabolic dysregulation (from excess food energy, or calories) and aging. Therefore, global public health research is needed in order to separate out these effects.

Aging in Human Biology

A Global Perspective

If aging is intrinsic to biology, then there should be a universal mechanism, or set of mechanisms, that causes aging. However, many of the currently proposed mechanisms of aging overlap and interact with metabolic stress from an overenergetic status in which there are more calories consumed than are needed for functioning or that can be stored (Cornu et al., 2013; Franceschi et al., 2018). To separate the effects of metabolic dysregulation from aging, research done outside of HICs is necessary. Further, elucidating links between infectious diseases and aging is crucial to understanding aging in an evolutionary context, and one with an increase in crowd-based diseases (Rook, 2023). Aging research needs to include people from varying cultures and environments to understand the ultimate nature of aging and its variability among humans.

Evaluation of Multiple Biological and Social Levels

The extended evolutionary synthesis includes the analysis of environmental and cultural factors in the explanation of human biological factors (Laland et al., 2015). Both human biology and the human environment include a complex array of varying levels and groupings (Figure 1). Part of the reason major questions in aging have caused disagreement is the complex expressions of aging at different levels of biology (e.g., genomic, cellular, organismal), and with myriad environmental, cultural, and social influences. For example, scientists who take an organ systems approach have aging models based on deficit (Mitnitski et al., 2013), alongside cellular and comparative models of aging that posit aging is programmed (Lathe & St. Clair, 2023). There is probably some truth to both of these assertions, and human biology provides the basis for understanding how they interact to form aging biology in humans.

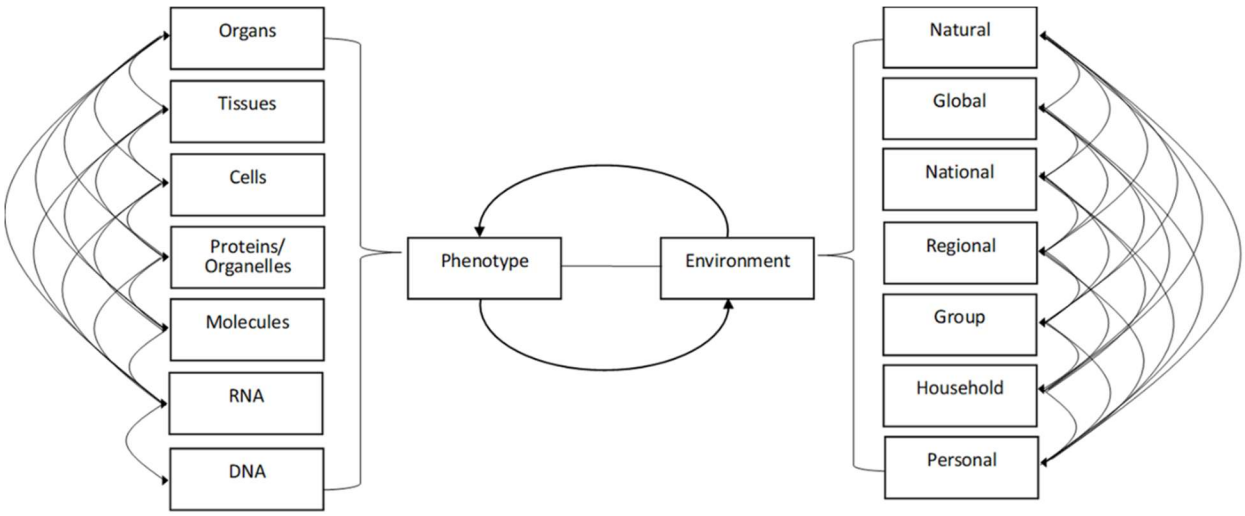


Figure 1. The Integration of Biological Levels. In reality, these relationships are even more complex with environmental factors having different effects on different levels of biology, but two arrows were drawn between phenotype and environment in the middle to convey these relationships.

The Integration of Disciplines

Human Biology is inherently interdisciplinary. It uses evidence and methodologies from anthropology, molecular, cell, and organismal biology, health sciences, psychology, epidemiology, and other disciplines. More commonly, academic disciplines exist in "silos," between which there is little integration of language, concepts, and research literature. This is partly why aging research has reached disparate conclusions, each discipline has created a multitude of different aging theories and research foci based on their unique perspectives and methodologies. In order to understand aging, we must pull from and integrate many different disciplinary perspectives.

Evolutionary Theory

Biological Anthropology is rooted in evolutionary theory. So far, aging research has settled on a wide array of mechanisms that researchers have agreed are a part of aging physiology (Kennedy et al., 2014; López-Otín et al., 2013, 2023). Calls have been made to understand why they variably appear in different people, and why some seem to be inversely correlated (Hodes, 2024). An evolutionary perspective can help sort out levels of causality and provide an integrative understanding of the biology and medicine of aging (Gluckman et al., 2011). It focuses on determining the ultimate origin of a trait, the limitations of natural selection and adaptation, and can explain vulnerability to disease. Understanding why aging is present, namely its evolutionary premises, will help elucidate the physiological basis and complex organization of aging processes.

Evolutionary medicine has been working to unite evolutionary theory with the biology of health and medicine. In general, diseases are present because evolution is slow, what natural selection can do is highly constrained, and we misunderstand what health factors selection has

shaped (Nesse & Stearns, 2008). Nesse and Stearns (2008) have outlined six major reasons why humans are vulnerable to disease: 1) mismatch with the environment; 2) pathogens coevolving with hosts; 3) constraints in what selection can do; 4) trade-offs; 5) selection maximizes reproduction and not health; 6) defenses (e.g., pain and fever) are useful despite causing suffering and complications. This dissertation will evaluate what causes and consequences of aging are due to mismatch with current environments, explore constraints and trade-offs that have shaped aging biology, and consider how natural selection maximizes reproduction over lifespan.

Summary of Dissertation

Chapter II: Energetic Constraints or Cellular Hyperactivity as an Ultimate Cause of Aging

A well-accepted evolutionary theory of aging, the disposable soma theory, states that due to tradeoffs in energy expenditure between growth, reproduction, and maintenance, cells do not invest enough energy in maintenance functions leading to cell death and ultimately aging (Kirkwood, 1977). However, it has been noted that this is inconsistent with literature showing that caloric restriction increases lifespan (Mitteldorf, 2001). Using the World Health Organization's (WHO) Tunisian Health Examination Survey, Chapter 2 explores changes in energy availability in the bloodstream (glucose and lipids; the three main molecules cells uptake to convert to adenosine triphosphate or cellular energy) when reproductive functions cease in women (menopause) and evaluates the implications of energetic tradeoffs not being the evolutionary basis of aging.

Chapters III & IV: Chronic Low-Grade Inflammation as a Mechanistic Cause of Aging

Inflammaging, or an increase in low-grade chronic inflammation with age, is thought to be a mechanistic driver of aging and aging-related diseases such as diabetes, cardiovascular disease, and dementia (Franceschi et al., 2000). On a cellular level, inflammation is released as a part of the senescent-associated secretory profile, which is an arrest in the cell cycle of cells that increases in frequency with age and dysfunction and often leads to cell death (Campisi, 2003). An over-energetic status (i.e., high blood glucose and lipids and/or low exercise) also leads to increased rates of chronic low-grade inflammation and is driven by the same molecular pathways (Finch, 2007; Franceschi et al., 2000; Hotamisligil, 2006). Shuar, who are Indigenous forager-horticulturalists in Ecuador, have different infectious disease profiles, spend more time in physical activity, and eat a diet with more fruits and vegetables, starches, and lean meats such as fish have low to no rates of chronic inflammation with age and low rates of cardiovascular disease (Liebert et al., 2013; McDade et al., 2012). Even studies in the United States show that some people do not have increasing low-grade inflammation with age. Therefore, it is unclear if low-grade chronic inflammation is a universal mechanistic driver of aging or a cumulative lifestyle effect from the widespread metabolic imbalance in high-income nations. Using data from the WHO's Study on Global AGEing and adult health (SAGE), Chapter 3 explores the relationship between inflammation and age in two low- to middle-income nations, Mexico and China, and evaluates the potential that an overenergetic status (measured as waist to height ratio) or lifestyle variables (physical activity and diet) mediate the relationship between aging and chronic low-grade inflammation. Chapter 4 uses non-linear generalized additive models to evaluate the possibility that increases in inflammation happen later in the lifespan in Shuar .

Chapter V: Lifestyle Factors Linking Market Integration with Metabolic Dysregulation

Non-communicable diseases have also increased due to cultural shifts toward market economies (called market integration in human biology). Although it has been presupposed that changes to diet, physical activity, and stress occur with market integration and lead to increased metabolic diseases, this has not been well documented. Cambodia is a lower- middle-income country that has moved rapidly towards economic development and globalization while also experiencing an epidemiologic transition between infectious and chronic diseases (due in part to successful public health campaigns addressing infectious diseases). Using data from the WHO's World Health Survey Plus (WHS+), Chapter 5 explores whether market-purchased diets, less time spent in physical activity, or traumatic stress mediate the relationship between market integration and metabolic dysregulation in Cambodia.

Bridge

Chapter I has outlined the open research questions associated with aging and explained the ways in which an anthropological framework is beneficial for answering some of these questions. This chapter then summarizes the theoretical framework and research goals for Chapters II through V, which highlight the use of evolutionary, multi-level, and global perspectives. The next chapter evaluates two evolutionary models of aging by looking at the difference in available energy in the blood among people who are pre- and post-menopausal. The implications of the different evolutionary models on aging are explored.

CHAPTER II

Energetic Constraints or Cellular Hyperactivity as an Ultimate Cause of Aging

Aging -- a functional decline over time -- is nearly ubiquitous in multicellular organisms and leads to morbidity and mortality, yet scientists still largely disagree on both the proximate (i.e., how aging occurs mechanistically) and ultimate (i.e., why aging occurs evolutionarily) causes of aging (Cohen et al., 2020). This is surprising given that aging has been a topic of research since at least Plato in the 4th century BCE, and the U.S. National Institute of Aging has a budget of over 4 billion US dollars annually (McKee & Barber, 2001; CRS, 2023). Understanding both proximate and ultimate reasons for aging is not just of theoretical interest. The human global population aged 60 and older reached 1 billion in 2020 and is expected to double by 2050 due to increases in population size and a shift in population age distributions (WHO, 2022). It is expected that this growth in the older adult population will lead to 1.2 billion women being post-menopausal in 2030 (WHO, 2024). This increase has shifted the global burden of disease towards chronic aging related disorders (e.g., heart disease, diabetes, and cancer) and hence the focus of international public health programs. Understanding the ultimate causes of aging is useful for separating the causes of aging from its consequences and can therefore shed light on the causal sequences that proximately drive aging and its outcomes (Trevathan, 2007).

Why aging occurs remains unexplained from an evolutionary standpoint because, all else equal, natural selection should favor continued survival in service of reproduction indefinitely. Although some theories of aging have brought us closer to understanding this evolutionary problem, such as mutation accumulation (Medawar, 1952), antagonistic pleiotropy (Williams, 1957), and programmed cell death (Ameisen, 2002), tests of others have produced conflicting

results. Here we propose a new evolutionary model for aging, the Cancer and Hyperactivity Model, and test it against the Disposable Soma Theory which has come under increasing scrutiny due to conflicting evidence.

Evolutionary Perspectives on Aging

Some evolutionary theories of aging rely on the principle that selective pressure is weaker later in the lifespan (Comfort, 1964; Fisher, 1930; Medawar, 1952). This principle is based in probability theory: If an organism does not live to reproductive age, its genes will make up 0% of the following generations. However, if an organism makes it to reproductive age and has one offspring, their genes will make up a low percentage of the next generation and an unknown (and perhaps higher) percentage of the second descending generation. This difference between zero probability – which inherently remains 0% forever - and random future probabilities is what makes it slightly more important for evolutionary success (defined here as a higher percentage representation of genes in the following generations) to survive through reproductive age and have one offspring than it is to survive to have subsequent offspring. Similar logic extends to each subsequent offspring, but with increasingly lower net probable payoff depending on extrinsic mortality rates of the species (Williams, 1957).

There are two main theories of aging based on this principle, mutation accumulation and antagonistic pleiotropy. The Mutation Accumulation Theory of Aging states that since the selective pressure in late life is lower, mutations that are only expressed later in life are less likely to be removed from the gene pool and hence will accumulate over generations, leading to organismal decline and death (Medawar, 1952). The Antagonistic Pleiotropy Theory of Aging states that since selective pressure in late life is lower, genes that cause benefits early in life, but are detrimental later in life, are more likely to be selected for than eliminated, leading to

organismal decline and death (Williams, 1957). Despite the fact that both of these theories have been well-evidenced at a population level, little work has been done to unite them with mechanistic causes of aging.

The Disposable Soma Theory

The Disposable Soma Theory (DST) links the ultimate mutation accumulation and antagonistic pleiotropy theories with the proximate causes of aging. It states that energy is preferentially invested in growth and reproduction over cellular maintenance, leading to somatic cell death and aging (Kirkwood, 1977). This can be seen as a form of antagonist pleiotropy because molecular mechanisms, such as a lack of cellular maintenance and cell death, which save energy for growth and reproduction benefit organisms earlier in life at a later cost. Since energy is restricted and not invested in cellular maintenance, cells undergo programmed cell death (apoptosis) due to an accumulation of errors. It is noted that the stem cell line must keep high integrity or be quickly discarded to allow for longevity; otherwise, mutations that are present in the stem cell will become prominent in a large population of differentiated cells.

The fact that the DST has two levels of explanatory causality has led to it having different interpretations or foci in different fields. Further, evolution, biology, and aging are so complex that a singular explanation is likely to fail. Following Kirkwood's original publications (Kirkwood, 1977, 1981, 1990; Kirkwood & Holliday, 1979), human biologists have used the above definition, which includes both the ultimate and proximate explanatory components. However, some evolutionary biologists have focused on the proximate level of causality in their definition of the DST: that somas are disposable (often due to accumulating damage) and this leads to aging (e.g., Congdon et al., 2003). This proximate causal explanation is well agreed upon since there is a plethora of evidence that cells undergo programmed cell death (apoptosis)

in a process often defined by stem cell proliferation, cell differentiation, then apoptosis. Further, this cell death increases as one ages and leads to deterioration in functioning. However, Kirkwood's original theory (Kirkwood, 1977, 1981, 1990; Kirkwood & Holliday, 1979) also includes an ultimate causal explanation, that energic tradeoffs lead to aging. We evaluate this ultimate explanation in the current study.

Critically Evaluating the DST

The ultimate explanation component of the DST has been questioned for at least two reasons: 1) caloric restriction and endurance exercise lead to a longer lifespan (Mitteldorf, 2001); and 2) aging related diseases (such as type 2 diabetes, heart disease, and cancer) are often associated with an over-energetic state, in which there is an excess of caloric energy, not an under-energetic state (Hoadley et al., 2018).

Although many energetic tradeoffs have been demonstrated, such as the preferential investment of energy in the immune system instead of growth in a high pathogen environment (Blackwell et al., 2010; Urlacher et al., 2018), but for energetic tradeoffs to exist the somatic functions must be synchronized. Changing circumstances can often counteract some of these effects through changing energetic investments. For example, children whose infections resolve or whose caloric intake improves can undergo catchup growth (Boersma & Wit, 1997; Bogin, 2020) and bone mineral density deficits caused by decreased calcium from lactation are resolved after weaning (Madimenos et al., 2012). The same is true of some aging-related damage (such as DNA mutation), which is sometimes corrected after the fact (Gao et al., 2016; Iyer et al., 2006). Therefore, energetic constraints would have to be consistent to prevent maintenance or repair functions. Yet, the rate of aging generally increases after growth and reproduction have ceased in humans (Levine et al., 2016), despite there being less demand for cellular energy and more

energy available for maintenance. It is possible that energetic tradeoffs exist and that they are not the ultimate cause of the disposable soma.

The Cellular Hyperactivity and Cancer Risk Model

Another possibility that could link the ultimate and proximate causes of aging is a model based on cellular hyperactivity and cancer risk (Figure 1). Both cellular hyperactivity and mutation accumulation have been proposed as proximate causes of aging (Blagosklonny, 2008; Freitas & de Magalhães, 2011); however, it is proposed here that a molecular tradeoff between the two constitutes the ultimate cause of aging. Nearly all multicellular organisms age (Harman,

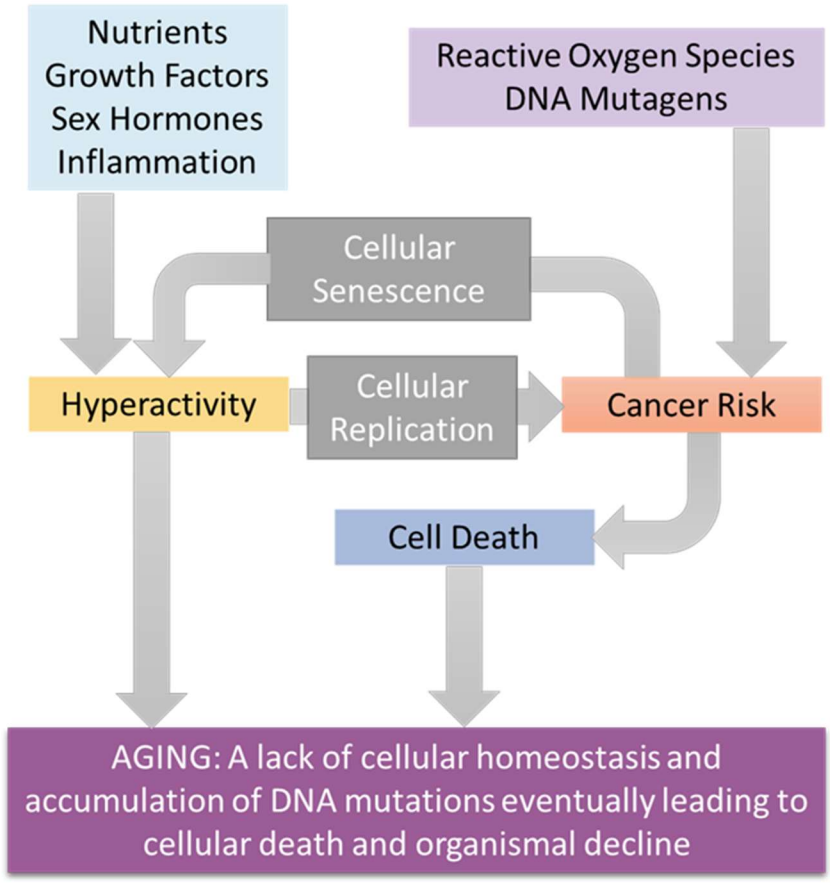


Figure 1. Model for Hyperactivity and Cancer Risk as the Cause of Aging

2001); if it is confirmed that some do not, this trait would likely be derived). Cancer and/or cancer-like processes, and mechanisms to suppress them, also occur in nearly all complex multicellular organisms (Aktipis et al., 2015). For approximately 75% of life on earth evolution selected for unicellular organisms, for which cell division equaled reproduction and obtaining energy from the environment led to more cell division. The transition to multicellularity required proliferation inhibition, cell death, division of labor, resource allocation, and maintenance of the extracellular environment (Aktipis et al., 2015). A lack of proliferation inhibition causes uncontrolled cell growth, or cancer. However, cells that do not proliferate or die enter the senescent-associated secretory phenotype, with adverse downstream effects on all levels of functioning. Aging in multicellular organisms could be due to the limitations of overcoming a transition to multicellularity, especially since many pathways that were inherited from single-celled organisms are vital for cellular functioning and are highly conserved.

Energetic availability is linked with metabolism and cellular activation by the target of rapamycin (TOR) pathway (Blagosklonny, 2010). This pathway is ubiquitous in eukaryotic cells and was inherited from unicellular organisms (Tatebe & Shiozaki, 2017; van Dam et al., 2011). In humans, this pathway is activated by glucose, phospholipids, insulin, growth factors, sex hormones, inflammation, oxygen availability and antigen stimulation (Liu & Sabatini, 2020); this leads to cellular activities such as cellular metabolism, protein and molecular production, and cellular replication (Laplante & Sabatini, 2009; Yang & Ming, 2012). A wide array of cellular receptors activate the mTOR pathway, then a wide array of pathways downstream from mTOR that initiate different cellular functions (commonly referred to as a bow-tie shaped transduction pathway (Oda et al., 2005). In this way, the TOR pathway links energetic cellular metabolism with cellular activation that is unique based on the cell type, its purpose, and its abilities. For

example, in humans, mammalian TOR (mTOR) activates the production of melanin and migration of melanocytes into the epidermis (Zhang et al., 2020), whereas in immune cells mTOR activates inflammation, cell migration, proliferation, immunomodulatory signaling, and the creation of surface receptors (Powell et al., 2012).

If cellular receptors are not activated in a way that promotes useful cellular functioning, energetic molecules (e.g., glucose and lipids) will activate the mTOR pathway, which will lead to the production of unneeded molecules and/or promote cell division. This cellular overactivation is considered cellular hyperactivity (Blagosklonny, 2008). As a cell goes longer without dividing, it gets larger and releases more unnecessary cytokine-signaling molecules (including inflammatory cytokines) due to the production of unnecessary molecules from cellular hyperactivity. Scientists measure cell size as a proxy for cellular aging and cellular senescence (Simons, 1967), demonstrating the overlap between hyperactivity and cell aging.

Cellular division can prevent cellular hyperactivity (Coppé et al., 2010; Cuyàs et al., 2014); however, cells are limited in the number of times they can divide (termed the Hayflick limit; Hayflick & Moorhead, 1961). It is likely a mechanism to prevent cancer since every time a cell divides, it increases mutational load and therefore risk of cancer (Campisi, 2001; Maciejowski & de Lange, 2017; Rode et al., 2016; Tomasetti & Vogelstein, 2015). This cellular senescence (lack of cellular division) leads to the senescent secretory phenotype, which is a permanently hyperactive state (Coppé et al., 2010). Therefore, there is a tradeoff between unnecessary cellular activity (cellular hyperactivity) and cancer risk.

Aging related dysfunction is often caused by cellular hyperactivity (Blagosklonny, 2008). Further, aging related dysfunction from an over-energetic status is supported by evidence that caloric restriction and physical activity elongate health span and lifespan (Carapeto & Aguayo-

Mazzucato, 2021; Ho et al., 2022; Mercken et al., 2012; Pifferi et al., 2019). This overenergetic status has been linked to cellular hyperactivity, which has then been shown to cause dysfunction and disease (Blagosklonny, 2010). The liver is a key metabolic organ that controls whole-body physiology in response to nutrient availability (Cornu et al., 2014). For example, evidence for the relationships between mTOR, cellular senescence, and cell death has been well documented in animal models (Li et al., 2021; Maiese, 2015; Tan et al., 2016; Weichhart, 2018; Xu et al., 2013). Cellular senescence, cellular hyperactivity, and apoptosis drive many aging related phenotypes, including immunosenescence, poor wound healing, atrophy, increased frailty and many other aging related disorders (Campisi, 2003; Muñoz-Espín & Serrano, 2014; O' Neill, 2013). A major cause of physical frailty, sarcopenia, has been linked to mTOR induced cellular hyperactivity and apoptosis (Sandri et al., 2013), along with arthritis and osteroporosis (Chen et al., 2014; Du et al., 2019). Both mTOR related cellular hyperactivity and the secretory profile of senescent cells are contributing factors to atherosclerosis, type II diabetes, and dementias (Chang & Harley, 1995; Leibowitz et al., 2008; Martin, 2001; Vasile et al., 2001; Yang & Ming, 2012; Zoncu et al., 2011). Further, the cellular hyperactivation of melanocyte stem cells has been shown to be a main driver in the aging related graying of hair (Zhang et al., 2020). Therefore, the cellular outcomes of cellular hyperactivity and cancer risk have been linked to many of the disparate characteristics that decline over time and constitute aging.

Glucose and lipids often enter the cellular matrix from the bloodstream and activate cellular metabolism and the mTOR pathway. Therefore, outcomes of cellular hyperactivity, such as excess chronic inflammation, are produced by an excess of these energetic molecules in the bloodstream (Liu & Sabatini, 2020). For example, a high-fat/high cholesterol diet fed to pigs led to high levels of cholesterol in the bloodstream, high rates of mTOR activation, decreased

cellular autophagy, and cardiac hypertrophy (Glazer et al., 2009). Further, this hypertrophy is a profile associated with the development of heart disease. This same pathway is activated by glucose and other forms of sugar and lipid molecules and implicated in the development of obesity and other obesity related diseases (in addition to heart disease) such as diabetes and kidney disease (Jia et al., 2014). Therefore, an excess of energy molecules in the bloodstream such as glucose, triglycerides, and cholesterol can be directly linked to cellular hyperactivity.

Cellular Energetics

Energetics is the transformation of food energy into metabolic processes that fuel health, survival, and reproduction, and the study of energetics forms the basis for many evolutionary theories (Leonard & Ulijaszek, 2002). Metabolism includes the absorption, transfer, and processing of food-based energetic molecules and the conversion of those molecules into chemical energy inside the cell (commonly referred to as cellular metabolism), Although many energetic studies use measures of oxygen consumption and/or carbon dioxide production to calculate energy expenditure (Snodgrass, 2012), energetics can also be tracked through self-report and observational measures of food consumption and biomarkers of energetic molecules in the blood (Naska et al., 2017). Calories from food travel to the liver which stores (in the short term), packages, and releases the molecules cells will use for energy into the bloodstream (triglycerides, glucose, and cholesterols). Lower caloric intake generally leads to lower levels of circulating glucose, HbA1c, triglycerides, and cholesterol (Nestel et al., 1970; Perry et al., 2021; Yang et al., 2023), less available energy, lower cellular oxidation of energy, and lower levels of cellular hyperactivity (Bobbioni-Harsch et al., 1997; O'Keefe et al., 2008). The presence of these glucose, triglycerides, and cholesterol in the bloodstream is directly linked to the metabolic consumption of energy in cells through the activation of mTOR signaling pathways (Laplante &

Sabatini, 2009; Yang & Ming, 2012) and HbA1c is a proxy for glucose (Rohlfing et al., 2002). Giving rats greater amounts of fructose led to widespread activation of mTOR pathways, although notably mTOR activity increased in the liver further regulating metabolic processes (Sangüesa et al., 2019). There has also been evidence for this association in humans, whereby mTOR mediated the effects of a diet high in sugars with the buildup of *tau* proteins in Alzheimer's disease (Orr et al., 2014). Evidence suggests that energy metabolism is not regulated internally by a cell but rather by factors outside of the cell, such as the presence of glucose, lipids, insulin, growth factors, sex hormones, and inflammatory molecules (Coppé et al., 2010; Nakamura et al., 2014; Wadsworth & Riddle, 1989). Therefore, energetic availability (in the form of glucose and lipids in the bloodstream) is intrinsically linked with metabolism and cellular functioning. If there is not enough energy for needed cellular metabolism, energetic tradeoffs occur between growth, reproduction, or maintenance. However, too much energy leads to cellular hyperactivity, increased risk of cancer, and aging.

If there are too many energetic molecules for the liver to be able to process, it shuttles some into the abdomen as central adiposity (Bacon, 2013). This usually only occurs after the liver has maximized the amount of energy it can release into the bloodstream; however, by setting a limit the liver is preventing a certain amount of cellular hyperactivity. There is evidence for this in a mouse model, whereby knockout of the mTOR pathway in adipose tissue leads to increased cellular mTOR activation (Polak et al., 2008). Fat stores are influenced by inherited, developmental, and environmental factors. Energetic molecules stored in fat cells can be released into the bloodstream if needed, providing an energy buffer for low-calorie environments over time, helping prevent against energy deficits. Therefore, in one way it can be conceptualized as

extra energy that can be used for cellular functioning and/or promote cellular hyperactivity when released into the bloodstream.

Menopause as a Natural Experiment

Living long after menopause is a unique life history trait that occurs in humans, some non-human primates, and some whales (Sievert, 2025). It provides a clear and consistent marker for the end of a direct energetic investment in reproduction in females. A known decrease in energy expenditure for reproduction, with evidence for a highly conserved energy expenditure, allows for us to compare hypotheses on the energetic causes of aging. If maintenance energy is restricted due to investments in growth and reproduction, it is expected that a release of these energetic constraints, after reproductive investment ceases, will go towards maintenance functions. However, if instead excess energy and cellular hyperactivity are involved with aging, then energy no longer being used increases excess energy driving hyperactivity and ultimately aging.

Menopause marks an end to the energetic investment in the female reproductive system, and is thought to have evolved, in part, to reduce energetic constraints (Hall, 2004). It marks the end of energetic investment to the endometrium, which is re-developed and shed each month in a cyclical process. This cyclical process, while energetically cheaper than maintaining a developed endometrium, increases the female energy budget by about 7% during the period when the endometrium is developing and maintained (Strassmann, 1996). If a woman forgoes this cost for 12 months, approximately 130 megajoules of energy is saved, or approximately a half a month worth of calories (Strassmann, 1996). Therefore, when controlling for age the menopausal transition can be seen as an energetic transition in which some of the energetic constraints associated with reproduction are lifted.

The rate of aging usually increases after menopause in humans (Levine et al., 2016). A study done in mice showed that ovariectomy mimics characteristics of menopause and leads to premature immunosenescence and sarcopenia (Baeza et al., 2010). This decrease in immunosenescence with ovariectomy was also seen in rhesus macaques (Engelmann et al., 2011). In humans, menopause has been shown to increase rates of epigenetic aging, immunosenescence, and cognitive decline (Giglio et al., 1994; Halbreich et al., 1995; Levine et al., 2016). The menopausal transition has also been associated with increases in central adiposity, decreases in energy expenditure, and increases in aging related chronic diseases (Slopien et al., 2018; Stampfer et al., 1990; Wellons et al., 2012). Therefore, menopause seems to be associated with a decrease in the use of energy and an increase in the rate of aging and its deleterious effects.

Aging Research in Cross-Sectional Studies

The Tunisian Health Examination Survey is a nationally representative study completed in collaboration with the World Health Organization. It collected point-of-care biomarker, survey, anthropometric, and performance data on 9,212 individuals during 2016 in order to assess the relationships between determinants of health and health status and evaluate the use of the health care system in order to improve health and health care policies. Aging should ideally be evaluated longitudinally, however difficulties in collecting this data in humans has led to improvements in the design and understanding of validity in cross-sectional studies. One such acknowledgement is that environment, circumstances, and developmental trajectories affect the rate at which aging occurs, and therefore studies are subject to sampling effects. Nationally representative studies with complex survey designs use random selection across all of the environments and circumstances within a country, reducing sampling bias. Another

consideration is cohort effects, in which different age groups have different group-based experiences that affect study outcomes. Despite this limitation, cross-sectional studies can still provide preliminary insight into longitudinal trajectories.

Objectives and Hypotheses

The objective of the current study is to evaluate energetic processes associated with menopause by considering metabolic blood biomarkers. This objective leads to three competing hypotheses: (H0) There will be no evidence of differences in the amount of metabolic biomarkers in the bloodstream (lipids, glucose, and glycated hemoglobin [HbA1c]) before and after menopause; (H1) there will be lower levels of metabolic biomarkers in the bloodstream in people who are post-menopausal (consistent with an energetic constraints model); or, (H2) there will higher levels of metabolic biomarkers in the bloodstream (consistent with a cellular hyperactivity model) in people who are menopausal. Testing these competing hypotheses will begin to provide insight into competing evolutionary theories of aging, which is beneficial to understanding the physiological mechanisms that drive aging processes.

Method

Participants

A stratified complex multistage cluster sampling design was used to select participants living in each of the 7 major regions of the Tunisian territory (District of Tunis, North-East, North-West, Center-East, Center-West, South-East, and South-West) in order to make the sample nationally representative. Data collection took place between March 09 and June 30, 2016. The response rate was 97% (N = 9,212). This study included participants who were women (53% of total sample) that were not pregnant (97% of women; N = 4,712). Women aged 17 to 69

answered the women's health section with questions pertaining to menopause; however, for the purposes of this study women under 17 were marked as being non-menopausal and women over the age of 69 were marked as being menopausal. The ages of non-pregnant women ranged from 15 to 101 (M = 46.99, SD = 16.99), and a majority agreed to the collection of point-of-care biomarkers (97%). The study protocol was approved by the institutional review boards associated with the Tunisian Ministry Health and the World Health Organization and was approved by the Tunisian National Council of Statistics and by the National Council for the Protection of Personal Data. All participants signed an informed consent before participating in the study, and only de-identified data were obtained for the current analyses.

Variables

Self-Report

Age. The age of participants was obtained by asking two questions, 1) "What day, month and year were you born?" and 2) "How old are you now?" In addition, interviewers verified that the answers matched those listed on birth certificates and identification documents when available.

Menopause. A woman's menopausal status was measured by asking "Are you menopausal?" and their age at menopause was measured by asking about their "Age of menopause."

Frailty. The frailty composite included questions on general health, diagnosed conditions, functioning assessments, and activities of daily living (Appendix A; Lee et al., 2020; Rockwood et al., 2005; Rockwood & Mitnitski, 2007). The four sections were weighted equally.

Physical Assessment

Anthropometrics. Waist circumference was measured using a Gulick tape measure without a spring tension device. Measurements were taken two inches above the iliac crest, taking care to keep the tape measure parallel to the floor, and were read to one-tenth of a centimeter.

Biomarkers. Biomarkers were collected with finger-prick capillary blood using point of care devices. Glycated hemoglobin (HbA1c) was measured using A1CNow+ (PTS diagnostics; Whitestown, IN, USA), and glucose, triglycerides, and total cholesterol were measured using CardioChek PA (PTS diagnostics; Whitestown, IN, USA). Low density lipoprotein (LDL) was calculated automatically by the CardioChek PA device.

Statistics

Statistics were performed using R (v. 4.3.0; R Core Team, 2023). All assumptions were checked before analysis and glucose, HbA1c, and LDL were log-transformed in order to meet the assumption of normality. Pairwise deletion was used for biomarker values that were out of range of the respective measurement devices. Descriptive statistics were performed where appropriate and mixed effects multiple linear regressions were used to assess the relationship between menopausal status and biomarkers/anthropometrics in 6 different models (one each for glucose, HbA1c, LDL, cholesterol, and triglycerides) while controlling for age as a fixed effect and region as a random effect.

Results

Approximately half of the sample was menopausal (44%, n = 2,079; Figure 2) and the average age of menopause was 47.66 years (SD = 4.74). The frailty index ranged from 0.00 to

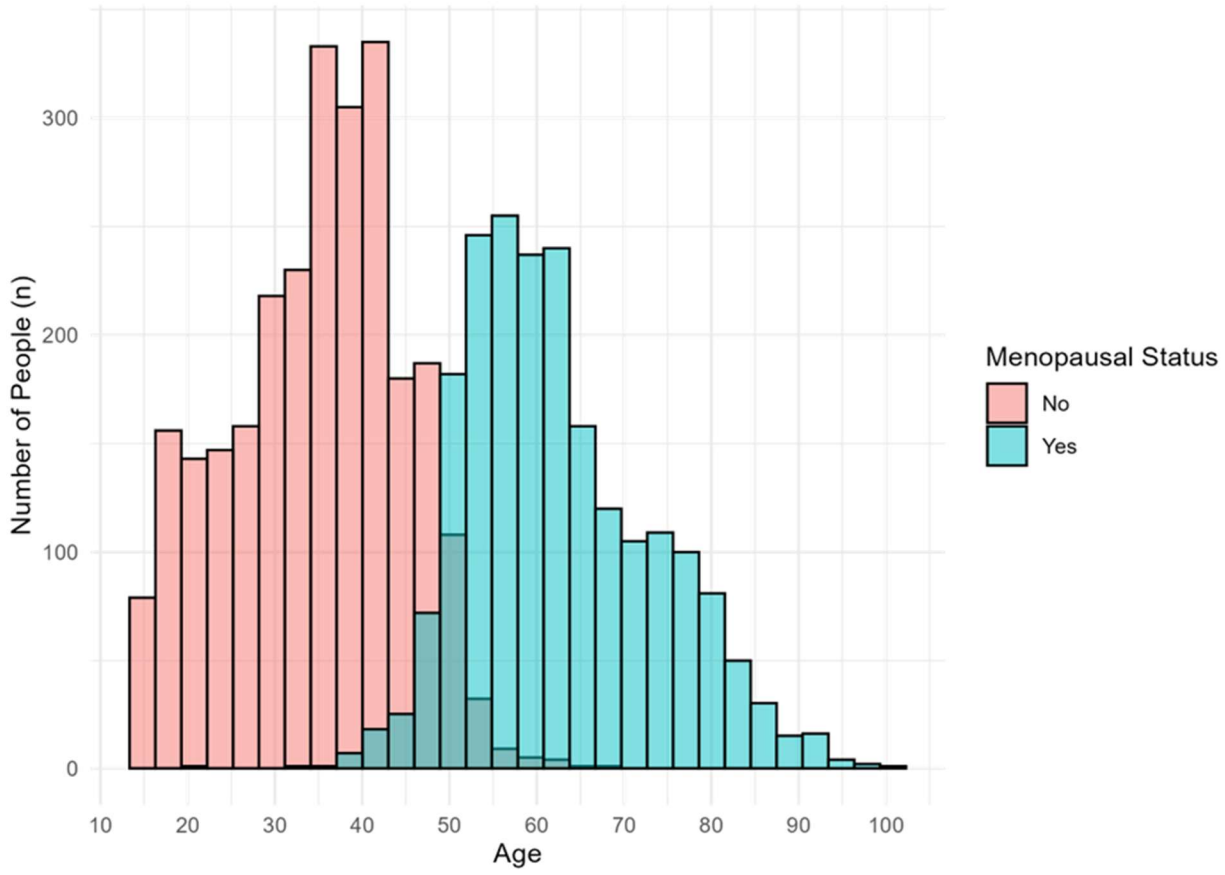


Figure 2. Histogram of age split by menopausal status

0.87 (*M* = 0.22, *SD* = 0.15). LDL cholesterol ranged from 15 to 500 mg/dL (*M* = 90.74, *SD* = 40.08), total cholesterol ranged from 100 to 400 mg/dL (*M* = 177.58, *SD* = 43.05), triglycerides ranged from 50 to 500 mg/dL (*M* = 182.54, *SD* = 87.81), HbA1c ranged from 4.0 to 13.0 % (*M* = 5.89, *SD* = 1.28), and glucose ranged from 20 to 587 mg/dL (*M* = 116.41, *SD* = 58.20). Waist circumference ranged from 40 to 189 cm (*M* = 92.35, *SD* = 15.46).

Mixed linear models showed that cholesterol, LDL, triglycerides, HbA1c, and glucose were higher in women who were menopausal (Table 1). Frailty and waist circumference did not vary by menopausal status. Cholesterol, LDL, triglycerides, HbA1c, glucose, frailty, and waist

Table 1. B Values for Mixed Linear Models

	Chol	HDL (ln)	LDL	Trig	HbA1c (ln)	Glu
Fixed Effects						
Intercept	151.68***	50.36***	4.21***	142.73***	1.62***	4.45***
Menopause	10.33***	0.76	0.08***	10.42*	0.04***	0.06**
Age	0.45***	.02	0.004***	0.75***	0.003***	0.004***
Random Effect						
Region ICC	.004	.003	.01	.01	.01	.01
Model Statistics						
Pseudo-R^2 (total)	.08	.01	.07	.05	.11	.08

Note. * $p < .05$, ** $p < .01$, *** $p < .001$; Chol: Cholesterol; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; Trig: Triglycerides; HbA1c: Glycated Hemoglobin; Glu: Glucose; WC: Waist Circumference; BMI: Body Mass Index.

circumference were higher as the age of individuals was higher. Random effects for region accounted for between 0.4% and 6.0% of the total variance.

Discussion

All blood biomarkers were higher in people who were menopausal when controlling for age. This indicated a greater availability of blood-based energetic molecules in people who had undergone the menopausal transition when controlling for age. Blood biomarkers were also higher at greater ages, as was waist circumference and frailty. However, waist circumference and frailty did not vary by menopausal status.

Implications for Evolutionary Theories of Aging

These results indicate that there is a higher amount of energy available in the bloodstream after menopause on average in some populations, as opposed to the same or less because of increasing cellular maintenance. This is inconsistent with a lack of cellular energy available for cell maintenance after menopause, when rates of aging are thought to increase. In a hyperactivity and cancer risk model, this metabolic energy can contribute to cellular hyperactivity, excess inflammation, and increases in chronic diseases. This provides evidence that cellular hyperactivity leads to increases in aging but does not rule out other explanations. Cellular hyperactivity could also co-occur with other dysregulating phenomena such as overactive hormonal signaling or an accumulation of unnecessary molecules or Garb-AGEing (Franceschi et al., 2017; Sansone & Romanelli, 2021).

The original DST is directly based on an energetic tradeoff, causing a lack of maintenance. It states that energy is preferentially invested in growth and reproduction over maintenance, leading to deterioration and aging (Kirkwood, 1977). Once these energetic constraints are lifted, such as with the end of energetic investment to some reproductive processes as seen in menopause, there should be an increase in maintenance and a slower rate of aging. This is not supported by the current study, where energetic constraints are lifted and energy becomes more plentiful in the known presence of increases to rates of aging and aging related diseases. It should be noted that the wider interpretation of the DST where there is a lack of cellular maintenance, without necessitating that it is due to a lack of energetic investment (e.g., Congdon et al., 2003), is still likely true. The wider interpretation could be due to limitations in the process of evolution, which necessarily retains critical molecular pathways. In

this way, the wider interpretation of the DST could be simultaneously true with the model of hyperactivity and cancer risk.

Menopause and Energy Availability

There are still many unknown aspects of the menopausal transition. This study adds to cross-sectional and longitudinal studies showing that menopause leads to increased levels of LDL, HDL, total cholesterol, glucose, and HbA1c (Auro et al., 2014; Bermingham et al., 2022; Wang et al., 2018). Further, meta-analysis shows that surgical menopause leads to similar increases in HDL, LDL, triglycerides, and risk of metabolic syndrome despite these menopausal transitions occurring at younger ages (Pu et al., 2017). These changes, along with an increase in central adiposity with age, lead to an increase in the prevalence of metabolic syndrome in post-menopausal women (Carr, 2003). This metabolic profile then increases the risk of metabolic disorders, such as cardiovascular diseases and diabetes (Slopien et al., 2018; Stampfer et al., 1990). Recently, public health scientists have brought attention to the fact that menopause is a global public health issue, and that more information is needed from LMICs (Delanerolle et al., 2025).

Metabolism and Aging

There are numerous metabolic processes that are known to change with age. Most components of energy expenditure, including physical activity and basal metabolic rate, decrease with aging (Roberts & Rosenberg, 2006). Cellular maintenance is a component of basal metabolic rate (BMR), so its decline is consistent with less maintenance as individuals age, not more (although this is confounded by the basal metabolic expenditure of fat mass.) While some studies indicate decreases in BMR are due entirely to changes in body composition (Bosy-

Westphal et al., 2003), others indicate that decreases in BMR exceed those associated with changes in body composition (Willis et al., 2002). Caloric consumption decreases, with an associated decrease in weight and fat storage, with greater decreases seen in obese older adults (Rolls et al., 1995; Sahyoun et al., 2004). Further, the ability to attenuate energetic imbalances also decreases. It takes longer for older adults to recover from both hypo- and hyper-glycemia and there is an increase in the amount of insulin that is secreted (Melanson et al., 1998). The higher levels of blood glucose seen with higher levels of insulin secretion also indicate a loss of insulin sensitivity. Therefore, many levels of metabolism change with age, including cellular metabolism which is increasingly influcenced by cellular hyperactivity.

Despite these individual-level metabolic dysfunctions increasing with age, they are predicated on aging processes at a cellular level. Even physical activity levels have been linked to the activation of mTOR in hepatocytes (liver cells; Cornu et al., 2014). Further, mTOR hyperactivation activates a feedback loop leading to insulin resistance (Jia et al., 2014; Ramasubbu & Devi Rajeswari, 2023; Stanciu et al., 2024). This could be a mechanism that was selected to limit the destruction of mTOR associated hyperactivity with age. Telomere shortening and apoptosis are associated with frailty (Bernabeu-Wittel et al., 2020; Marzetti et al., 2011), implicating cancer prevention mechanisms in aging. Therefore, a cellular explanation is still needed when evaluating how all levels of metabolic functioning change with age.

Implications for Health

The higher values of HbA1c, glucose, triglycerides, LDL, and total cholesterol seen with this study are also strongly associated with aging related chronic diseases, such as diabetes, heart disease, and dementia (Assmann & Schulte, 1988; Hassen et al., 2023; Zheng et al., 2018). In 2019, these were 3 of the top 10 causes of death globally (WHO, 2020). Further, even though

waist circumference was not associated with menopausal status, it did increase with age which has been shown before (Han et al., 1997; Kuk et al., 2005). Higher levels of central adiposity are also associated with aging related chronic diseases, such as heart disease and diabetes, and disability (Angleman et al., 2006; Janssen, 2009). This is also in agreement with both less energy being used and more energy being available into older ages.

Limitations

This study was not longitudinal, meaning results might be due to cohort effects and not aging or menopausal status per se. Further, there were many unmeasured confounds that could not be controlled for such as the amount of blood energy that will end up as fat deposition, variation in caloric intake, hormonal replacement therapy, and variation in exercise. Further, measuring the overlapping shifts in hormones such as estradiol and progesterone that happen with menopause would further elucidate this relationship. In general, there was no evidence that people who were menopausal had differences in central adiposity compared to those that had not undergone menopause, indicating that fat deposition in the midriff did not vary on average between groups. It is still possible that fat deposition varied between groups in other areas of the body, and average amounts of overall fat may or may not be correlated with the rate of fat deposition. One way to control for some of these confounds would be to replicate the study with additional energetic measures, such as total daily energy expenditure and basal metabolic rate. These are more standard ways of measuring energetic output.

Summary

The finding that the amount of energetic blood molecules is higher in people who are menopausal is consistent with a higher level of chronic diseases that are due to overenergetic

status in this cohort. The elongation of lifespan usually occurs with low caloric intake and exercise, which limit the energy available for cellular maintenance. If it were low energy availability alone preventing cellular maintenance, we would expect environments with excess energy availability to increase lifespan. However, the reverse is true (Weindruch & Sohal, 1997). Therefore, it could be that an increase in energy availability after growth and reproductive functions have ceased lead to aging through cellular hyperactivity. This could be true even in energy-scarce environments unless caloric intake went down along with the cease in growth and reproduction which utilize energy. If this excess energy does not go to productive functioning, such as exercise, it could lead to cellular hyperactivity and many correlates of aging including increased inflammation and metabolic disorders.

Bridge

Chapter II looked at competing hypotheses supporting two evolutionary models of aging. It adds to a growing body of evidence for the limitations of the Disposable Soma Model and provides evidence for the Cancer and Hyperactivity Model. Overall, it highlights the need for more research into the evolutionary basis of aging. The next chapter is the first of two chapters evaluating inflammaging, or the increase in chronic low-grade inflammation that is associated with age. They are among the first to evaluate inflammaging outside of high-income nations, Chapter III uses data collected in two lower- to middle-income countries, China and Mexico, and Chapter IV uses data collected from Shuar, an Indigenous group in Ecuador. This global perspective will help separate metabolic from intrinsic causes of inflammaging, a key mechanism in aging-related decline and dysfunction.

CHAPTER III

Population Differences in Aging-Related Inflammation are Strongly Associated with Central Adiposity and Lifestyle

Chronic low-grade inflammation (i.e., inflammation that is not associated with acute infection) is thought to be a hallmark of aging, and has been termed "inflammaging" (Franceschi et al., 2000; López-Otín et al., 2013). Inflammaging has been associated with many aging-related diseases, such as diabetes, cardiovascular diseases, arthritis, chronic obstructive pulmonary disorder, kidney disease, liver diseases, neurogenerative diseases, and cancers (e.g., Dregan, Charlton, Chowienczyk, & Gulliford, 2014; Guo, Pan, Du, Ren, & Xie, 2013; Kuo et al., 2005; Lund Håheim, Nafstad, Olsen, Schwarze, & Rønningen, 2009; Man et al., 2006; Ridker, Buring, Shih, Matias, & Hennekens, 1998; WHO, 2014), and is also associated with all-cause mortality (Li et al., 2017). Despite extensive research, two important issues remain: 1) determining if inflammation is universal with increasing age and 2) identifying the key mechanisms underlying inflammaging (e.g., Fulop & Larbi, 2018; Salvioli et al., 2013). Differences in the association between aging and inflammation and the lack of well-evidenced mechanisms could be due to mediational effects, in which environmental factors, such as diet and physical activity, change widely through populations with age and cause inflammation. Studies with blood pressure showed similar findings. Increases in blood pressure were once thought to be a part of normative aging, but instead evidence points to the increases in blood pressure seen with age being due to cumulative lifestyle effects and risk for cardiovascular disease (Najjar et al., 2005). Therefore, inflammation could be aging-related instead of a marker of senescence.

Aging, or a deterioration in function over time in organisms ultimately culminating in death, is nearly ubiquitous across multicellular organisms, yet aging biologists still largely

disagree on how and why it occurs (Cohen et al., 2020). Twelve hallmarks of aging—or processes that are associated with aging and cause aspects of aging related dysfunction—have been identified, with chronic inflammation (or inflammaging) being one of them (López-Otín et al., 2023). This excess inflammation is thought to be a downstream effect of other hallmarks of aging, such as genomic instability, altered cellular signaling, deficient proteostasis, immunosenescence, and decreased autophagy. It is also produced during cellular senescence, which is an arrest of the cell cycle, as a part of the senescent associated secretory phenotype (Coppé et al., 2010). Inflammatory signals then link these cellular processes with the aging of organ systems and other phenotypic aspects of aging. Manipulating inflammatory pathways in mouse models has been shown to accelerate or decelerate aging processes (Desdín-Micó et al., 2020; Gocmez et al., 2020; Sciorati et al., 2020; Yousefzadeh et al., 2021). Therefore, inflammation has been posited as a key mechanism that drives organismal aging. However, since it is downstream from other aging processes that occur differentially, it is unclear if this is a ubiquitous driving effect of organismal decline.

Studies in humans so far have mostly supported the inflammaging model of organismal decline, with chronic low grade inflammation increasing both over time and with metabolic dysregulation in overlapping processes that are thought to have distinct causes (Franceschi et al., 2018; Milan-Mattos et al., 2019). C-reactive protein (CRP) is a common biomarker of inflammation because it is released by the liver and is both signaled by and signals inflammatory cytokine release, allowing for systemic measurement (Luan & Yao, 2018; Yeh, 2004). Increasing CRP with age has been documented in many population based studies in high income countries, including the United States, Poland, Italy, and Japan with mean levels below that of the 3.0 mg/dL cutoff usually associated with a high risk of metabolic diseases (Arima et al., 2008;

Mendall et al., 1996; Morrisette-Thomas et al., 2014; Pearson et al., 2003; Puzianowska-Kuźnicka et al., 2016a). A smaller study in Brazil (a middle to high income country) showed similar results (Milan-Mattos et al., 2019). CRP even increases, on average, in healthy older adults and is seen at increased levels in centenarians in high-income nations (Alberro et al., 2021; Ballou et al., 1996; Puzianowska-Kuźnicka et al., 2016a; Spazzafumo et al., 2013). However, a small study in India (a low to middle income country; LMIC) showed that healthy older adults did not have higher CRP than young adults (Krishnaswamy et al., 2020). Therefore, population-based studies in LMICs are needed to evaluate how inflammaging occurs in different contexts.

Although most population-based research indicates a positive association between aging and inflammation, a few studies have shown that this is not always the case. Since most of the data on inflammation and aging have been collected from high-income nations, the consistent increases in inflammation seen with aging might be due to the cumulative effects of lifestyle factors in these settings such as an excess of energy-rich and ultra-processed food sources, modest levels of physical activity, and greater adiposity (e.g., Bruunsgaard, Pedersen, & Pedersen, 2001; Franceschi & Campisi, 2014; McDade, Hawkley, & Cacioppo, 2006; Schmidt et al., 2002). In populations with divergent lifestyles, such as forager-horticulturist or other subsistence-focused groups, aging does not seem to be associated with progressively increasing CRP level or the age-related diseases it predicts, such as cardiovascular disease, that are common in other population groups (Gurven et al., 2008). In support of this association, no chronic elevation of CRP at any age was found in the Shuar of lowland Ecuador (McDade et al., 2012) and despite relatively high CRP in the Tsimané of lowland Bolivia, it was not associated with arterial aging or an increase in cardiovascular disease (Gurven et al., 2008, 2009; Kaplan et al.,

2017; Vasunilashorn et al., 2010). Even within higher-income population groups, there is significant variation in the extent to which inflammation increases with age (Wener, Daum, & McQuillan, 2000). Thus, despite some convergence of results in wealthier nations, data from other settings suggest that higher levels of inflammation might not be universal in older adults. It is possible that inflammaging is due to changing central adiposity driven by lifestyle factors that change with age in certain populations.

There are many factors that are associated with aging in industrialized nations that have the potential to cause chronic inflammation. For instance, central adiposity, sleep dysregulation, smoking, and chronic psychosocial stress are associated with both epigenetic measures of aging and inflammation (Gibson et al., 2019; McDade, Hawkley, & Cacioppo, 2006; Palma-Gudiel et al., 2020; Wang et al., 2024). One key factor, central adiposity, already has a well-defined molecular pathway linking it to systemic inflammation (Gaal, Mertens, & Block, 2006). Visceral adipose tissue releases interleukin-6 (IL-6), which is transported to the liver where it signals the production of CRP. In addition, central adiposity is the strongest predictor of inflammation in older adults aged 52 to 70, and older adults in a cohort from the United States tended to gain between 0.46 cm and 0.82 cm in waist circumference consistently every year (McDade et al., 2006). The increases in central adiposity seen with aging might be due to biological changes (such as differential tissue maintenance as people age, changes in resting metabolic rate, or changes in endocrine signaling) or closely related to lifestyle changes commonly associated with aging (such as changes in nutrition or physical activity; Jafarinasabian, Inglis, Reilly, Kelly, & Ilich, 2017). Several lines of evidence suggest that lifestyle factors play a primary role. For instance, people who consume a diet high in fruits, vegetables, and whole grains have a 0.89 cm lower gain in waist circumference per year than people with diets high in processed

carbohydrates (Newby et al., 2003). The adoption of a Mediterranean diet, which is high in vegetables and fruits, has been shown to decrease inflammation by 0.34 mg/L to 0.54 mg/L and is associated with lower inflammation in older adults (Estruch et al., 2006; Trøseid et al., 2009; Wu et al., 2021). In addition, regular exercise has been shown to lower or prevent aging-related inflammation (Reuben, Judd-Hamilton, Harris, & Seeman, 2003; Woods, Wilund, Martin, & Kistler, 2012). However, physical activity levels tend to decrease after the age of 65 in many countries (Bauman et al., 2009; Guthold et al., 2018), and older adults aged 60 years and over from two Mexican National Health and Nutrition Surveys reported a diet low in micronutrients, and high in fats and sugars (Cruz-Góngora et al., 2017). Therefore, central adiposity and associated lifestyle factors, such as diet and exercise, are strong candidates as mediators between aging and inflammation and will be further investigated in this study.

Clarifying the underlying mechanisms and universality of age-related increases in chronic inflammation is critical because most populations in the world have experienced or are going to experience a major increase in the number of older adults (age 60 and older). In 2020 there were more people 65 years of age or older than those under 5 years of age and the rate of population aging is increasing in LMICs (Phillips & Gyasi, 2021). Increases in inflammation are associated with non-communicable diseases (NCDs) and NCDs are responsible for 74% of deaths globally, with 77% of these deaths occurring in LMICs (Banait et al., 2022; World Health Organization (WHO), 2023). In addition, the global obesity epidemic has been affecting middle-income nations at higher rates (Caballero, 2007). Currently, approximately 44% of people are overweight or obese, with 70% residing in LMICs (Shekar & Popkin, 2020). As the cohort of older adults and burden of obesity grow, so does the economic and public health burden of NCDs such as diabetes, cardiovascular disease, and stroke. The personal, familial, and economic

burdens caused by chronic diseases are detrimental to societies and are expected to increase dramatically in the future. The COVID-19 pandemic might exacerbate this increase since inflammation is both a contributing factor to and outcome of COVID-19 syndrome, leading to a high mortality rate among older individuals (Bonafè & Olivieri, 2022). There is already some evidence that COVID-19 infection leads to increased rates of new onset diabetes and heart disease (Kim et al., 2023; Shaikh et al., 2023). Understanding population-level differences in how inflammation and diseases manifest in old age could lead to their prevention and improve both health and economic outcomes.

To investigate the role of central adiposity in age-related inflammation, we used the World Health Organization's Study on global AGEing and adult health (SAGE) Wave 1 China and Mexico data collected between 2008 and 2010. Despite these countries' large populations, the association between age and inflammation has not been well-tested. SAGE was created to investigate the health and well-being of older adults and associated age-related processes through the collection of self-report and biological measures. By adding these two middle income countries to the current global evidence base, we aim to further investigate whether inflammaging is universal. Our objectives and hypotheses are as follows:

Objective 1. To investigate whether increased inflammation with age is due to differences in central adiposity.

H1: WSR will be more strongly related to CRP than age.

Objective 2. To investigate whether the relationship between age and inflammation varies based on differences in central adiposity with age.

H2: WSR will mediate the association between aging and CRP.

Objective 3. To investigate if lifestyle factors are associated with differences in central adiposity as people age, and whether these lead to different inflammation levels.

H3: Physical activity and diet will mediate the relationship between aging and WSR. WSR in turn, will mediate the relationship between physical activity/diet and CRP.

Method

SAGE is a longitudinal study on the patterns and determinants of aging in six middle-income countries: China, Mexico, Russia, Ghana, South Africa, and India (Kowal et al., 2012). Data were collected between 2008 and 2010 using stratified multi-stage cluster sampling (Naidoo, 2012). Detailed information on survey administration and physiological measurement collection guidelines can be found in the survey manual on the SAGE website (WHO, 2006).

Participants

Biomarkers were not collected for all SAGE participants therefore the current study used data on a subset of individuals from China (*n* men = 3,506, *n* women = 3,859) and Mexico (*n* men = 708, *n* women = 1,159). Although SAGE collected a small comparison sample of adults age 18 to 49, only participants age 50 or older were included in the present study (Tables 1 & 2).

SAGE was approved by the World Health Organization's Ethical Review Committee and each location's independent review board. All participants provided informed consent before being interviewed.

Variables

All data were collected based on the SAGE individual questionnaire and protocol, which is described in detail elsewhere (Kowal et al., 2012). Sociodemographic variables included age,

gender, education, and wealth. Two questions were combined as a measure for education, "*Have you ever been to school?*" and [if so] "*How many years of school, including higher education have you completed?*" Wealth (labelled income in the WHO database) is a composite variable where different housing and lifestyle characteristics were separate observations of wealth included in an item response theory model (Schrock et al., 2017). Self-reported health asked "*In general, how would you rate your health today?*"

Anthropometrics. Height and waist circumference were measured at the time of the interview using standard anthropometric techniques**.** The waist measurement was divided by the height measurement to produce the waist-to-stature ratio (WSR).

C-Reactive Protein (CRP). Whole blood was collected onto Whatman 903 filter paper cards to create dried blood spot (DBS) samples, though the procedures differed slightly in the two countries. Finger-pricks following standard practice (McDade et al., 2007) were used to collect blood in China, while in Mexico, 20 uL venous blood (obtained via venipuncture) was spotted onto blood spot cards. Because of this collection difference, data were not combined in statistical analyses. CRP was analyzed using a high sensitivity enzyme-linked immunosorbent assay (ELISA; Diagnostic Biochem Canada Inc, London, Canada) for samples in China and the Abbot Architect CI8200 (Green Oaks, Illinois, USA) for samples in Mexico. Analyses were conducted using concentrations measured in DBS without conversion to serum or plasma equivalents to minimize measurement error. A raw DBS cutoff of 5 mg/dL was used to exclude participants who had a high likelihood of acute infection.

Diet. Two self-report variables (number of daily servings of fruit and number of daily servings of vegetables; see Kowal et al., 2012) were combined to create the measure of diet used

Table 1. Descriptive statistics of participants 50 years of age or older living in China

	Men				Women			
	Min	Max	*M*	*SD*	Min	Max	*M*	*SD*
Age (yrs)	50.00	95.00	63.11	9.22	50.00	93.00	62.96	9.32
Education (yrs)	0.00	23.00	6.59	4.38	0.00	23.00	5.00	4.55
Health	1.00	5.00	2.75	0.83	1.00	5.00	2.88	0.82
WSR	0.32	1.02	0.52	0.06	0.18	1.25	0.55	0.07
CRP (DBS)	0.02	4.99	1.09	1.00	0.01	4.99	1.17	1.09
DQ	0.00	80.00	12.23	6.85	0.00	70.00	12.52	6.78
Vigorous PA (min/day)	0.00	780.00	35.88	92.20	0.00	720.00	12.63	50.63
Moderate PA (min/day)	0.00	1680.00	108.88	137.27	0.00	1440.00	96.28	120.81

Note. WSR = waist to stature ratio, CRP = c-reactive protein, DQ = dietary quality, PA = Physical Activity

in this study. Servings of fruit was then multiplied by two and added to servings of vegetables to create the diet variable following the equation for dietary quality (Leonard & Robinson, 1997).

Physical activity. A composite variable was created using the Global Physical Activity Questionnaire (WHO, 2004). The questionnaire contains three different sets of questions about moderate or vigorous levels of physical activity in broad categories such as travel/commuting, work, and leisure. METs (Metabolic Equivalents) were used to calculate physical activity from the different intensities.

Statistical Analysis

Statistical assumptions were checked before analyses. Dietary quality and exercise were $\log_e$ transformed due to non-normality. Two outliers were removed for having significant leverage; one had an extreme diet value and the other had an unlikely WSR. In China, 7% of

Table 2. Descriptive statistics of participants 50 years of age or older living in Mexico

	Men				Women			
	Min	Max	*M*	*SD*	Min	Max	*M*	*SD*
Age (yrs)	50.00	99.00	67.85	9.15	50.00	105.00	68.31	9.45
Education (yrs)	0.00	21.00	4.81	4.34	0.00	25.00	4.13	4.03
Health	1.00	5.00	2.66	0.72	1.00	5.00	2.79	0.71
WSR	0.38	1.00	0.60	0.07	0.35	1.00	0.64	0.09
CRP (DBS)	0.15	4.92	1.45	1.11	0.09	4.99	1.71	1.20
DQ	0.00	20.00	5.09	3.00	0.00	21.00	4.79	2.77
Vigorous Physical Activity (min/day)	0.00	720.00	50.21	119.85	0.00	600.00	6.39	40.09
Moderate Physical Activity (min/day)	0.00	1200.00	105.28	155.37	0.00	1020.00	90.67	145.90

Note. WSR = waist to stature ratio, CRP = c-reactive protein, DQ = dietary quality

participants were excluded for possible acute infection (CRP > 5) and in Mexico 8% were excluded. In China, participants with possible acute infection were older ($t = 5.78$, $p < .001$) and reported being less healthy ($t = -3.07$, $p = .002$), had higher WSR ($t = 2.76$, $p = .006$), and reported getting less exercise ($t = -5.81$, $p < .001$) than those who were included in the sample. In Mexico, participants with a possible acute infection had a higher WSR ($t = 4.61$, $p < .001$) than those that were included in the sample, possibly indicative of dysregulated metabolic processes.

H1. Four hierarchical multi-level regressions with restricted maximum likelihood estimation were performed in R version 4.3.0, one for men and women in both China and Mexico. The genders were run separately due to the possibility of differences between men and women in inflammation that could stem from differences in adiposity between these two groups

(Karastergiou, Smith, Greenberg, & Fried, 2012). Model 1 included age predicting CRP while controlling for education, wealth, and self-reported health as fixed effects and basic geo-statistical area as a random intercept in Mexico or village/neighborhood, township/community, and province as random intercepts in China. Its purpose was to see if age and WSR were related to inflammation in the presence of controls. Model 2 included the variables from Model 1, plus WSR and model 3 included variables from model 2 plus diet and physical activity level. These models were intended to explore the possible unique contribution of WSR and behavioral variables to CRP and to evaluate how these additions affected the other regression coefficients. The alpha level was set to 0.05.

H2. Four multi-level mediational analyses were performed with restricted maximum-likelihood estimation in R version 4.3.0. Models were run on men and women separately in China and Mexico. The first set of four mediational models included the mediation of the relationship between age (x) and inflammation (y) by WSR (m2), with village/neighborhood as a random intercept in China and basic geo-statistical area as a random intercept in Mexico.

H3. Eight multi-level mediational models included the first mediational model, with an additional mediation between age and WSR by either diet or physical activity (m1; Figure 1).

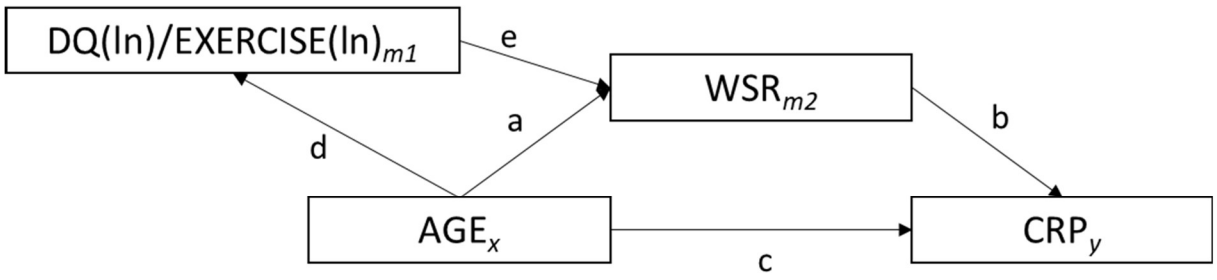


Figure 1. Multilevel multiple mediation model

Results

Descriptive statistics are presented for Model 1 and showed that CRP was higher with increasing age among men in China and Mexico (Tables 3 and 4). Women living in China had no difference in CRP levels with age and women living in Mexico had lower CRP levels at older ages. Higher CRP levels were associated with more central adiposity for all groups (Tables 3 to 6). WSR was more strongly related to CRP than age in all models; however, this difference might be negligible for men in both countries given the overlapping confidence intervals. Some of the variance shared between age and CRP was due to WSR in all groups except for women in Mexico, and the decrease in the significance of the association between age and CRP for men

Table 3. Multi-level regression results predicting CRP for men in China

	Model 1		Model 2		Model 3	
	β	*[CI]*	*β*	*[CI]*	*β*	*[CI]*
(Intercept)	1.08 ***	[0.87, 1.30]	1.08 ***	[0.87, 1.29]	1.07 ***	[0.87, 1.27]
Age	0.09 ***	[0.05, 0.12]	0.07 ***	[0.04, 0.11]	0.05 *	[0.01, 0.08]
Education	0.00	[-0.04, 0.05]	0.01	[-0.03, 0.05]	0.01	[-0.04, 0.05]
Wealth	-0.04	[-0.08, 0.00]	-0.05 *	[-0.09, -0.01]	-0.06 *	[-0.10, -0.01]
Health	0.04 *	[0.00, 0.07]	0.04 *	[0.00, 0.07]	0.03	[-0.01, 0.07]
WSR			0.09 ***	[0.06, 0.13]	0.09 ***	[0.06, 0.13]
DQ (ln)					-0.04 *	[-0.08, -0.00]
Exercise (ln)					-0.06 **	[-0.10, -0.02]
ICC_{ssu}	0.02		0.01		0.01	
ICC_{psu}	0.02		0.02		0.02	
ICC_{strata}	0.13		0.13		0.12	
AIC	9175.94		8980.08		8137.99	
BIC	9231.02		9041.10		8210.03	
R^2 (fixed)	0.01		0.02		0.03	
R^2 (total)	0.17		0.17		0.17	

Note. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$. All continuous predictors are mean-centered and scaled by 1 standard deviation. The outcome variable is in its original units. PSU = Basic Geo-Statistical Area.

Table 4. Multilevel regression results predicting CRP for women in China

	Model 1		Model 2		Model 3	
	β	*[CI]*	*β*	*[CI]*	*β*	*[CI]*
(Intercept)	1.16 ***	[0.89, 1.44]	1.16 ***	[0.89, 1.43]	1.15 ***	[0.88, 1.43]
Age	0.03	[-0.01, 0.06]	-0.00	[-0.04, 0.03]	-0.01	[-0.05, 0.03]
Education	-0.03	[-0.07, 0.02]	-0.01	[-0.05, 0.04]	0.00	[-0.04, 0.05]
Wealth	-0.00	[-0.04, 0.04]	0.00	[-0.04, 0.04]	-0.01	[-0.06, 0.03]
Health	0.05 **	[0.02, 0.09]	0.04 *	[0.01, 0.07]	0.04 *	[0.01, 0.08]
WSR			0.20 ***	[0.16, 0.23]	0.20 ***	[0.16, 0.23]
DQ (ln)					-0.01	[-0.05, 0.03]
Exercise (ln)					0.00	[-0.04, 0.04]
ICC_{ssu}	0.02		0.02		0.01	
ICC_{psu}	0.02		0.02		0.02	
ICC_{strata}	0.19		0.19		0.19	
AIC	10306.65		10073.37		9039.99	
BIC	10362.49		10135.28		9113.02	
R^2 (fixed)	0.00		0.03		0.04	
R^2 (total)	0.22		0.25		0.25	

Note. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$. All continuous predictors are mean-centered and scaled by 1 standard deviation. The outcome variable is in its original units. PSU = Basic Geo-Statistical Area.

indicates the possibility of partial and full mediation effects. The addition of lifestyle variables in Model 3 showed that men in China who had higher physical activity levels and ate more fruits and vegetables had lower CRP levels, and women in Mexico who ate more fruits and vegetables had higher CRP levels. The addition of the lifestyle variables for men resulted in a weaker association between age and CRP, indicating that lifestyle factors account for some of this variance in some groups. In all models, the random intercept of location accounted for the most variance in CRP, ranging from 10% to 23%. Health was also significantly related to CRP in women in China and models 1 and 2 for men in China. The addition of lifestyle variables attenuated the relationship between health and CRP for men in China. Wealth was also related to

Table 5. Multiple regression predicting CRP for men in Mexico

	Model 1		Model 2		Model 3	
	β	*[CI]*	*β*	*[CI]*	*β*	*[CI]*
(Intercept)	1.49 ***	[1.39, 1.58]	1.45 ***	[1.35, 1.55]	1.44 ***	[1.34, 1.54]
Age	0.11 *	[0.03, 0.19]	0.09 *	[0.01, 0.18]	0.08	[-0.01, 0.17]
Education	-0.08	[-0.17, 0.02]	-0.05	[-0.15, 0.04]	-0.04	[-0.14, 0.05]
Wealth	-0.01	[-0.10, 0.08]	-0.03	[-0.12, 0.06]	-0.04	[-0.13, 0.06]
Health	0.07	[-0.02, 0.15]	0.08	[-0.00, 0.16]	0.08	[-0.01, 0.17]
WSR			0.17 ***	[0.09, 0.25]	0.18 ***	[0.09, 0.27]
DQ (ln)					-0.00	[-0.09, 0.09]
Exercise (ln)					-0.06	[-0.15, 0.04]
ICC_{psu}	0.10		0.10		0.10	
AIC	2169.48		2024.89		1934.04	
BIC	2201.37		2060.88		1978.50	
R^2 (fixed)	0.02		0.04		0.05	
R^2 (total)	0.12		0.13		0.14	

Note. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$. All continuous predictors are mean-centered and scaled by 1 standard deviation. The outcome variable is in its original units. PSU = Basic Geo-Statistical Area.

CRP in Models 2 and 3 for men in China. The increased significance of wealth between Models 1 and 2 indicates overlapping variance between WSR and wealth in this group.

The first mediational model, in which age and CRP was mediated by WSR, showed different relationships in China and Mexico (Table 7). In China, WSR significantly mediated the relationship between age and CRP. Women in China had a full mediation, whereby 77% of the relationship between age and inflammation was due to central adiposity and there were no direct effects between age and inflammation. Men in China had a partial mediation accounting for 8% of the full effect. All variables were positively associated. In Mexico, WSR was positively associated with CRP but WSR did not vary by age, therefore there were no mediational effects. In Mexico, older men and women did not have more or less central adiposity than younger men

Table 6. Multiple regression results predicting CRP for women in Mexico

	Model 1		Model 2		Model 3	
	β	*[CI]*	*β*	*[CI]*	*β*	*[CI]*
(Intercept)	1.74 ***	[1.64, 1.83]	1.74 ***	[1.65, 1.83]	1.73 ***	[1.63, 1.82]
Age	-0.12 ***	[-0.20, -0.05]	-0.12 ***	[-0.20, -0.05]	-0.13 ***	[-0.21, -0.06]
Education	0.02	[-0.06, 0.10]	0.03	[-0.06, 0.11]	0.03	[-0.06, 0.11]
Wealth	0.02	[-0.06, 0.10]	0.02	[-0.07, 0.10]	0.01	[-0.07, 0.09]
Health	0.02	[-0.06, 0.09]	-0.02	[-0.09, 0.05]	-0.03	[-0.10, 0.05]
WSR			0.27 ***	[0.20, 0.35]	0.28 ***	[0.21, 0.36]
DQ (ln)					0.08 *	[0.00, 0.15]
Exercise (ln)					-0.02	[-0.09, 0.06]
ICC_{psu}	0.11		0.12		0.11	
AIC	3409.81		3195.36		3093.16	
BIC	3444.59		3234.69		3141.97	
R^2 (fixed)	0.01		0.06		0.07	
R^2 (total)	0.13		0.17		0.18	

Note. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$. All continuous predictors are mean-centered and scaled by 1 standard deviation. The outcome variable is in its original units. PSU = Basic Geo-Statistical Area.

Table 7. Multilevel mediation model with age and CRP mediated by waist-to-stature ratio (WSR)

	b_a	b_b	b_c	IE_{xy}	$Prop_{xy}$
China					
Men	0.08***	0.11***	0.09***	0.008***	0.08***
Women	0.18***	0.19***	0.009	0.03***	0.77**
Mexico					
Men	0.008	0.14***	0.09*	0.001	0.01
Women	-0.007	0.22***	-0.11***	-0.002	0.01

Note. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

and women. Both central adiposity and age were related to inflammation. Although men's CRP was higher with age, women's CRP levels were lower with age in Mexico.

The second set of mediational models, with the addition of physical activity and diet, showed the importance of behavioral factors on WSR and CRP (Tables 8 and 9). Age was negatively associated with increases in fruit and vegetable consumption in men and women from

Table 8. Multilevel multiple mediation model with exercise as second mediator

	b_d	b_e	IE_{xm2}	$Prop_{xm2}$	IE_{m1y}	$Prop_{m1y}$
China						
Men	-0.23***	-0.07***	0.01**	.15**	-0.008***	.09***
Women	-0.21***	-0.04*	-0.000	-.003	-0.008*	.30
Mexico						
Men	-0.31***	-0.11**	0.04**	.48	-0.01**	.16*
Women	-0.19***	-0.07*	0.01*	.19	-0.02*	.34

Note. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

Table 9. Multilevel multiple mediation model with dietary quality (DQ) as second mediator

	b_d	b_e	IE_{xm2}	$Prop_{xm2}$	IE_{m1y}	$Prop_{m1y}$
China						
Men	-0.08***	0.03	-0.003	-.04	0.002	-.05
Women	-0.21***	-0.04*	-0.001	-.003	-0.007*	.26
Mexico						
Men	-0.02	0.14***	-0.002	-.002	0.02***	.30
Women	-0.05	-0.05	0.002	-.002	-0.01	-.15

Note. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

China, but not Mexico. Men from Mexico had higher WSR with a diet higher in fruit and vegetable intake, and women from China had a lower WSR with higher fruit and vegetable intake. There were no mediational effects of diet between age and WSR, however WSR positively mediated the effect between diet and CRP in men in Mexico and negatively mediated the effect between diet and CRP in women in China. Physical activity was more frequently a significant mediator than diet (Table 8). In all four groups, older people tended to have lower physical activity levels. This lower level was associated with a higher WSR in all groups. In both countries men had an indirect effect of exercise between age and WSR, and all groups except women from Mexico had a negative indirect effect of WSR between exercise and CRP.

Discussion

The hypothesis (H1) that central adiposity would be more strongly associated with inflammation than age was supported in at least two groups—women in China and Mexico. The relationship between aging and inflammation varied among the four groups, with higher inflammation seen in men at older ages, no relationship between inflammation and age in women from China, and lower inflammation seen at older ages in women from Mexico. Since inflammation is associated with non-communicable diseases (NCDs), a selection effect due to NCD related mortality cannot be ruled out; however, men tend to die at higher rates at all ages from NCDs in Mexico and China (Guerrero-López et al., 2023; Yin et al., 2019). Men, but not women, in Brazil also had lower CRP values at higher ages (Almeida et al., 2012), and in the USA age was not associated with CRP in a group of adults age 52 to 70 when controlling for demographic, anthropometric, behavioral, and psychosocial factors (McDade et al., 2006). This calls into question the assumption that there is an inherent link between aging and higher chronic

inflammation. Rather, these results suggest that inflammation is more consistently related to increased central adiposity than with increased age.

Central adiposity mediated the association between aging and inflammation in China, but not Mexico (H2). Increases in inflammation with age were fully mediated by central adiposity in women living in China. It is thought that inflammation from metabolic dysregulation overlaps mechanistically with but is distinct from the chronic low-grade inflammation that is inherent to aging, however studies on aging and metabolic dysregulation have been largely separate research fields and inflammaging has not been well studied in animal models (Franceschi et al., 2018). Increases in inflammation with age are thought by some to be under genetic control and associated with a remodeling of the immune system that is universal, whereas inflammation associated with metabolic dysregulation has mainly been attributed to lifestyle and environmental factors (Franceschi & Bonafè, 2003). This result suggests that they might not be distinct processes, and that inflammaging might occur because of a propensity for cellular hyperactivity that is activated by diverse causes, such as infection and energy rich environments, in a cumulative process over time. Differences in results among groups could be due to there being multiple causes of this inflammation, therefore more mediators of the relationship should be explored to determine if increases in inflammation are due to lifestyle and environmental factors. Inflammation could be aging-related instead of inherent to senescence.

In Mexico, there was a lack of association between age and central adiposity and age was negatively associated with inflammation in women. This is consistent with literature reporting that although on average central adiposity increases with age, these gains can be prevented by lifestyle factors such as diet and exercise (Mete et al., 2024; Poehlman et al., 1995; Stevens et al., 2010). In addition, caloric restriction and exercise have been shown to reduce aging-related

increases in inflammation (Kalani et al., 2006; Meydani et al., 2016; Woods et al., 2011). Although decreases in inflammation are rarely seen at the population level, a longitudinal study in England showed that 10% of the population had decreasing inflammation with age (Lassale et al., 2019). Since differences in central adiposity were not associated with age universally, neither metabolic nor inflammatory processes were consistently associated with age in this study despite both being posited as key mechanisms of universal aging effects (Chen & Yung, 2019; Franceschi et al., 2000, 2018).

Lifestyle factors also seemed to be associated with aging, central adiposity, and inflammation (H3). Age was negatively associated with fruit and vegetable intake in China, and age was negatively associated with physical activity levels in all groups. Physical activity levels were associated with a decrease in central adiposity in all groups and it was a significant mediator of the relationship between aging and central adiposity in men. In men, age was still a comparatively strong independent predictor of inflammation when controlling for central adiposity; however, this relationship was completely or partially attenuated in men in Mexico and China (respectively) by controlling for exercise and fruit and vegetable intake. This adds to literature showing that populations with different lifestyles do not necessarily have the same increases in inflammation seen in industrialized nations (Gurven et al., 2009; Harris et al., 2019; McDade et al., 2012) and that lifestyle factors, but not age, explain some interpopulation differences in inflammation (McDade et al., 2006). For example, Shuar living in lowland Ecuador have a median CRP level of 0.53 mg/L, lower than the 1 mg/L cutoff for chronic inflammation (McDade et al., 2012). Given that these self-report lifestyle variables have a moderate to high amount of measurement error (Herrmann et al., 2013; Medina et al., 2013), the relationship between diet and exercise and inflammation is likely even stronger than reported

here. Further, these are only two of many lifestyle and psychosocial factors that contribute to inflammation. Another major contributor is stress and adversity (Johnson et al., 2013; Lin et al., 2016; McDade et al., 2006). Therefore, they are likely a strong contributing factor to the relationship between age and inflammation.

Relationships were different between separate groups, including among men and women. Studies show that although greater central adiposity is associated with higher levels of inflammation in both women and men, the association is stronger in women (Khera et al., 2009; Thompson et al., 2016; Valentine et al., 2009). This effect was mirrored in the current study, with the relationship between WSR and CRP greater in women than in men in both countries. Women who live in Mexico had the strongest association between central adiposity and inflammation, and they were the only group that had lower inflammation levels at older ages than younger ages when controlling for central adiposity. In addition, women in China and men in Mexico had opposing effects of dietary quality on waist circumference, likely because the variable is related to varying types of diets.

Despite evaluating well-established metabolic and inflammatory changes that occur with age, the strongest predictor of CRP in all models was location, which accounted for 10% to 23% of the variance in CRP. Further, the beta values exceeded one in all cases which is indicative of multicollinearity effects with the other predictors, likely because location influences behavioral lifestyle factors and environmental exposures. Therefore, there are group level differences in included and excluded social and behavioral factors due to living in different locations and environments. Socioeconomic status (education and wealth in the current models) has long been shown to be related to location due to differences in land value and preferences (Moriarty, 1974), and geographic location, culture, and economics likely influence health (Thomas et al., 2014). A

study of overweight and obesity in four sub-Saharan African populations found the presence of overweight and obese adults varied between 46% and 85% by location (Ajayi et al., 2016). Further, both diet and exercise behaviors vary by location (Haglund, 1984; McCullough et al., 2022). Decreases in physical activity, widespread availability of calorie-dense foods, psychosocial stress, pollution, and other factors that vary by location could contribute to the differing associations seen between aging and inflammation. Given the importance of location to inflammation, more research needs to be done into the geographical and population-level differences that cause inflammation. This could lead to more interventions targeting structural factors, as opposed to individual factors, to promote healthy aging and prevent aging-related disease.

Since this study was not longitudinal it is possible that some of the current findings are due to cohort effects. Inflammation has been shown to increase slightly with every subsequent generation (Hulsegge et al., 2016), and if these cohort effects are larger in the populations studied, they could have masked individual effects and produced the decline in inflammation with age seen in women from Mexico. It is also difficult to determine directionality and causality of the effects. Although many studies have shown that central adiposity directly affects inflammation (e.g., Kopp et al., 2013; Nicklas et al., 2004), at least one longitudinal study has shown that elevated inflammation preceded weight gain in middle-aged males (Engström et al., 2003). Further, it is possible that the age range was not large enough to pick up differences in inflammation and the physical activity and diet questions were limited. More large studies are needed to understand age-related increases in inflammation in human populations.

This study challenges long held notions that aging and inflammation are inherently linked. Previously, it was also thought that increasing blood pressure and hypertension were

biomarkers of senescence, however studies have shown that these are largely due to accumulated lifestyle effects (Law, 1997; Najjar et al., 2005). We showed that age-related changes in physiological factors that are influenced by lifestyle and environment, such as central adiposity, might drive age-related inflammation in many instances. Lifestyle factors, such as diet and physical activity, play a role in age-related weight changes, inflammation, and health. It is possible that decreases in physical activity, widespread availability of calorie-dense foods, psychosocial stress, pollution, and other factors could contribute to the differing associations seen between aging and inflammation. These lifestyle factors can be targeted to reduce or eliminate age-related inflammation and, possibly, the associated negative health outcomes. In addition to differences between people living in Mexico and people living in China, associations between age, central adiposity, and inflammation were different in men and women. More research is needed to explore the differential mechanisms that affect aging-related inflammation to improve health outcomes in different cohorts. Although inflammation is an important aspect of aging and disease in many current environments, it is not universal. Therefore, more efforts should be made to try to prevent the increase in inflammation with age.

Bridge

Chapter III provided evidence that not all groups undergo inflammaging, or an increase in chronic inflammation with age. This is surprising since inflammation has been closely linked with known aging mechanisms such as cellular senescence. This chapter also highlights the importance of a global perspective on health and disease. Knowing that most, but not all, people and groups experience this aging mechanism helps elucidate what might be causing inflammation. This research has shown that metabolic factors (such as central adiposity) and lifestyle factors (such as diet and exercise) could partially explain these differences. The next

chapter is an independent research article that expands on these results. Namely, it is intended to evaluate whether the relationship between age and inflammation is non-linear and whether it is partially or wholly due to metabolic factors in Shuar, an Indigenous group living in lowland Ecuador.

CHAPTER IV

Inflammaging in Shuar is due to Metabolic Factors

Older adult populations are increasing at unprecedented rates globally. In 2020, adults over age 60 outnumbered children younger than 5 for the first time, and the older adult population is expected to double, from 12% to 22% of the world's population, between 2015 and 2050 (WHO, 2024). However, there is still a lack of consensus on the most basic scientific principles of aging, or decline in organismal functioning over time (Cohen et al., 2020). This is especially problematic when considering how aging is related to non-communicable diseases, which accounted for 75% of non COVID-19 related deaths globally in 2021 (WHO, 2024). "Inflammaging" is an increase in low-grade chronic inflammation over time that results from cellular aging processes, including immunosenescence, and is a cause of non-communicable diseases (Franceschi et al., 2000). High rates of chronic inflammation were seen in healthy centenarians, leading to the notion that increasing chronic inflammation is a universal aspect of aging (Arai et al., 2015). These inflammatory stressors combine with the presence of certain genetic variants to make an individual susceptible to a particular non-communicable disease (Franceschi et al., 2018). Given its universality and strong links to aging-related decline and disease, increasing low-grade chronic inflammation with age has been posited as a key mechanism of aging processes.

Despite this being one of the most well-accepted models of aging, some lines of evidence suggest that increases in chronic inflammation with age might not be universal, and rather, are primarily related to dysregulated metabolic processes associated with high-calorie diets and low amounts of physical activity. High-income nations, where most of the data on inflammation has been collected, are socially and environmentally very different from those in which we evolved

and different than other populations that have different lifeways and ecology. Evidence shows that chronic inflammation and non-communicable diseases, such as cardiovascular disease, are lower in populations with divergent lifestyles (Gurven et al., 2008). In the Shuar, an Indigenous group living in the Santiago Morona region of Ecuador, levels of chronic inflammation are consistently very low, and always below levels that predict non-communicable disease (McDade et al., 2006). The Tsimané, an Indigenous group living in lowland Bolivia, have high levels of inflammation, but this inflammatory profile is associated with a high pathogen load and is not associated with cardiovascular disease in the same way as in high-income nations (Gurven et al., 2008, 2009; Kaplan et al., 2017; Vasunilashorn et al., 2010). Further, even in high-income nations, a small minority of individuals do not have increasing inflammation with age (Wener et al., 2000). The present study investigates whether low-grade inflammation increases with age in Shuar, who have moderate amounts of physical activity and primarily eat a subsistence-based diet. This process, termed inflammaging, is thought to be caused by both aging and metabolic dysregulation separately.

Inflammaging

"Inflammaging," or the gradual increase of chronic low-grade inflammation that is not associated with an acute infection, has been designated a hallmark of aging (Franceschi et al., 2000; López-Otín et al., 2013). This process includes increases in both acute phase proteins, such as C-reactive protein (CRP), which is released into the bloodstream by the liver to signal for inflammatory processes systemically, and in inflammatory cytokines, such as Interleukin-6 (IL-6), which act both locally and systemically to activate macrophages (Liu et al., 2023). Higher levels of inflammation with age is partially caused by immunosenescence, including shifts in the populations of T cells, cellular hyperactivity of inflammation-producing TH1 and TH17 cells,

and the defective elimination of infections, malignant, and senescent cells (Carrasco et al., 2022; López-Otín et al., 2023). Cells are limited in how many times they can divide, and cell cycle arrest leads to the senescent-associated secretory profile (SASP). SASP is the hypersecretion of numerous pro-inflammatory and growth-stimulating molecules by non-dividing cells, the most well-studied of which are interleukin (IL) 1α, IL-1β, IL-6, IL-8, and transforming growth factor-β (TGFβ; Coppé et al., 2010). Once chronic low-grade inflammation has started, it can lead to a lack of maintenance and repair of biological barriers, such as the blood-brain barrier, the blood-retinal barrier, and the blood-nerve barrier, leading to more widespread chronic inflammation (Rönnbäck & Hansson, 2019). Therefore, as cells and cell systems age, they promote the release of inflammatory cytokines, leading to downstream negative effects on physiology and health.

A major strength of the inflammaging paradigm is its ability to link cell-mediated aging processes with organismal aging-related decline and disease. Chronic low-grade inflammation is associated with many non-communicable diseases, such as diabetes, cardiovascular diseases, cancers, arthritis, pulmonary disorders, kidney diseases, liver diseases, and neurodegenerative diseases as well as all-cause mortality (Banait et al., 2022; Li et al., 2017; Seo & Park, 2021; Yeh, 2004). Approximately half of all deaths are due to diseases and disorders with a chronic inflammatory etiology (Furman et al., 2019). Further, since inflammation is associated with immune system decline, older adults are more susceptible to infectious diseases (Liu et al., 2023). Inflammation is also associated with frailty (Soysal et al., 2016), making it a main contributor to both aging-related decline and disease.

Meta-Inflammation

Inflammaging research has primarily come out of gerontology. Meanwhile, health scientists whose research mostly focused on obesity and type 2 diabetes were also studying the

link between inflammation and non-communicable disease but were doing it from a metabolic viewpoint. Meta-inflammation is the overproduction of proinflammatory cytokines by adipose tissue, which directly promotes the release of CRP and other pro-inflammatory molecules from the liver into the bloodstream (Hotamisligil, 2006a). In addition to obesity related inflammation, cholesterol, triglycerides, and sugars in the blood directly activate inflammatory processes in macrophages and other cells (Poznyak et al., 2020). Therefore, obesity is not necessary for metabolic syndrome or metabolic disorders (Alberti et al., 2005; Samson & Garber, 2014), as decreased insulin sensitivity also leads to an increase in adipose tissue (Klöting & Blüher, 2005). Instead, an overall over-energetic status, where caloric intake exceeds energy needs, seems to promote chronic inflammation and its negative sequelae.

It has been noted that the pathways and processes in inflammaging and meta-inflammation are the same, and they are thought to be overlapping but distinct. In this "unifying hypothesis," meta-inflammation and inflammaging can both precede and contribute to each other, with aging-related decline and disease from metabolic dysregulation being a manifestation of accelerated aging (Franceschi et al., 2018). However, this hypothesis has not been well tested (Hotamisligil, 2006) and meta-analysis shows that CRP and IL-6 are associated with frailty in cross-sectional, but not in longitudinal studies (Soysal et al., 2016). If meta-inflammation exacerbates inflammaging, then increases in inflammation with age might exist below the threshold needed for non-communicable disease risk in communities with low metabolic dysregulation.

Evolutionary Theory

Some aspects of evolutionary theory have been applied to inflammaging. Degeneracy is common in the immune system and consists of an overlap in the functioning of different

components and pathways (Edelman & Gally, 2001). Redundancy is both a feature of natural selection, allowing for greater evolvability by natural selection, and an outcome of natural selection, because a similar host of environmental pressures affect the same assortment of genes (Edelman & Gally, 2001). It could also be seen as an adaptation because it improves robustness, or the ability to maintain function given an environmental or biological perturbation (Whitacre, 2010). Humans have an unusually large geographic distribution, which, combined with diverse ecologies and diets, means we are exposed to a wide range of parasites and pathogens. There is a lot of degeneracy in the receptors that activate inflammation, leading to the activation of inflammation by various inputs, including chronic infectious agents, the microbiome, environmental and dietary inputs, and internal molecular and cellular components (Franceschi et al., 2018). Although this degeneracy leads to increasing rates of chronic inflammation with time, the pressure of natural selection also weakens over time. This decrease in selective pressure over time is because there is a slight diminishing of returns on the amount each child increases the probability of contributing to the future population gene pool, and is a major pillar of most aging theories (Comfort, 1964; Fisher, 1930; Medawar, 1952). Therefore, inflammaging might persist because it mainly affects individuals in late life, when selective pressure is weaker.

Part of this degeneracy in inflammatory signaling is a functional overlap between immune and metabolic factors. There are a large amount of macrophages in adipose tissue, and they are known to regulate a vast amount of physiological processes (Chavakis et al., 2023). The release of inflammatory markers from these macrophages blocks growth factor and insulin signaling, possibly as an evolved mechanism to redirect energy to immune functions that eliminate pathogens (Hotamisligil, 2006). The stimulation of these macrophages by adipocytes and energetic molecules to produce inflammatory cytokines and chemokines could have also

been advantageous in an environment with energetic constraints and chronic parasitic infections. Essentially, excess energy is directed towards an immune response. Even in the absence of pathogen-associated molecular patterns (PAMPs) this response is useful for clearing cell debris, damaged cells, and malignant cells and can therefore be stimulated by damage-associated molecular patterns (DAMPs; Tang et al., 2012). If there is normally never enough of an immune response due to energetic constraints, then upregulating immune systems during times of excess energy availability might have been advantageous.

Scientists have grappled with the fact that there are not more evolved mechanisms to deal with an overenergetic status. Some have argued that there is no need to defend against obesity, but a strong need to defend against starvation, yet also state that obesity is a liability related to metabolic disease (Franceschi et al., 2018; Hotamisligil, 2017). Instead, it is likely because this system did not evolve in the current nutrient surplus, which was created by the relatively recent advent of industrialization, large scale agriculture, and the concentration of economic resources (Lea et al., 2020; Liebert et al., 2013; Stearns et al., 2010; Urlacher et al., 2016). Beyond primates, the only known species to get type-2 diabetes are cats, dogs, and captive animals, further pointing towards human-created environments in the advent of the disorders (Niaz et al., 2018). It is possible that these two different selection mechanisms – aging diminished selection, and evolutionary mismatch, produced the overlapping but distinct mechanisms of inflammaging and meta-inflammation.

Shuar Health and Life History Project (SHLHP)

The SHLHP was designed to investigate health transition in the Shuar, an Indigenous group living in lowland neotropical Ecuador. Most Shuar live in two main regions; the Cross-Cutucú (CC) region is more geographically isolated, whereas the Upano Valley (UV) region has

greater access to roads, electricity, healthcare facilities, and market centers (Liebert et al., 2013; Urlacher et al., 2016). Shuar in both regions engage in small-scale horticulture of staples such as plantains, manioc, sweet potatoes, and yams. Amounts of foraging, fishing and hunting vary but are generally greater in the CC region (Liebert et al., 2013; Urlacher et al., 2016). This allows for the study of how transition in market integration, economics, and diet affects health, and gives insight into how a vastly different lifestyle from those in the human evolutionary past affects biology, health, and disease. If rising chronic inflammation with age is due to metabolic factors associated with current lifestyles, there are likely to be differences in inflammation between the two regions.

Shuar that live in the CC region have higher rates of parasitic infections, including whipworm and roundworm (Cepon-Robins et al., 2014; Gildner et al., 2016, 2020). However, CRP has been shown to be low in both regions, with a median of 0.52 mg/L and no one consistently over the threshold of 3 mg/L that indicates an increased risk of disease (McDade et al., 2012). Yet 35% of participants had values over 3 mg/L at one timepoint, possibly due to it being a high infectious disease environment. In addition, approximately 40% of Shuar juveniles experience stunting, with similar rates among the regions, indicating energetic tradeoffs from a lack of macronutrients (Blackwell et al., 2009; Urlacher et al., 2016). Therefore, CRP will be evaluated in an environment where inflammation is commonly elevated due to infectious disease, and less-so because of excess macronutrients and metabolic dysregulation, with variation between regions in both.

Objectives and Hypotheses

Objective 1. Assess whether the relationship between CRP and age is linear or not linear.

H1. The relationship between CRP and age will be non-linear.

Objective 2. Investigate differences in CRP with age.

H2. CRP will be positively associated with the age of individuals.

Objective 3. Investigate whether differences in inflammation with age are associated with metabolic functioning.

H3. Higher inflammation with age will be associated with higher lipids, glucose, and central adiposity.

Objective 4. Evaluate the variance in aging-related differences in CRP by location

H4. The association between age and CRP will vary by community.

H5. The association between age and CRP will vary by region.

Objective 5. Evaluate differences in the attenuation of the relationship of CRP and age by metabolic factors in different locations.

Method

Participants

There were 456 participants from 8 CC communities (n = 146) and 11 UV communities (n = 283), and nearby towns (n = 27). Slightly more women (n = 290, 64%) than men (n = 166, 36%) participated, with ages ranging from 15 to 86 years (M = 34.54, SD = 14.71). Data was collected across 7 field seasons between 2008 and 2014. In instances where participants had two CRP values, the visit with the least amount of missing data (when applicable) or the most recent visit was included. Participants who reported being sick currently or within the past week and those with a CRP value over 10 mg/dL, indicating infection, were excluded from analysis (28%, n = 129). Participants who were sick were similar in age (t = -0.91, p = .36) and sex (χ^2 = 1.39, p = .24) to those that were not, however more people were sick in UV communities (26%) than CC ones (4%, χ^2 = 37.08, p < .001).

Adults (≥15 years of age, the age of legal consent in Ecuador) provided informed consent to participate. The study was approved by the University of Oregon IRB, by community leaders upon community consensus, and by the *Federacíon Interprovincial de Centros Shuar*.

Measures

Survey Questions

Survey questions were administered in Spanish, with a few cases where a community member translated to Shuar. Demographic information was collected, including name, age, formal education, and household composition. Estimates of age were verified with official school records and/or government-issued identification cards. Participants also indicated whether they were currently sick or had been sick in the last week.

Anthropometrics

Height was measured to the nearest 1.0 mm using a portable stadiometer (Seca Corporation 214, Hanover, MD). Waist circumference was measured to the nearest 1.0 mm, approximately 2 in above the iliac crest, using a tape measure. Waist was divided by height to create waist to stature ratio (WSR).

Blood biomarkers

Inflammatory. Finger-prick capillary blood was collected onto filter paper (Whatman 903, GE Healthcare, Pascataway, NJ) for dried blood spot (DBS) analysis of CRP following standard practices (McDade et al., 2006). DBS cards dried for approximately 4 hours at ambient temperature, protected by a small net. They were then stored at −20°C in sealed bags with desiccant for the remainder of the field season. Upon completion of the field season they were express shipped on dry ice to the United States where they were stored at −30°C until analysis.

Samples were analyzed in the Global Health Biomarker Laboratory at the University of Oregon using enzyme-linked immunosorbent assays (ELISA) using a protocol previously developed for use with DBS (Brindle et al., 2010; McDade et al., 2004). Most samples were run in duplicate with excellent intraassay variability (*ICC* = .99). A conversion formula was created by analyzing 51 matched DBS and serum samples. The correlation between the sample types was high (r = .98), with the Deming conversion formula as follows: serum (mg/L) = 1.84 × DBS (mg/L).

Metabolic. Point-of-care testing with finger-prick capillary blood was used to measure HDL cholesterol and glucose. All measures were taken after a 12-hour fast. Samples were assessed using a CardioChek PA device (Polymer Technology Systems, Indianapolis, IN).

Statistics

R version 4.3.0 was used for statistical analyses. All CRP DBS values were transformed to serum equivalents. Statistical assumptions were evaluated prior to analysis, and CRP and glucose were log-transformed to meet requirements for normality. The distribution of age was similar between UV and CC Shuar. However, CRP estimates were transformed back to the original scale for reporting. The fit of a linear multi-level model with maximum likelihood estimation will be compared to a generalized additive mixed model using penalized quasi-likelihood estimation with smoothed age to determine if the relationship between age and CRP is linear (H1). Both models will control for sex (fixed effect) and community (random intercept), and the edf (complexity of smooth), R^2 (percent variance in CRP accounted for), and appearance of the smoothed relationship were used to determine if linear or generalized additive models would be used for the remainder of the analyses. The selected model was then used to evaluate the strength of the relationship between age and CRP (Model 1, H2). The metabolic

measurements, glucose, HDL, and WSR, were then added to the model and the strength of the fixed effects, R^2 values, and attenuation of the relationship between CRP and age were evaluated (Model 2, H3). Finally, the fit of fixed effect, random intercept, and random slope models with community as the random effect were evaluated to determine if the relationship between CRP and age varies by community (H4). They were compared using a likelihood-ratio test. For region, separate fixed-effect models will be compared to determine if the relationship between CRP and age varies between the CC region and UV region (H5). Models for both H4 and H5 were run with (Model 2) and without (Model 1) metabolic controls in order to evaluate the differential contribution of metabolic factors to the relationship between CRP and age between UV and CC Shuar (excluding those who live in town).

Results

On average CRP values were fairly low (M = 1.22, SD = 1.63) with males (M = 1.43) having higher values than females (M = 0.86, $t(398) = 3.47$, $p < .001$) and the CC region (M = 1.51) having higher values than the UV region (M = 0.96, $t(223) = 2.69$, $p < .001$). Shuar living in the CC region were slightly younger on average (M = 31.16) than those living in the UV region (M = 34.92, $t(323) = -2.45$, $p = .01$), however the differences in CRP between the regions were similar when controlling for age (b = 0.68, $t(378) = 4.12$, $p < .001$). Participants living in towns (M = 1.41) had similar CRP to participants living in the UV region (M = 0.90), although the analysis was underpowered ($t(33) = 2.02$, $p = .05$). The mean age was similar between people living in towns (M = 34.04) and the UV region (M = 34.92, $t(33) = -0.30$, $p = .77$). Year was not related to CRP overall ($r = .10$, $n = 406$, $p = .05$), but it is highly confounded with community as different communities provided data in different years. The linear multilevel model accounted for more variance in CRP than the generalized additive mixed model ($edf = 1$, $R^2 = .09$), and the

smoothed relationship appeared linear (Figure 1). Therefore, linear models were used for the remainder of the analyses.

Overall, there was a positive association between CRP and age (Model 1, Table 1). However, this association was completely attenuated with the addition of glucose, HDL, and WSR (Model 2, Table 1). Further, the addition of a random slope for community to Model 1 completely attenuated the relationship between age and CRP. For Model 1, the model fit for the fixed effect and random intercept models was similar ($\chi^2 = 0.75$, $p = .39$), but the random slope model provided a better fit for the data ($\chi^2 = 10.45$, $p = .005$). For Model 2, the random intercept model was a better fit for the data than the fixed effect model ($\chi^2 = 13.42$, $p < .001$), however the addition of a random intercept or slope for community did not significantly improve the model ($\chi^2 = 2.73$, $p = .25$). Men had higher CRP values in Model 1, but this effect was fully attenuated by the addition of metabolic factors. Fasting glucose was positively related to CRP when

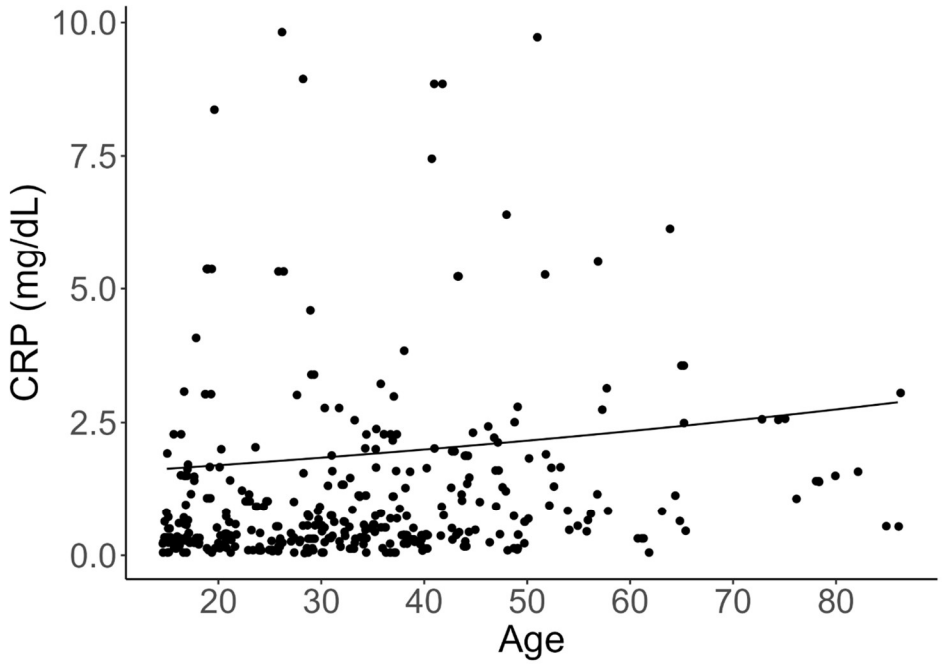


Figure 1. Generalized Additive Mixed Model Fit Between Smoothed Age and CRP

accounting for different slopes between age and CRP among communities, and WSR was positively related to CRP in both models.

There was a positive relationship between CRP and age in Shuar living in the UV region, but there was no relationship between CRP and age in Shuar living in the CC region (Model 1, Table 2). When controlling for metabolic factors the association between CRP and age in the UV was fully attenuated (Model 2, Table 2). Fasting glucose, HDL cholesterol, and WSR were not related to CRP in the CC region, but glucose and WSR were positively related to CRP in the UV region.

Discussion

The relationship between inflammation and age was linear, discounting the possibility that inflammation rises to unhealthy levels quickly in older adults. However, the gradual increase in mean CRP as the sample got older suggests that mean levels might still approach those that cause risk for disease towards the end of the lifespan. However, the relationship between age and inflammation was entirely due to only a few indicators of metabolism (fasting glucose, fasting HDL, and WSR). Further supporting this idea, there was no relationship between CRP and age in the CC region, which is hard to access and has not been as influenced by market integration at the time samples were collected. This is despite CRP levels being higher overall in the CC region, likely due to higher rates of unreported infectious disease below the 10 mg/L CRP cutoff. This demonstrates that the immune system evolved for a different infectious disease burden (Cepon-Robins et al., 2014; Gildner et al., 2020; Rook, 2023), which becomes hyperactivated in settings with metabolic dysregulation.

The evaluation of community random effects supports the idea that different trajectories between age and inflammation are occuring in different communities because of differences in

Table 1. Multi-Level Models Predicting CRP

	Model 1						Model 2					
	Random Intercept			Random Slope			Random Intercept			Random Slope		
	b	*SE*	*p*	*b*	*SE*	*p*	*b*	*SE*	*p*	*b*	*SE*	*p*
Intercept	0.58	0.07	< .001	0.65	0.14	.005	-0.91	1.18	.002	-0.76	0.41	< .001
Age	0.01	0.002	< .001	0.01	0.003	.05	0.004	0.002	.06	0.002	0.003	.51
Sex	-0.18	0.05	< .001	-0.19	0.05	< .001	0.02	0.06	.76	0.01	0.06	.88
Glucose (ln)							0.35	0.18	.07	0.005	0.002	.03
HDL							0.003	0.002	.26	0.002	0.002	.39
WSR							16.19	0.69	< .001	17.68	0.67	< .001
$SD_{community}$	.16			.47			.18			.37		
SD_{age}				.01						.01		
ICC	.10			.53			.16			.45		
Pseudo R^2	.18			.26			.29			.31		

Note. CRP (mg/L) reported in serum equivalents. HDL = High Density Lipoprotein; WSR = Waist to Stature Ratio.

Table 2. Linear Regression Models Predicting CRP

	Model 1						Model 2					
	Cross-Cutucú			Upano Valley			Cross-Cutucú			Upano Valley		
	b	*SE*	*p*	*b*	*SE*	*p*	*b*	*SE*	*p*	*b*	*SE*	*p*
Intercept	1.30	0.12	< .001	0.18	0.07	.02	14.05	5.57	.15	-0.99	1.20	< .001
Age	0.002	0.003	.58	0.01	0.002	< .001	0.00	0.01	.88	0.004	0.002	.06
Sex	-0.33	0.09	< .001	-0.10	0.06	.05	-0.12	0.15	.36	0.12	0.06	.06
Glucose (ln)							-0.54	0.52	.07	0.84	0.19	.001
HDL							0.01	0.004	.10	-0.00	0.002	.95
WSR							7.64	3.77	.17	45.00	0.64	< .001
R^2	.11			.14			.07			.37		

Note. CRP (mg/L) reported in serum equivalents. HDL = High Density Lipoprotein; WSR = Waist to Stature Ratio.

energetic status. Without metabolic controls, the relationship between age and inflammation varied by community as indicated by the random slope model providing the best fit. However, when controlling for metabolism, there was variation in CRP by community but the relationship between age and CRP did not vary (it stayed a null effect in all communities). Therefore, this study is one of the first to show that the increase in inflammation with age is due to metabolic factors associated with energy-dense environments created relatively recently in human evolutionary history.

Implications for Aging

Three possibilities emerge: 1) metainflammation is distinct from intrinsic aging processes, 2) CRP only measures metainflammation, or 3) metabolic dysregulation is a key part of aging.

These findings run counter to many studies from animal models and in high-income nations that suggest increased chronic inflammation over time is a central part of intrinsic aging processes. However, geroscience has long been biased by the confusion between aging and aging-related disease (Franceschi et al., 1995; Ligthart et al., 1984). For example, it was once thought that blood pressure was a measure of aging because it increased over time in the populations studied, but this finding was later shown to be due to the cumulative effects of salt intake and other environmental factors (Law, 1997; Pickering, 1997). Studies on both blood pressure and inflammation with age are heavily biased by the fact that most research occurs in high-income nations, where market foods and other cultural factors are confounded with aging-related processes. Therefore, inflammaging and metabolic dysregulation could be disease processes that are unrelated to intrinsic aging processes. However, a broad definition of aging as

a decline in organismal functioning over time includes metabolic dysregulation and inflammation.

It is possible that CRP is only a measure of meta-inflammation but that other inflammatory molecules increase with age due to inflammaging universally. This would make sense since CRP is produced by the liver with known signaling pathways from central adiposity (Hotamisligil, 2006b). Conversely, IL-6 also increases with age but is produced by the SASP and hyperactive macrophages and therefore might be a measure of inflammaging (Hotamisligil, 2006b). Separating inflammatory biomarkers of aging from inflammatory biomarkers of metabolic dysregulation would be very useful for investigating aging processes in energy-dense environments.

Another possibility is that energetic and metabolic factors are responsible for aging processes. It is not only an over-energetic status that leads to aging, as caloric restriction elongates lifespan (Colman et al., 2009; Kraus et al., 2019; Mercken et al., 2012; Speakman & Mitchell, 2011). Further, insulin, insulin-like growth factor (IGF-1) signaling, and mammalian target of rapamycin (mTOR) signaling have been closely linked with lifespan and aging such that the downregulation of energy going through a cell elongates lifespan (Blagosklonny, 2010; Bonafè et al., 2003; Klöting & Blüher, 2005). This is also in line with some evidence from life history theory, that links slow growth with longer lifespans (Lee et al., 2013; Lind et al., 2017; Metcalfe & Monaghan, 2003; Walker et al., 2006). Given the complete overlap demonstrated here, metabolism may always be intricately linked to aging.

Evolutionary Theory

This study shows that new energy-dense environments cause inflammaging due to an evolutionary mismatch. Three components are important for identifying evolutionary mismatch

in humans: 1) comparison between post-industrial and subsistence-level groups, such as the Shuar, 2) an environmental reason why the two might be different, and 3) a physiological explanation that links the environmental difference to the outcome (Gurven & Lieberman, 2020; Lea et al., 2023). This study contrasts with numerous studies from high-income nations showing a relationship between CRP and age, even at young ages, in individuals without metabolic diseases, and when controlling for some metabolic variables (Ahmadi-Abhari et al., 2013; Puzianowska-Kuźnicka et al., 2016b; Randall et al., 2022; Yamada et al., 2001). This likely stems from differences between subsistence-based societies and post-industrial societies in diet, exercise, infectious diseases, social, and economic variables (Cepon-Robins et al., 2014; Gildner et al., 2020; Gurven et al., 2013; Gurven et al., 2016; Jaeggi et al., 2021; Liebert et al., 2013; Urlacher et al., 2016). There is particularly strong evidence that greater physical activity and low-calorie diets cause lower chronic inflammation (Fedewa et al., 2017; Kalani et al., 2006; Pitsavos et al., 2007). This is because excess energy stimulates the mTOR pathway unnecessarily, leading to the production of inflammatory cytokines, especially in macrophages (Blagosklonny, 2010; Jia et al., 2014; Saxton & Sabatini, 2017). Therefore, inflammaging is likely a result of evolutionary mismatch in humans.

Numerous extrinsic factors lead to organismal decline in functioning and/or mortality, and there are numerous pathways involved. The network model of aging points out that a variety of cellular stressors, such as infectious agents, mutagens, heat, and intrinsic molecular stressors, lead to a network of defense mechanisms, and that all of these defense mechanisms must be considered when conceptualizing aging (Franceschi et al., 2000). The addition of excess energy as a cellular stressor that leads to organismal decline highlights the fact that these "stressors" are not always inherently damaging but rather are any condition the species has not evolved to cope

with. The defense network is comprised of evolutionary adaptations to these cellular stressors. Similar to other adaptations, they sometimes lead to tradeoffs and constraints that affect organismal functioning. Determining what these tradeoffs and constraints are will be key in understanding aging processes.

Both extrinsic and intrinsic stressors affect cellular aging, with some effects being cumulative. For example, mutagens and dysregulation from excess energy accumulate across the lifespan (Ren et al., 2022; Rigamonti et al., 2021). Therefore, a release of selective pressure resulting in a longer lifespan can lead to new selective pressures from previously adapted to cellular stressors. Although intrinsic cellular stressors could constitute a narrower definition of aging processes, the distinction between the two is complex. For example, a new mutagenic environment, an increase in menstrual cycles in industrialized nations, and the number of times a cell divides can all cause cancers (Singer & Grunberger, 2012; Strassmann, 1999; Tomasetti et al., 2017). Therefore, both intrinsic and extrinsic factors increase the mutational load, which increases cancer risk. Further, some stressors that are considered intrinsic, such as a lack of proteostasis or accumulation of damaged cell parts and debris, are likely due to environmental factors. Therefore, environmental factors might be inseparable from aging processes in humans.

Although selective pressure is weaker later in the lifespan, this selective pressure is likely stronger in humans, and meta-inflammation can affect survival at younger ages. Humans have evolved an unusually long post-menopausal/older adult period, although what caused selective pressure for this is unclear (Hawkes et al., 1998; Hawkes & Coxworth, 2013; Marlowe, 2000; Tuljapurkar et al., 2007). Further, it is estimated that approximately 134 out of every 100,000 people die of hypertension before age 40, with deaths also occurring from hyperlipidemia, type 2 diabetes, obesity, and non-alcoholic fatty liver disease (Chong et al., 2023). Further, 2.8% of

children and 4.8% of adolescents have metabolic syndrome globally, with some populations experiencing rapid increases in prevalence (Amer et al., 2021; Noubiap et al., 2022; Park et al., 2021). Therefore, if increases in metabolic inflammation are a part of senescence, then it is likely due to evolutionary mismatch rather than weaker selective pressure later in the lifespan.

Limitations

This study is cross-sectional, not longitudinal and therefore is confounded by cohort effects. It is possible that inflammation does increase with age and a similar increase in inflammation is happening in younger cohorts. However, we would expect young adult Shuar living in the UV region would experience these effects more than those living in the CC region. In addition, due to the logistics of getting to remote Shuar communities, usually only a few communities are sampled each year. Therefore, community is confounded with year of collection. Finally, controlling for infectious disease is important when evaluating chronic inflammation. The standard cutoff of 10 mg/L along with self-reported illness was used to exclude participants with infection (Giollabhui et al., 2020). However, it was shown that values above 3g/dL were rarely repeated (i.e., chronic) and instead likely indicated the beginning or end of an infectious state (McDade et al., 2012). However, values between 3 g/dL and 10 g/dL appeared to be equally distributed across ages. Finally, only a few metabolic measures had adequate sample sizes for inclusion. Despite this, the effects between age and inflammation were wholly accounted for.

Conclusions

The overlap between inflammaging and meta-inflammation has been noted, but they have still been thought to be distinct processes (Franceschi et al., 2018). However, evidence for inflammaging has primarily come from high-income nations. Shuar, a population with little

market integration, has increases in inflammation with age that are entirely attributable to metabolic processes. Further, Shuar who live in extremely remote regions of the Amazon basin have no increase in inflammation with age. This challenges the proposition that inflammaging and meta-inflammation are distinct processes and instead points to meta-inflammation being a main causal factor in aging-related decline and disease. This is in line with many studies showing the metabolic regulation of lifespan.

Bridge

Chapter IV provides additional evidence that inflammation does not go up intrinsically with age, but is instead associated with the consumption of excess energy in many human environments. This is likely due to an evolutionary mismatch because the environments in which humans evolved were more energy scarce than they are today. This chapter highlights the importance of both an evolutionary perspective and a global perspective. Collaborating with participants from different environments, subsistence strategies, and lifestyles helps elucidate physiological and evolutionary mechanisms of biological processes. The next chapter, Chapter V, evaluates the lifestyle factors, including market diet, sedentary behavior, and psychosocial stress, that could link market integration with metabolic disorders and chronic diseases. It also evaluates, and improves upon, previous measures of market integration.

CHAPTER V

The Mediation of Market Integration and Non-Communicable Disease

Non-communicable diseases (NCDs), such as cancers, cardiovascular diseases, diabetes, and chronic respiratory diseases, account for 74% of all deaths globally, with 77% occurring in lower- to middle-income countries (LMICs; WHO, 2023). Further, 86% of premature deaths (before age 70) occur in LMICs (WHO, 2023). Although a clear epidemiological transition is occurring with the global burden of chronic disease increasing alongside market integration and globalization, the variability in how and where this happens has yet to be well integrated with calls for increased attention to economic, social, demographic, and environmental factors alongside molecular biological information (Zuckerman et al., 2014). Here we consider potential pathways by which market integration is associated with NCDs using biomarkers from the World Health Survey Plus (WHS+) in Cambodia, an LMIC undergoing rapid economic and epidemiological transition. Specifically, we look at the mediation of the relationship between market integration and cardiometabolic risk factors and frailty by market food consumption, sedentary behavior, and post-traumatic stress.

NCDs also increase with aging (or organismal decline with time) and have a possible overlap with aging physiology. Phenotypic aging, or frailty, is also closely related to both biological aging (the rate at which one ages compared to their chronological age) and cardiometabolic risk factors (Pyrkov & Fedichev, 2019; Shakya et al., 2022). Yet, studies have shown that this increase in metabolic disorders coinciding with epidemiological transition is not associated with changes in phenotypic aging (frailty; Krenz & Strulik, 2023). Further, the Study on Global AGEing and adult health (SAGE) found that older adults in six middle-income countries had higher frailty with lower market integration (Hoogendijk et al., 2018). A systematic

review confirmed that the relationship was often disparate (J. Wang & Hulme, 2021). In addition, psychosocial stress, sedentary behavior, and diet have been closely linked to frailty (Kehler & Theou, 2019; Lorenzo-López et al., 2017; Shakya et al., 2024). Therefore, evaluating the mediation of market integration and frailty, and comparing it to that of cardiometabolic health, will give insight into changing trajectories of health and aging.

Market integration, or the amount of participation in a market-based economy, has been shown to affect health in a variety of ways. Although there is often a lower risk of infectious diseases and infant mortality (Cepon-Robins et al., 2019; Gildner et al., 2020; Nishiyama, 2011; Omran, 2005), there is an increased risk of metabolic and cardiovascular disorders. These effects have been seen both in individuals who move between more traditional subsistence strategies (e.g., pastoralism, horticulturalism, hunting, and gathering) to market subsistence strategies (Lea et al., 2020; Liebert et al., 2013; Lu, 2007), and with increasing market integration between rural and urban areas within LMICs (Ajayi et al., 2016; Allender et al., 2011; Angkurawaranon et al., 2014; Lea et al., 2020; Salgado et al., 2020; Yusuf et al., 2001). Both processes are considered to be a part of an epidemiological transition toward increased chronic diseases.

Market Integration, Urbanization, and Evolutionary Mismatch

Humans have undergone rapid demographic, social, and environmental change over the last ten thousand years—with particularly rapid changes happening in the last several hundred years—leading to an evolutionary mismatch with the ancestral lifeways in which our genetic makeup was selected (Eaton et al., 1988). Infectious disease treatment and control, water treatment, and biomedicine can reduce early life deaths, while increases in calorie-dense and processed foods (with high levels of salts, sugars, and fats), sedentism, maladaptive stressors, pollution, and other carcinogens lead to increases in non-communicable diseases (Omran, 2005).

For example, these environmental factors have been associated with increases in cardiovascular diseases, diabetes, cancers, dementias, and nonalcoholic fatty liver disease (McCarthy & Rinella, 2012; Peters et al., 2019; Popkin, 2015; Singer & Grunberger, 2012; Vineis & Xun, 2009). Further, treatments, prevention, and increases in public health initiatives have led to overall decreases in mortality and disease (both infectious and degenerative) and increases in health (Gage, 2005).

The theory of epidemiological transitions noted "peculiar" variations in the pattern, pace, determinants, and outcomes of the transition between infectious and chronic disease (Omran, 2005). The theory has continued to be plagued by criticism due to the high amount of variation and complexity in epidemiological transitions between groups and contexts (Santosa et al., 2014). For example, a meta-analysis showed that socioeconomic status is often differentially related to diabetes presence (Williams et al., 2018). The theory of health transitions has more widely incorporated this variation by evaluating the social, behavioral, and cultural determinants of health (Caldwell, 2001; Caldwell & Caldwell, 1991; Caselli et al., 2002). Despite variation in life expectancy trajectories and causes of death, a clear trend exists whereby changes that accompany industrialization and globalization are associated with a lower burden of infectious disease and a higher burden of non-communicable, often chronic, diseases (Santosa et al., 2014). This transition has been noted as a major problem facing LMICs, yet its supposed causal factors have not been well-studied (Malekzadeh et al., 2020). More research is needed to understand which social, behavioral, and environmental characteristics are causing this evolutionary mismatch in what contexts in order to better understand the epidemiological transition between infectious and chronic disease burdens.

This underlying complexity has led to variation in the outcome of studies on market integration (Liebert et al., 2013). Market integration is not a good indicator of growth and nutrition between communities (Blackwell et al., 2009; Houck et al., 2013), which could be due to different social and environmental causes in different areas or differences in the measurement of market integration between communities. Further, different groups of people can experience transition differently in the same population. For example, children, women, and men experience epidemiological transitions differently and socioeconomic status affects health in different ways in different social groups (Braveman et al., 2005; Omran, 2005; Santosa et al., 2014; Urlacher et al., 2018). In general, those that are wealthy and live in urban areas have more access to healthy foods, whereas people who are poor and live in urban environments often have more unhealthy diets (Hawkes, 2006). This is because energy-dense refined grains, added sugars, and added fats are cheaper in many market economies (Drewnowski & Darmon, 2005). Therefore, it is necessary to determine which social and environmental factors change with market integration and affect health negatively.

Potential Mechanisms

Diet

Diet has been closely linked with risk of NCDs, and therefore dietary transitions that accompany cultural shifts have been cited as the cause for increasing rates of NCDs. Increased globalization and market integration have led to a dietary transition between reliance on grains, legumes, fruit, and vegetables to processed foods with added sugar and salt, animal foods, oils, and increased eating out (Hawkes, 2006; Popkin, 2015; Popkin et al., 2012). The Mediterranean Diet, which commonly includes fruits, vegetables, nuts, legumes, whole grains, and lean animal and plant-based proteins, has been shown to improve cardiometabolic health and lower the rate

of NCDs (Pagidipati et al., 2025; Sofi et al., 2008). Associations between sugar, oils, and fats and health have been mixed, but there is a strong effect of caloric restriction on health, and higher consumption of sugars has been shown to increase calories (Johnson et al., 2009; Pressler et al., 2022). Increased consumption of market-based foods typically increases the consumption of sugar in addition to decreasing cardiometabolic health (Pressler et al., 2022). However, a change in the consumption of market-based foods has not been linked with cardiometabolic health changes directly.

Despite the clear link between diet and cardiometabolic health, the transition between self-production subsistence strategies and those that are market-integrated impacts on health is complex. In LMICs, rural areas do tend to eat more self-produced food; however, those with the highest levels of food production sell to and buy from markets to a greater degree (Reardon et al., 2014). Urban areas are associated with a higher amount and diversity of fruit and vegetable intake, alongside an increase in processed foods that contain more salt, sugar, and other potentially unhealthy ingredients (Reardon et al., 2014). However, rural areas still consume market foods and there is a socioeconomic gradient by which people of lower socioeconomic status consume more calorie-dense market foods with fewer micronutrients (Darmon & Drewnowski, 2008; Reardon et al., 2014). Non-market diets that are high in animal fat are associated with heart disease in Inuit (Hu et al., 2018), yet in general, groups that hunt and forage for food have diets high in animal products yet a low rate of cardiovascular disease (Cordain et al., 2002). Further, LMIC's tend to face a double burden of malnourishment and food insecurity alongside overweight, obesity, and NCDs (Turner et al., 2018). Therefore, the transition between the consumption of self-produced and market foods is complex and it is not clear if diet is causing the increase in NCDs that are sometimes seen with market integration.

Physical Activity

There is a consensus that increased physical activity promotes health and reduces the risk of numerous NCDs. Physical activity and measurements of health have a linear relationship with cardiovascular disease, hypertension, hypercholesterolemia, obesity, type 2 diabetes, cancer, and all-cause mortality (Warburton et al., 2006). Beyond this, sedentary behavior is inversely related to cardiometabolic health in many instances (Azevedo et al., 2024; Rezende et al., 2014; Shi et al., 2024). Therefore, sedentary behavior and physical activity are independently related to health effects.

Although daily energy expenditure seems to be highly conserved (Pontzer, 2018), the time spent in physical activity varies greatly. Therefore, exercise might reduce excess energy leading to decreased cardiometabolic disease. LMIC's have a large variation in the prevalence of insufficient physical activity (as defined by the 202 WHO Physical Activity Guidelines; Bull et al., 2020; Strain et al., 2024). The same is true of groups with low levels of market-integration. Tsimané, who primarily engage in foraging and farming subsistence strategies, have low levels of sedentism with most physical activity being light or moderate, which is within the range of high-income countries (HICs; Gurven et al., 2013). Indigenous Shuar of lowland Ecuador have a light to moderate physical activity level and low levels of cardiovascular disease, supporting other research that shows intense physical activity might not always be needed for positive health outcomes (Liebert et al., 2013; Madimenos et al., 2011; Powell et al., 2011). However, within the Yakut (Sakha) of Siberia individuals who participated in fewer subsistence activities had significantly lower physical activity levels (Snodgrass et al., 2006). Therefore, it is possible that sedentary behavior is a distinguishing factor between those who participate in subsistence economies versus those who participate in market economies that affect health.

Chronic Psychological Stress

During the stress response, the hypothalamic-pituitary-adrenal (HPA) axis signals for many downstream neural, cardiovascular, endocrine, metabolic, energetic, and immune system effects. These changes are often adaptive when dealing with an acute stressor; however, can become detrimental to health with over- or under-sensitivity or prolonged activation (Sapolsky et al., 1983). Overly traumatic stressors can lead to post-traumatic stress disorder, during which there is often a chronic hyperactive stress response that drives avoidance, flash-backs, and sleep problems, and prolonged stressors can lead to mental disorders such as depression and anxiety (Hammen, 2005; Kendler et al., 1999; Stam, 2007). Therefore, it is hypothesized that there is a cultural mismatch in which the stress response has become maladaptive.

Chronic activation of the HPA axis leads to many downstream health effects, including increased risk for poor cardiometabolic health. Mouse models have shown that the sympathetic nervous system activates the release of catecholamines, such as epinephrine, from the adrenal cortex (Ramey & Goldstein, 1957). At the same time, the hypothalamus produces corticotropin-releasing factor, which stimulates the pituitary to produce adrenocorticotropin. Adrenocorticotropin then stimulates the adrenal cortex to secrete cortisol. Together, these increase the available energy in the bloodstream by promoting lipolysis and gluconeogenesis. Chronically elevated blood sugar is a diagnostic factor for diabetes and predisposes individuals to other NCDs such as cardiovascular disease and some cancers (Schoen et al., 1999; Schwarz et al., 2018; Wei et al., 2024). Further, vasodilation and restriction along with increased heart rate lead to increased blood pressure, and chronically increased blood pressure is a diagnostic factor for hypertension and predisposes individuals to ventricular hypertrophy, and arterial plaques. Finally, the stress response activates the immune system, leading to increased infiltration of

leukocytes along with increased inflammation. After prolonged activation, these systems lead to insulin resistance, tissue damage, a buildup of plaques, and cellular hyperactivity, resulting in increased cardiometabolic disorders (Hotamisligil, 2006b). Therefore, chronic, maladaptive stressors can lead to non-communicable diseases and adverse health outcomes.

However, in humans the relationship between stress and health is more complex. In addition to wide variability in sensitivity and buffers to stress, stress and its related disorders in humans often lead to behaviors that affect health such as drinking, smoking, eating calorie-dense foods, and other addictive behaviors. Nevertheless, groups that experience more stress or trauma often have worse health outcomes. For example, women who have experienced intimate partner violence have a higher risk of cancer, cardiovascular disease, diabetes, musculoskeletal disorders, and respiratory disorders (Goldberg et al., 2021). There is also evidence that job strain affects health (Landsbergis et al., 2013), which might increase with the participation of wage labor in market economies. However, Tsimané have similar rates of depression to many countries, which has been linked to functional disability and social conflict – usually affecting resources (Stieglitz et al., 2015). Yet, the group has low rates of cardiovascular disease (Kaplan et al., 2017). Therefore, there is still uncertainty as to when, where, why, and what kinds of stress cause poor health effects in humans.

Measuring Market Integration

The concept of market integration is complex. The transition to or into a market-based economy happens in various contexts and changes an individual's ecology. Even within the same region that market integration happens in different ways (Lu, 2007). Therefore, it is possible that market integration needs to be measured in group and context-specific ways, although this impedes cross-study comparisons. Different aspects of MI can be measured at different levels

(e.g., individual, household, community) and are differentially related to various outcomes (Mattison et al., 2022). This highlights both the complexity and importance of both between and within-group comparisons of participation and success in market-based economies.

Market style of life questionnaires employed by human biologists have often used a sum score of assets (Bindon et al., 1997; Leonard et al., 2002; Snodgrass et al., 2006). Different fields have created similar measures, an index based on the possession of durable goods and referred to it as different things: wealth index, asset index, style of life questionnaire, and market integration scale (Hoogendijk et al., 2018; Kowal et al., 2012; Liebert et al., 2013; Naveed et al., 2021). In epidemiology, wealth indices are more commonly created using item response theory models (Kowal et al., 2010; Traynor & Raykov, 2013). The creation of a measure using item response theory (IRT) increases the variation in market integration scales by differentially weighting how strongly items are related to the latent construct (Lord, 2012). Increasing the variation of the market integration scale helps prevent confounding between the different applicable levels in which market integration might affect outcomes (Neale et al., 2005). The IRT model will also show how well the construct is being measured and what types of questions are needed to equally differentiate people between different levels of the construct (Frances & Solon, 2014). Increasing the measurement quality of the market style of life index will help identify relevant relationships between market integration, lifestyle factors, and cardiometabolic health.

The WHS+ in Cambodia

The World Health Organization's World Health Survey Plus (WHS+) monitors and supports public health goals by collecting nationally representative survey, anthropometric, functional test, and biomarker data. The first country to participate was Cambodia in 2023. WHS+ expands on the 2003 World Health Survey, which took place in 69 countries, by

integrating new and updated health measures along with finger-prick point-of-care blood testing. This allows for the reporting of results to participants and provides robust health data to support sustainable development health goals.

Cambodia is undergoing rapid economic and epidemiological transitions. Industrialization, globalization, and economic development between 1999 and 2019 made it one of the fastest-growing economies in the world (World Bank, 2024). Most commonly shifts have been made away from work in subsistence and agriculture to tourism, service, and manufacturing. Cambodia transitioned from a low-income economy to a middle-income economy in 2014 and has goals to become upper-middle-income by 2030 and high-income by 2050. Cambodia has been undergoing a clear transition between infectious and chronic diseases in the past two decades, although some areas might experience dual burdens. Successful public health programs have reduced infectious diseases, eradicated malaria, and reduced maternal and infant mortality. These shifts have also been accompanied by transitions from the self-production of rice, fruits, vegetables, and lean protein to one that contains more market-purchased processed foods (*Cambodia*, 2024).

Using WHS+ data in Cambodia, we can explore the potential mechanisms by which integration into market economies leads to increases in non-communicable diseases in a country undergoing economic and epidemiologic changes. The Material Style-of-Life (MSOL) scale measures the variation in the participation and accumulation of goods and infrastructure associated with market economies and is tailored toward the measurement of countries globally. It is expected that the percentage of foods that comes from the market, sedentism, and stress will mediate the relationship between market integration and non-communicable diseases. Despite these being commonly assumed mechanisms linking market integration and non-communicable

diseases (Lea et al., 2020; Liebert et al., 2013; Snodgrass et al., 2006; Urlacher et al., 2016), it is not clear under what contexts and to what extent each of these contributes to an increasing burden of non-communicable diseases with market integration and globalization.

Objectives and Hypotheses

Objective 1. Improve measurement variability of the M-SOL scale and evaluate its measurement quality and characteristics.

Objective 2. Evaluate if market diet, physical activity, or stress could be responsible for differences in cardiometabolic health with market integration.

> **Prediction.** There will be a positive indirect effect of market diet, physical activity, and stress between material style of life and blood pressure (BP), HbA1c, low-density lipoprotein (LDL), glucose, total cholesterol, waist-to-stature ratio, triglycerides, and frailty. There will be a negative indirect effect of market diet and stress on high-density lipoprotein (HDL).

Objective 3. Explore whether the relationship between market integration and diet, physical activity, and stress differs between locations

> **Prediction.** Models predicting market food, sedentary behavior, and stress from market integration with region as random slopes will fit the data better than models where the predictors are random-intercepts or fixed effects when controlling for demographic factors.

Method

Participants

The WHS+ took place in Cambodia between March and May of 2023 and collected computer-assisted personal interviews, performance tests, and biomarkers. Random selection of communities included 6,072 people, and the study had an 87% completion rate. Therefore, 5,275 participants across 275 communities in all 25 provinces participated in the present study. Participants' ages ranged from 18 to 88 years old (M = 47.28, SD =14.91) and more women (69%) than men (31%) participated. Most of the participants were currently married (n = 4,072), followed by widowed (n = 662), never married (n = 297), separated/divorced (n = 228), and cohabiting (n = 16). More participants lived in rural areas (61%) than urban areas (39%). The WHS+ was approved by the WHO ethical review committee, and written informed consent was obtained from all study participants.

Variables

Demographics

Participants were asked, "*How old are you now?"* which was checked against self-reported date of birth and a birth certificate if available. The interviewer recorded the gender of the participant. Participants were also asked about their current marital status. Education was made up of two questions: "*Have you ever been to school?*" and if they said yes, they were asked, "*How many years of school, including higher education have you completed?*" No answers to ever being in school were coded as zero and combined with the years of school variable to create years of education.

Market Style of Life (M-SOL)

Dichotomous housing characteristics (e.g., floor type, 2 rooms or more) and asset items (e.g., television, refrigerator, car) were used as independent observations of the latent variable using item response theory (IRT; Appendix 2).

Lifestyle Mediators

Market Food. The Household Consumption and Expenditures Surveys (HCES) was created to fix limitations in the 24 hr dietary recall (Fiedler et al., 2012). Market food was the percentage of food and beverages consumed that were purchased by the household divided by the total value of consumed food. The total value of consumed food included food purchased and food that came from their own production and/or from in-kind receipts. The Household Consumption Expenditure section of the survey states, "*I would like to ask you some questions about your household and all its members consumption of food and other non-food products and services*." Then, "*I will ask you ask you first about your household consumption of food and beverages prepared at home . . . over the past 7 days.*" The survey then asks three questions about 16 food group items. The three questions include: 1) "*In the last 7 days, did you or any member of your household consume (out of your own production, purchases or in-kind receipts)* [insert food group items]," 2) "*What was the total value of [insert food group items] that came from your own production and/or from in-kind receipts over the last 7 days? Your best estimate is fine. Report value in local currency*, and 3) "*What was the total value of [insert food group items] that came from your purchases over the last 7 days?"* Food group items included things such as "*noodles, similar pasta products, and flour*," "*butter, lard, and other animal based oils and fats*," and "*other food items not mentioned elsewhere (e.g., salt, condiments, sauces, spices, herbs, seeds, baby food)*."

Sedentary Behavior. The sedentary behavior question was prefaced by, "*The following question is about sitting or reclining at work, at home, getting to and from places, or with friends including time spent [sitting at a desk, sitting with friends, travelling in car, bus, train, reading, playing cards or watching television], but do not include time spent sleeping.*" A showcard was used to illustrate examples. Participants were then asked, "*How much time do you usually spend sitting or reclining on a typical day?"* and the answer was recorded in hours and minutes. Minutes was divided by 60 and added to hours to get total number of hours.

Stress. The stress variable was a mean of four questions about symptoms that can result from a traumatic stressor. It states, "*People who are exposed to extremely stressful experiences, like being assaulted or involved in a serious accident, often have a number of negative reactions. The next questions are about reactions of this sort.*" Then, "*Overall in the last 30 days, how much were you bothered by the following reactions to any extremely stressful experience that ever happened to you?"* and participants were offered a 5-point Likert scale from 1 *(Not at all)* to 5 *(Extremely).* The four questions were: 1) "*Avoiding external reminders of a stressful experience, for example, people, places, conversations, activities, objects, or situations?*" 2) "*Feeling distant or cut off from other people?*" 3) "*Feeling irritable, having angry outbursts, or acting aggressively?*" and 4) "*Suddenly feeling or acting as if a stressful experience were actually happening again, as if you were actually back there reliving it?"*

Health Outcomes

Blood Biomarkers. Finger-prick capillary blood was collected and biomarkers were measured using point-of-care devices. Glycated hemoglobin (HbA1c) was measured using A1CNow+ (PTS diagnostics; Whitestown, IN, USA), and glucose, triglycerides, and total

cholesterol were measured using CardioChek PA (PTS diagnostics; Whitestown, IN, USA). Low density lipoprotein (LDL) was calculated automatically by the CardioChek PA device.

Anthropometrics. Waist circumference was measured using a tape measure to the nearest 0.1 cm. Measurements were taken two inches above the iliac crest, taking care to keep the tape measure parallel to the floor. Height was measured using a portable stadiometer to the nearest 0.1 cm (Seca 213; Hamburg, Germany). Waist-to-stature ratio (WSR) was calculated by dividing waist circumference by height in cm.

Blood Pressure. Blood pressure (BP; mmHg) was measured using a battery-powered upper arm blood pressure monitor (Omron Healthcare Inc. Series 3; Kyoto, Japan). It was hot at the time of data collection, however if needed participants were asked to remove bulky jackets or sweaters. Blood pressure was taken with participants in a seated position, after a 5 minute rest in which the participant was instructed not to talk. Participants were told to place both feet on the ground and to place their arm on a table at heart level. The measurement was taken three times, and the average of the last two was used for analysis (Muntner et al., 2019).

Frailty. The frailty index was made up of four sections that were weighted equally: general health, diagnosed disorders, functional activities assessment, and physical assessment (Appendix C). It was scored according to the Rockwood Frailty Index (Rockwood et al., 2005; Rockwood & Mitnitski, 2007; Searle et al., 2008)

Statistics

R version 4.3.0 was used for analysis (R Core Team, 2021). Assumptions were checked, and the relationship between MSOL and market food was shown to be heteroscedastic. Therefore, multi-level models were completed first. Since the addition of a random slope by region accounted for some of the heteroscedasticity while maintaining the general linear trend

across communities (Figure 1), linear analyses for structural equation modeling were still performed. In addition, HbA1c, market food, and sedentary behavior were not normally distributed and, therefore, were log-transformed. Variables were z-scored for structural equation models. The alpha level was set at .05.

Objective 1

Item response theory (IRT) is a series of scalar measurement models used to create a unidimensional latent trait (Lord, 2012). Maximum likelihood estimation was used to fit dichotomous response data using the MIRT package in R (Chalmers, 2012). More information on this analysis can be found in Appendix A.

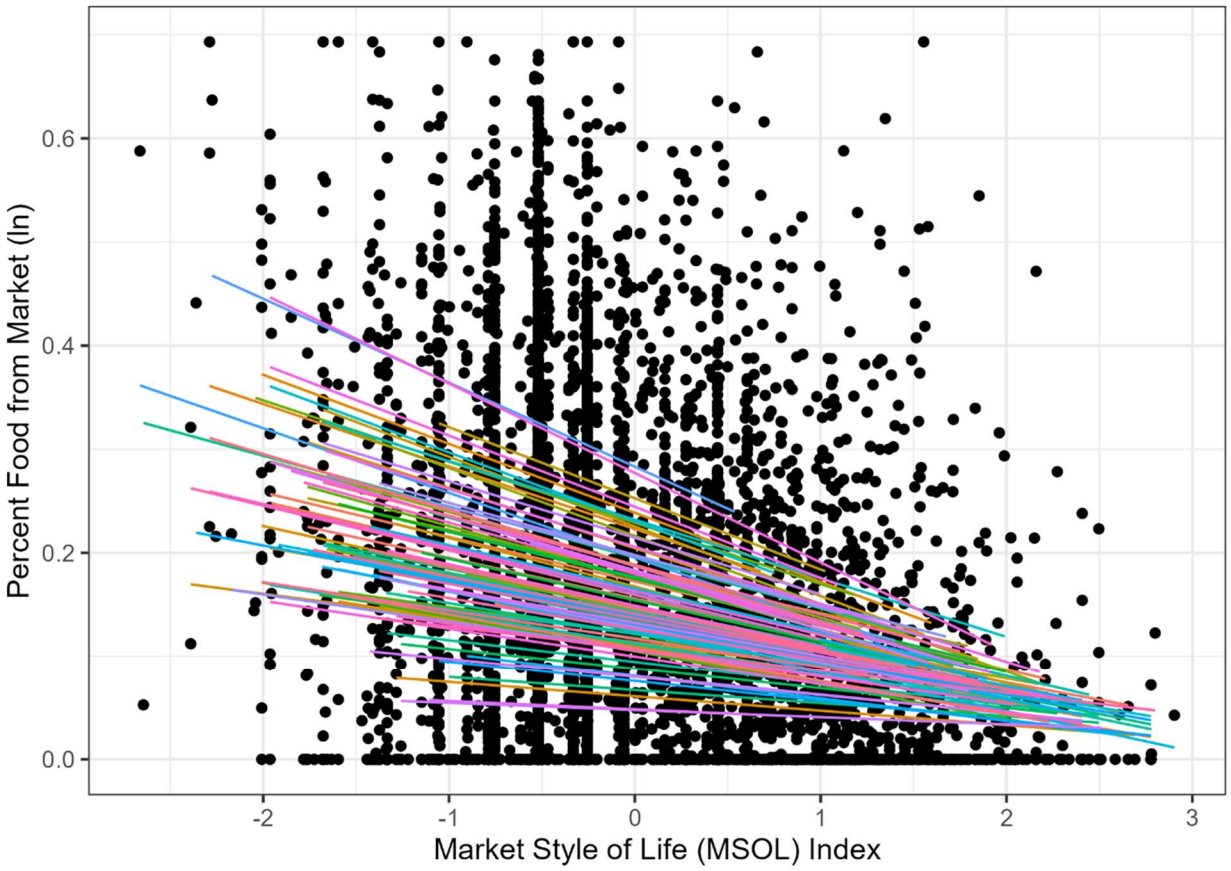


Figure 1. Multi-level model showing the relationship between market integration and market food with region as a random slope

Objective 2

Multi-level structural equation modelling with maximum likelihood estimation was performed using the lavaan package in R (Rosseel, 2012). Region was controlled for with robust standard errors. First, indirect effects were measured separately with MSOL as the predictor, market food, sedentary behavior, and stress as mediators, and HbA1c, total cholesterol, LDL cholesterol, triglycerides, WSR, systolic BP, and frailty as cardiometabolic health and aging outcomes. Then all indirect effects were run in a combined model (Figure 2).

Objective 3

Multi-level linear regression models were estimated using maximum likelihood estimation with the lme4 package in R (Bates et al., 2015). Three fixed-effect models were fit with market food, sedentary behavior, and stress as outcomes in separate models. MSOL was the predictor of interest in all three models, with age, gender, marriage, and years of education as demographic controls. The same three models were then fit with the addition of region as a random intercept

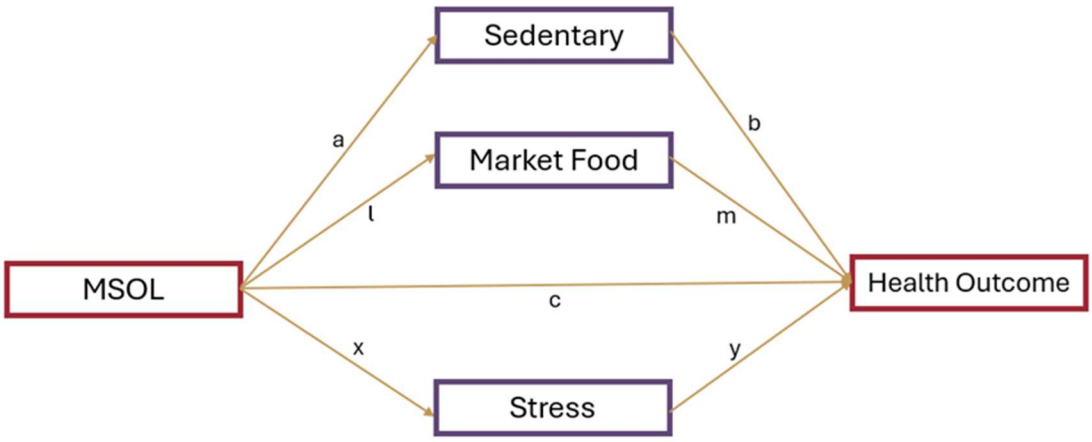


Figure 2. Combined structural equation model with market food, sedentary behavior, and stress as mediators between market integration and metabolic health and aging

and a random slope. Fixed effect, random intercept, and random slope models were compared. The variance inflation factor (VIF) was checked for all fixed effects, and none exceeded the recommended cutoff of 4 (VIF_{min} = 1.06, VIF_{max} = 1.44).

Results

Descriptive Statistics

HbA1c ranged from 4.00 to 13.00 (*M* = 5.87, *SD* =1.35), total cholesterol from 100 to 400 (*M* = 187.94, *SD* = 54.44), LDL from 5.00 to 332.00 (*M* = 108.67, *SD* = 44.53), HDL from 20.00 to 120.00 (*M* = 43.66, *SD* = 13.03), and triglycerides from 50.00 to 500.00 (*M* = 171.60, *SD* = 87.52). Systolic blood pressure ranged from 76.00 to 207.00 (*M* = 121.02, *SD* = 17.05), and WSR ranged from 0.29 to 0.77 (*M* = 0.52, *SD* = 0.07). Participants were sedentary between 0.00 and 24.00 hours a day on average (*M* = 2.04, *SD* = 1.81) and stress scores ranged from 1.00 to 5.00 (*M* = 1.65, *SD* = 0.72).

Objective 1

The MSOL had a strong one-factor solution. Although normally a 1 parameter logistic (PL) model is used for creating wealth and asset indices, the 3 PL model provided the best fit for the data. However, it only accounted for 0.25% change in variance compared to the 1 PL model. The 3rd guessing parameter accounted for variance in walls, floor, water, and electricity (as well as TV) and therefore may have been useful for controlling for communism. There was a gap in measurement between housing characteristics (along with having a motorcycle) and having a TV. Therefore, items that are leisure items but cost less than a TV are needed to fill the gap. The majority of people fell within this gap, having the necessities, but none of the luxury assets. The scale had low information value and appeared more probabilistic until this point as well, then became strongly scalar. Therefore, despite the strong one-factor solution, it is possible that

market integration can only be measured in a scalar fashion once individuals have entered into a market-based economy.

Objective 2

In the mediation models, MSOL had a negative relationship with market food (β = -0.33, $p < .001$), and a positive relationship with sedentary behavior (β = 0.06, $p < .01$) and stress (β = -0.08, $p < .001$; Tables 1 & 2). MSOL was related to most health and aging outcomes, such that

Table 1. Standardized β Values from Individual SEM Mediations

		Sedentary		Market Food		Stress	
	c	b	IE_{ab}	b	IE_{ab}	b	IE_{ab}
Men							
HbA1c	0.12***	0.04	0.004	-0.03	0.01	-0.00	0.00
Trig	0.13***	0.09**	0.01	-0.09**	0.03**	0.08*	-0.01
TC	0.15***	0.04	0.003	-0.10***	0.04***	.04	-0.002
LDL	0.16***	0.03	0.002	-0.11***	0.04***	0.05	-0.003
HDL	-0.04	0.00	0.00	-0.03	0.01	-0.02	0.001
Sys BP	0.07**	0.03	0.003	-0.003	0.001	-0.03	0.002
WSR	0.27***	0.05	0.004	-0.07**	0.03**	-0.02	0.001
Frailty	-0.12***	0.07*	0.01	-0.02	0.01	0.39***	-0.03***
Women							
HbA1c	0.10***	-0.001	0.00	-0.02	0.01	0.01	-0.00
Trig	0.03	0.03	0.002	-0.03	0.01	0.03	-0.00
TC	0.12***	0.003	0.00	-0.06**	0.02**	0.02	-0.002
LDL	0.10***	-0.002	0.00	-0.05*	0.02*	0.02	-0.001
HDL	0.07*	0.01	0.00	-0.07***	0.02***	0.01	-0.00
Sys BP	-0.07**	-0.01	0.00	0.01	-0.002	-0.03	0.002
WSR	0.14***	0.06***	0.003	-0.07***	0.02**	0.04**	-0.003
Frailty	-0.13***	0.05*	0.003	-0.02	0.01	0.37***	-0.02*

Note. *$p < .05$, ** $p < .01$, $p < .001$. HbA1c was natural log transformed. HbA1c = Glycated Hemoglobin; Trig = Triglycerides; TC = Total Cholesterol; LDL = Low Density Lipoprotein; HDL = High Density Lipoprotein; Sys BP = Systolic Blood Pressure; WSR = Waist-to-Stature Ratio.

Table 2. Standardized β Values from the Combined SEM with Three Mediations

		Sedentary		Market Food		Stress	
	c	b	IE_{ab}	m	IE_{tm}	y	IE_{xy}
Men							
HbA1c	0.11***	0.04	0.004	-0.03	0.01	-0.02	0.001
Trig	0.07*	0.04	0.003	-0.002	0.001	-0.04	0.002
TC	0.11***	0.04	0.002	-0.10***	0.04**	0.02	-0.001
LDL	0.13***	0.02	0.002	-0.10***	0.04**	0.03	-0.001
HDL	-0.04	0.001	0.00	-0.03	0.01	-0.01	0.00
Sys BP	0.07*	0.04	0.003	-0.002	0.001	-0.04	0.002
WSR	0.25***	0.05	0.004	-0.07	0.03**	-0.05*	0.002
Frailty	-0.09**	0.02	0.002	0.02	-0.006	0.36***	-0.02
Women							
HbA1c	0.10***	-0.01	-0.00	-0.02	0.01	0.01	-0.001
Trig	-0.07*	-0.002	-0.00	0.003	-0.001	-0.03	0.002
TC	0.10***	0.001	0.00	-0.06**	0.02*	0.02	-0.002
LDL	0.09***	-0.002	-0.00	-0.04*	0.02*	0.02	-0.001
HDL	0.06*	0.01	0.00	-0.07***	0.02***	0.002	-0.00
Sys BP	-0.07**	-0.002	-0.00	0.003	-0.001	-0.03	0.002
WSR	0.12***	0.06**	0.003	-0.07**	0.02**	0.04*	-0.003
Frailty	-0.10***	0.01	0.001	0.01	-0.002	0.39***	-0.03**

Note. *$p < .05$, ** $p < .01$, $p < .001$. HbA1c was natural log transformed. HbA1c = Glycated Hemoglobin; Trig = Triglycerides; TC = Total Cholesterol; LDL = Low Density Lipoprotein; HDL = High Density Lipoprotein; Sys BP = Systolic Blood Pressure; WSR = Waist-to-Stature Ratio.

higher MSOL was related to higher cardiometabolic biomarkers and lower frailty. It was not related to HDL cholesterol in men and triglycerides in women and was negatively related to systolic BP in women. However, only market food frequently had a positive indirect effect between MSOL and aging. As MSOL was higher, market food consumption was lower, and as market food consumption was lower, health outcomes were higher/worse. This was true for total

cholesterol, LDL, and WSR, along with triglycerides in men and HDL in women. The only other indirect effect was the mediation of MSOL and frailty by stress. MSOL is negatively associated with stress and stress is positively related to frailty, leading to a negative indirect effect. The combination of models attenuated the indirect effects between MSOL and triglycerides by market foods in men and between MSOL and frailty by stress in men.

Objective 3

Market Food

For market food, the random intercept model provided a better fit to the data than the

Table 3. Multi-Level Model *B* Values Predicting Market Food from Market Style of Life (MSOL)

	Fixed Effect		Random Intercept		Random Slope	
	B	*SE*	*B*	*SE*	*B*	*SE*
Fixed Effects						
Intercept	9.03***	0.14	8.20***	0.15	8.01***	0.15
Age	0.00	0.00	0.003*	0.001	0.003*	0.001
Gender	-0.08*	0.04	-0.11**	0.04	-0.10**	0.04
Marriage	0.10	0.05	0.08	0.05	0.08	0.05
Education	-0.02***	0.01	-0.02**	0.01	-0.02**	0.01
MSOL	-0.36***	0.03	-0.27***	0.03	-0.27***	0.03
Random Effects						
$SD_{\text{Intercept}}$			0.53		0.54	
SD_{Slope}					0.19	
ICC			.14		.15	
Model Fit						
AIC	18355.06		17926.68		17916.43	
LogLik	-9170.53		-8955.34		-8948.22	
R^2/*Pseudo* R^2	.08		.18		.19	

Note: *$p < .05$, ** $p < .01$, $p < .001$. Analysis was done with the natural log of market food (%), but the exponentials of the coefficients are reported.

fixed effect model ($\chi^2 = 14.25$, $p < .001$) and the random slope model provided a better fit to the data than the random intercept model ($\chi^2 = 444.63$, $p < .001$; Table 3). The random intercept model showed that people who had higher MSOL values were similar in the percentage of food

purchased from the market across regions; however, there was a lot of variability in the percentage of food purchased from the market for people with lower MSOL, depending on region. Some regions have a slope that is near zero, indicating that percentage of food from the market is not related to MSOL, whereas in most regions the two have a negative slope, indicating market food consumption is lower when MSOL is higher. Fixed effects showed that after controlling for community, age was positively related to market food. Women reported lower household market food consumption than men. As both education and MSOL were higher, the consumption of market foods was lower.

Sedentary Behavior

For sedentary behavior, the random intercept model provided a better fit to the data than the fixed effect model ($\chi^2 = 129.42$, $p < .001$), but the random slope model provided no further improvement ($\chi^2 = 5.48$, $p = .06$; Table 4). People who were married or cohabiting had lower levels of sedentary behavior than those who were single, divorced, or widowed. Education and MSOL were both positively related to sedentary behavior. The positive relationship between MSOL and sedentary behavior was attenuated by the addition of a random slope for region, indicating an overlap in variance. However, the best fitting model was that with MSOL as a significant fixed effect and region as a random intercept.

Stress

For stress, the random intercept model provided a better fit to the data than the fixed effect model ($\chi^2 = 23.34$, $p < .001$), and the random slope model provided a better fit to the data than the random intercept model ($\chi^2 = 5.16$, $p = .08$; Table 5). Women experienced more stress than men, and as MSOL was higher stress was lower. Age was not related to stress, despite frailty being strongly related in the previous models. Therefore, higher stress is related to higher frailty regardless of age.

Table 4. Multi-Level Model B Values Predicting Sedentary Behavior from Market Style of Life (MSOL)

	Fixed Effect		Random Intercept		Random Slope	
	B	*SE*	*B*	*SE*	*B*	*SE*
Fixed Effects						
Intercept	1.59***	0.05	1.55***	0.05	1.55***	0.05
Age	0.00	0.00	0.00	0.00	0.00	0.00
Gender	0.02	0.02	0.02	0.02	0.02	0.02
Marriage	-0.06***	0.02	-0.06***	0.02	-0.06***	0.02
Education	0.004*	0.002	0.01*	0.002	0.01*	0.002
MSOL	0.03**	0.01	0.02*	0.01	0.02	0.01
Random Effects						
$SD_{Intercept}$			0.12		0.12	
SD_{Slope}					0.05	
ICC			.06		.06	
Model Fit						
AIC	7714.91		7587.49		7586.01	
LogLik	-3850.45		-3785.74		-3783.01	
R^2/*Pseudo* R^2	.01		.06		.07	

Note: *$p < .05$, ** $p < .01$, $p < .001$. Analysis was done with the natural log of sedentary behavior (hr), but the exponentials of the coefficients are reported.

Table 5. Multi-Level Model B Values Predicting Stress from Market Style of Life (MSOL)

	Fixed Effect		Random Intercept		Random Slope	
	B	*SE*	*B*	*SE*	*B*	*SE*
Fixed Effects						
Intercept	1.41***	0.07	1.42***	0.07	1.43***	0.07
Age	0.00	0.001	-0.001	0.001	-0.001	0.001
Gender	0.15***	0.02	0.15***	0.02	0.15***	0.02
Marriage	0.003	0.02	0.003	0.02	0.002	0.02
Education	0.001	0.003	0.001	0.003	0.001	0.003
MSOL	-0.05***	0.01	-0.06***	0.01	-0.06***	0.01
Random Effects						
$SD_{Intercept}$			0.09		0.09	
SD_{Slope}					0.04	
ICC			.02		.02	
Model Fit						
AIC	11438.06		11416.71		11415.55	
LogLik	-5712.03		-5700.36		-5697.78	
R^2/*Pseudo* R^2	.01		.03		.03	

Note: *$p < .05$, ** $p < .01$, $p < .001$.

Discussion

Market integration was associated with worse cardiometabolic health for all health outcomes tested, with some differences between men and women. However, it was also associated with decreased frailty. This could be due to the strong association between stress and frailty and the negative relationship between stress and market integration. This outcome corroborates many other studies that link market integration with worse cardiometabolic health (Angkurawaranon et al., 2014; Lea et al., 2020; Liebert et al., 2013). However, this study did not provide evidence for this relationship being due to the three main mechanisms that are usually cited: increased market food consumption, increased sedentary behavior, or increased stress.

Instead, this study showed that more market food consumption was related to lower market integration. This happened along a gradient such that lower levels of market integration were associated with a high level of variability in market food consumption among regions. The highest amount of variability in individuals was right under the mean level of market integration, near the intersection of having housing and having assets. These findings support the idea that the transition into market integration is associated with worse health outcomes, but that the effects are felt the most by those that are low in socioeconomic status in a market economy (Hawkes, 2006). Increasing inequality with market integration should be evaluated as a possible contributor to the relationship between market integration and health. Yet we provide evidence for worsening cardiometabolic risk factors with increased asset wealth, possibly because many individuals in Cambodia still live a subsistence and/or communist lifestyle.

Measurement of Market Integration

This study evaluates and improves upon the current measurement of market integration; however, there is still a large amount of improvement that is needed. The current measurement of market integration by assets is a measure of wealth, and therefore the two effects cannot be separated. Either different questions need to be included, or a consensus should be made that market style of life is a form of asset wealth. Since the amount of asset wealth is negatively related to the percentage of foods from markets, the relation of both to the concept of market integration needs clarification. Ultimately, it was asset wealth and not market food that was related to worse cardiometabolic health. Further, market integration is happening at the household, community, regional, and national levels (Mattison et al., 2022). That effect was shown here by the attenuation of the positive relationship between market integration and sedentary behavior with the addition of a random slope for region. Separating these different

levels could lead to insight into the complexity of the relationships between market integration and health.

The MSOL measure of market integration created here has a low discrimination and information criterion at low levels of market integration. A scalar measurement of market integration using housing characteristics and assets may be applicable only in a community that is market integrated. A continuous distribution between a subsistence economy and a market economy has not been created, and previous studies have shown that a subsistence style of life and a market style of life are different constructs (Liebert et al., 2013). If the transition between subsistence and market economies does happen at a single point, it is important to identify the distinguishing factors. If the transition is gradual, then a better measure of this transition is still needed. One possibility for improvement is to find better criteria for low market integration than housing characteristics, which are largely shared among communities. Measuring market style of life correctly is important for the analysis of how changing cultures affect health.

Links between Market Integration and Cardiometabolic Health

Different aspects of diet, physical, and stress could be the mediating factors between market integration and cardiometabolic health. In most cases market foods are not inherently bad for you, rather, they sometimes lead to the consumption of a caloric surplus. Notable exceptions are salt and, perhaps, sugary drinks (Law, 1997; Stanhope, 2016). Metabolic disorders are most commonly linked with obesity, which is another indicator of a caloric surplus (Cuthbertson et al., 2017; Finkel, 2015; Gaal et al., 2006; Popkin et al., 2012; Stanhope, 2016). An increased frequency of dining out also increases caloric consumption (Oh et al., 2015). Therefore, it is likely that health depends on what foods, and how much of those foods, are consumed. Sedentary behavior is just one aspect of physical activity, and although it is the worst for health, health

tends to increase with increasing physical activity (Powell et al., 2011). Therefore, the entire amount of physical activity is likely relevant, and not just time spent in sedentary behavior. Finally, there are numerous causes of stress. The stress measured here tends to align closest with a post-traumatic stress (Yehuda et al., 2015), which is likely prevalent in the population due to recent political turmoil and genocide. Childhood adversity, anxiety, social, and occupational stress could lead to different associations. More research needs to be done to isolate the causes of increasing cardiometabolic risk with market integration.

Stress and Frailty

The strong relationship between stress and frailty could be bidirectional, psychosocial stress leads to increased frailty but increased frailty also leads to more stress. The sympathetic nervous system, which is activated in moments of stress or chronically with stress, leads to insulin resistance, inflammation, and cellular hyperactivity, all of which can increase frailty (Gruenewald et al., 2009; Perazza et al., 2022; Vlachakis et al., 2017). Further, studies have linked early-life stress, cumulative stressful experiences, and low socioeconomic status with epigenetic aging, which is a leading measure of biological aging (Palma-Gudiel et al., 2020b). Therefore, there are possibly numerous physiological mechanisms that link stress and aging.

While stress was most closely related to frailty, market integration was more closely related to cardiometabolic disease. Further, market integration was inversely related to stress. These findings suggest that the mechanisms of aging triggered by psychological stressors are different than the worsening of cardiometabolic health with market integration. The relationship between stress and aging could provide insight into physiological aging mechanisms that remain elusive (Cohen et al., 2020). Despite there being much disagreement as to the causes of aging,

this study showed a strong relationship between stress and aging that was independent of chronological age and metabolic dysregulation.

Limitations

This study documented specific limitations in the measurement of market-style-of life that should be considered in future studies. Self-report physical activity and sedentary behavior is poorly correlated with physical activity recorded by an accelerometer (Keating et al., 2019), and it is possible that this error variance affected results. Further, it may have been difficult for some participants to accurately recall how much the food they consumed cost and where it was obtained. This study was cross-sectional, and therefore, it is difficult to assess causality and directionality. Although the addition of a random slope for region improved the model fit, it did not account for all heteroscedasticity. The peculiar relationship between market style of life and market food in Cambodia should be further explored. Salt, alcohol, or tobacco may be driving health effects related to the consumption of market foods or market style of life (Bell et al., 2011; He & MacGregor, 2009). Finally, there is a chance that linear models do not accurately represent the data, especially since there was unequal variance. Future research should explore non-parametric relationships between market integration, lifestyle behaviors, and health.

Conclusion

Although it has been assumed that the relationship between market integration and the increased risk of cardiometabolic diseases is due to an increase in market diets, an increase in sedentary behavior, and an increase in maladaptive psychosocial stress this study did not provide evidence for those associations. It showed a clear and strong link between higher market style of life, measured similarly to an asset or wealth index, and lower cardiometabolic health using

biomarker measurements but that relationship was not mediated by consumption of market food, sedentary behavior, or post-traumatic stress. It is likely that market integration leads to poor health via numerous pathways in different locations and groups and understanding what leads to these differences and how to prevent worsening cardiometabolic health is of primary importance for global public health. Cambodia is undergoing economic and epidemiologic transitions, and the public health department is now focusing on NCD management. Understanding exactly why rates are increasing is of utmost importance to these goals, yet common assumptions on causality could be mistaken, leading to wasted resources.

Bridge

Chapter V evaluated the measurement quality and increases variation in the scale for market integration, then uses it to explore the mediation between market integration and health by market diet, sedentary behavior, and post-traumatic stress. Although these are the most commonly cited causes for this link, there was little to no evidence of their involvement. This chapter highlights the importance of measuring cultural transitions and their effects on health as a part of a global perspective. There are many different levels of causality for biological and health outcomes; however, research is usually focused on an individual level. The next chapter, Chapter VI, evaluated the significance of this and other findings and conclusions reached herein. It then reviews future directions for aging research in Human Biology.

Chapter VI

Conclusion and Future Directions

The research contained within this dissertation has provided preliminary evidence for a new evolutionary model of aging, based on the tradeoff between mutational load and cellular hyperactivity. In doing so, it highlights weaknesses in the Disposable Soma Theory. It provides evidence that there is not a universal increase in inflammation with age and, instead, this effect is likely due to dysregulated metabolism. This points to a mismatch as a cause of inflammaging and the disorders it is associated with, alongside possibly being an evolutionary mechanism of aging itself. Finally, it shows that assumptions that have been made about the link between market integration and aging might not be supported and highlights the need for more research to understand how transitioning societies lead to environmental mismatches that cause aging. Taking an evolutionary and global perspective on aging has led to unexpected findings herein and can further benefit the field of gerontology.

Evolutionary Basis of Aging

These findings highlight that even the evolutionary basis of aging is multilevel and complex, with many different overlapping facets. This makes sense, given that aging is as old as multicellular organisms (Nelson & Masel, 2017), and therefore have evolved for at least one and a half billion years (Brunet & King, 2017). Understanding how aging has been shaped by natural selection, and the tradeoffs and mismatches that lead to aging, will be crucial to finally understanding how all of the mechanistic pieces of aging fit together. Further, there is still a need to link traditional evolutionary theories of aging, such as mutation accumulation and

antagonistic pleiotropy, to the mechanistic causes of aging. One possibility is a molecular tradeoff between mutation accumulation and cellular hyperactivity.

Integrating the Biological and Social Levels of Aging

Across both the studies contained here, and many others I have completed (e.g., DeLouize, 2023; DeLouize, in prep; Greenblum et al., 2022), the vast majority of variance in NCDs occurs at city/region level (i.e., community-level variables, and not individual-level variables are likely responsible). This is consistent with other research showing that NCDs cluster by location (Freedman et al., 2011; Kuuire et al., 2023; Stanifer et al., 2016). One study showed that up to 70% of what we consider individual lifestyle factors affecting health (such as diet and exercise) are widely determined at a community level (DeLouize et al., in prep). Repeatedly, I have found that community is the biggest contributor to non-communicable disease. Chapter 5 showed market diet, sedentary behavior, and post-traumatic stress were 66% to 100% attributable to the group level, with sedentary behavior being almost entirely based on the community. Public health often tells people to eat less and exercise more to improve health and wellness, and while these are the best ways to prevent NCDs and aging related decline (DiPietro, 2001; Kraus et al., 2019), there is a lack of acknowledgement that one's culture, along with other social, environmental, and developmental factors, largely shape your propensity to engage in these behaviors alongside other risk factors. This work highlights that both aging and NCD risk are deeply social and environmental. We need to identify these social and environmental factors because public policy tailored to entire groups and environments could have an even greater impact on health than the current interventions focused on individuals.

In addition to the epidemiological significance, the high level of clustering highlights a major methodological issue with the way much of science is conducted. If one is not collecting

data from numerous communities and controlling for group effects, then models are likely to be biased and confounded. This could be a major reason behind the replicability crisis (Earp & Trafimow, 2015). Communities and regions are deeply unique in all of the factors that lead to NCDs and increased rates of aging, and not controlling for this clustering makes it appear as if community-level factors are individual factors and can bias the overall results depending on what communities are included. This highlights the major strength of large, national, population-based studies run by the World Health Organization, and is just one of many contributions they make to understanding disease and improving public health globally.

A Global Perspective on Aging and Disease

The findings that CRP was lower in older age groups in women in Mexico and was entirely related to metabolic factors in Shuar were surprising, and this is due to both the deep need for, and shortage of, a global perspective. Biased metabolic results from high-income nations have driven "aging" mechanisms, and without a global perspective, aging research has created misleading narratives. This is partly because most aging research has been deeply embedded in medicine in high-income nations. While this approach has led to clinical progress, it has not allowed for a global perspective on aging or a deeper understanding of aging mechanisms. A broader global perspective on aging is essential for deepening our understanding of its complexity and variability in humans.

The dominance in the aging literature of metabolic disorders and their correlates, and findings here showing differences in inflammaging among Shuar communities, highlights the need to continue improving the measurement of market integration. Evolutionary mismatches occur in high-income nations and drive aging trajectories (Gurven & Lieberman, 2020); however, we do not know enough about how countries and groups undergoing this transition are

affected. That knowledge is deeply valuable to LMICs and other groups that want to try to prevent or mitigate the impacts of NCDs in a rapidly globalizing economy.

Future Directions

In addition to the questions outlined here, the study of aging overlaps with many topics that Biological Anthropologists specialize in. For example, rates of aging are affected by climate change, pollution, minority health, sex and gender, and migration/displacement (Calabrò et al., 2023; Forrester et al., 2020; Sciubba, 2020; Ward-Caviness et al., 2016). The research contained in this dissertation raises three interesting questions: 1) How do we measure biological aging?; 2) What factors lead to the large amount of community-level clustering in health and aging?; and, 3) What causes aging among Shuar? Exploring these ideas will further elucidate the environmental, social, and biological determinants of aging.

The Biomarker-Based Measurement of Aging

The fact that aging mechanisms are so variable, and we do not have a strong understanding of how aging works, has led to another problem: we cannot measure it well. Historically, the measurement of biological age was done by recording telomere length (a certain repeated DNA pattern that flanks the ends of DNA), with telomere length shortening as we age (Blasco, 2005; Chakravarti et al., 2021; Shammas, 2011). Although it was known that an enzyme, telomerase, could add telomeres onto the ends of DNA, it was thought that this process occurred during aberrant oncogenic processes and in specialized stem cells (Cong et al., 2002). However, a spaceflight in 2015 through 2016 highlighted that we knew less about telomere biology than we thought (Luxton et al., 2020; Luxton & Bailey, 2021). A study on twin astronauts was conducted where one twin, Scott Kelley, went to the International Space Station

for a year, and the other twin, Mark Kelley, stayed earthbound. Samples from numerous timepoints were measured for telomere length, and while Mark Kelley's stayed relatively stable, Scott Kelley's elongated while he was in space (Luxton et al., 2020; Luxton & Bailey, 2021). Beyond this high-profile result, many studies showed that telomeres were rarely related to NCDs, and the Health and Retirement Study showed that it was not a good predictor of any form of aging-related decline (Brown et al., 2018; Sanders & Newman, 2013). This led to the creation of NIH grants for the purpose of clarifying pathways to health outcomes associated with aging in order to measure and monitor them (The Biomarker Network, 2025).

Other available biomarkers of aging have varying problems and shortcomings. The creation of "epigenetic clocks" using DNA methylation has variably been associated with chronological age, senescence, mortality, and aging-related disease and therefore is a useful indicator (Levine, 2020). However, it is not clear why these methylation changes occur over time or the extent of their downstream effects (Horvath & Raj, 2018). One of the most common measures of the increase in inflammation with age, CRP, was shown here to be due to metabolic changes. More research is still needed to separate out metabolic effects from other inflammatory biomarkers including interleukin 6 (IL-6), IL-1β, and tumor necrosis factor alpha (TNF-α; Franceschi et al., 2000). Allostatic load is a composite measure of stress and metabolic dysregulation across numerous biological systems (DeCaro & Helfrecht, 2022; Seeman et al., 1997) and given the complexity and variation in aging, the creation of a composite measure is a strong approach. However, there is both a large amount of variability in how the measure is constructed, along with variability in its performance to predict senescence, mortality, and aging-related NCDs (Singer et al., 2004). Finally, -omics approaches that measure the epigenome, transcriptome, proteome, metabolome, and microbiome are becoming popular ways to measure

aging because of the rise of high-throughput technologies and big data approaches such as machine learning. However, they are limited by selection, timing, and cohort effects (Rutledge et al., 2022), largely because of the exploratory nature of the concept (Drouard et al., 2024; Gomez-Cabrero et al., 2021). However, some scoring methods coming out of -omics research are promising (Higgins-Chen et al., 2022; Rutledge et al., 2022). More research is needed to improve the measurement of aging. Using biomarkers to further understand the physiological and environmental causes of aging and their effects on health can improve early interventions for age-related deterioration to promote health and longevity.

Understanding Community-Level Factors of Health

Chapter 5 adds to a body of literature showing that the socioeconomic status (SES) of a location matters for health; however, why and how is less well understood. The most well-researched location-based effect is that living in a low SES area in a HIC leads to a higher risk of NCDs (Connolly & Kesson, 1996; Majcherek et al., 2020; Weaver et al., 2022). This finding has been replicated in some LMICs (Kuuire et al., 2023); however, others mirror the finding in Chapter 5 that a higher SES is associated with a higher disease risk (Darikwa & Manda, 2020; Ganasegeran et al., 2024). One study showed that NCD risk was associated with living in a high-income district in a low-income region (Bischops et al., 2020). Further, race and ethnicity vary by location and are associated with disease risk because of social determinants, including interpersonal and structural racism (Gravlee, 2009; Hui-Fang et al., 2019; Paradies et al., 2015; Sharma et al., 2004). Therefore, while SES matters for health, where and how varies.

Partly this is because SES is linked to health through various mechanisms. Pollution is a major factor linking some neighborhoods to NCDs, and some infectious diseases (Boffetta, 2006; Carrasco-Escobar et al., 2020; Fuller et al., 2018; Landrigan et al., 2018; Peters et al., 2019;

Ward-Caviness et al., 2016). Further, some of these effects are due to infrastructure and the built environment. Walkability, green spaces, proximity to major roads, industry, landfills, facilities for physical activity, and unhealthy food can affect health (Zhang et al., 2023). However, these findings have not been consistent across studies (Zhang et al., 2023), potentially because how people utilize neighborhood spaces will also vary based on individual and cultural factors. Investigating the interconnectedness of these individual, social, cultural, and environmental factors will lead to more comprehensive theories explaining how where you live influences your risk for NCDs.

Longitudinal Data from the Shuar Health and Life History Project

Investigating how aging occurs in Shuar will shed light on universal aging processes. Shuar visibly undergo aging; however, many of these processes have been rooted in inflammation (Pessa et al., 2014; Soysal et al., 2016). Future research should evaluate other inflammatory biomarkers (such as IL-6, IL-1β, TNF-α), allostatic load, mutational load, telomere length, and DNA methylation, biomarkers of metabolism (e.g., HbA1c, triglycerides, cholesterol), and other aspects of the immune system. A longitudinal study would not only provide insights into aging, but it would also allow for the evaluation of change over time as Shuar become increasingly market-integrated and are influenced by globalization. This is a major goal of the Shuar Health and Life History Project.

Concluding Remarks

Cancer has been noted as the most complex human disease (Grizzi & Chiriva-Internati, 2006). This makes aging even more complex since it includes oncogenic processes alongside many other aspects and layers of complexity. Aging is a dynamic, multifaceted phenomenon

shaped by evolutionary pressures, molecular pathways, and cellular stressors that lead to systemic dysregulation. For researchers to reach a consensus on what aging is, studies need to be more interdisciplinary, with a focus on exploring variability in humans. By identifying different, intersecting levels of causality, we can further elucidate the evolutionary, physiological, and social/environmental basis of aging.

APPENDIX A

Variables Included in the Tunisian Health Examination Survey Frailty Index

Table 1: Survey questions and criteria used to create the self-report frailty index

Variable Set	Variable Name	Survey Question	Criteria
General Health			0 = Very good, .25 = Good, .5 = Moderate, .75 = Bad, 1 = Very bad
	Self-rated health	In general, how would you rate your health today	
		In the last 30 days how much…	
	Body Aches	…of bodily aches or pains did you have?	0 = None, .25 = Mild, .5 = Moderate, .75 = Severe, 1 = Extreme
	Health Feelings	…have you been emotionally affected by your health condition(s)?	
		In the last 30 days how much difficulty did you have…?	
	Sleep Quality	…With sleeping, such as falling asleep, waking up frequently during the night or waking up too early in the morning?	
	Vision - Far	…In seeing and recognising an object or a person you know across the road (from a distance of about 20 meters)?	
	Vision - Near	…In seeing and recognising an object at arm's length (for example, reading)?	
	Concentration	…With concentrating or remembering things?	
	Memory	…In learning a new task (for example, learning how to get to a new place, learning a new game, learning a new recipe)?	
Medically Diagnosed Conditions			0 = No, 1 = Yes
	Arthritis	Have you ever been diagnosed with/told you have arthritis (sometimes called rheumatism or osteoarthritis)?	
	Stroke	Have you ever been diagnosed with stroke?	
	Angina	Have you ever been diagnosed with angina or angina pectoris (a heart disease) (chest pain)?	
	Diabetes	Have you ever been diagnosed with diabetes (high blood sugar)? (Not including diabetes associated with a pregnancy)	
	COPD	Have you ever been diagnosed with chronic lung disease (emphysema, bronchitis, COPD)?	
	Depression	Have you ever been diagnosed with depression?	
	Hypertension	Have you ever been diagnosed with hypertension?	
	Cataracts	In the last 5 years, were you diagnosed with a cataract in one or both of your eyes (cloudiness in the lens of the eye)?	
	Edentulism	Have you lost all of your natural teeth?	

Variable Set	Variable Name	Survey Question	Criteria
Functional Activities Assessment		In the last 30 days how much difficulty did you have…?	0 = None, .25 = Mild, .5 = Moderate, .75 = Severe, 1 = Extreme/cannot do
		…In sitting for long periods?	
		…In walking 100 meters?	
		…In standing up from sitting down?	
		…In standing for long periods?	
		…With climbing one flight of stairs without resting?	
		…With stooping, kneeling or crouching?	
		…Picking up things with your fingers (such as picking up a coin from a table)?	
		… In walking a long distance such as a kilometer?	
		…With moving around?	
		…In vigorous activities ('vigorous activities' require hard physical effort and cause large increases in breathing or heart rate)?	
		Besides any vision aids (eyeglasses or contact lenses) or hearing aids mentioned above, do you use any other assistive devices (cane, walker or other) for any difficulties you experience?	0 = No, 1 = Yes
Activities of Daily Living Assessment		In the last 30 days how much difficulty did you have…?	0 = None, .25 = Mild, .5 = Moderate, .75 = Severe, 1 = Extreme/cannot do
		…In taking care of your household responsibilities?	
		…In joining in community activities (for example, festivities, religious or other activities) in the same way as anyone else can?	
		… In extending your arms above shoulder level?	
		… Concentrating on doing something for 10 minutes?	
		… In bathing/washing your whole body?	
		… In getting dressed?	
		… In taking care of and maintaining your general appearance (for example, grooming, looking neat and tidy)?	
		… In your day to day work?	
		… With carrying things?	
		… With moving around inside your home (such as walking across a room)?	
		… With eating (including cutting up your food)?	
		… With getting up from lying down?	
		… With getting to and using the toilet?	
		… With getting where you want to go, using private or public transport if needed?	
		… In getting out of your home?	
		… In staying by yourself for a few days (3 – 7 days)?	
		… Overall, how much did these difficulties interfere with your life?	

APPENDIX B

Market Style of Life Scale Development Using IRT

The M-SOL index is designed to measure market integration. Questions about wall material, water availability, and floor type were combined with questions about assets. The assets section of the survey stated, "*I would like to ask you a few more questions about your home and items you might have in your home. Remember that any information you provide will be kept confidential. Does your household or anyone in your household have…?*" and included items such as a television, electricity, and a refrigerator. Q0716 about livestock was excluded because owning livestock could be a part of a non-market subsistence strategy or a business providing food for markets, and Q0721-Q0772 about property and land ownership were excluded because Cambodia still has some land rights issues. There were 23 items total (Table 1).

It was verified that the items produced a one-factor solution by evaluating the scree plot and a principal axis factor analysis using varimax rotation (DeMars, 2010). Pearson's correlations showed no excessive interdependence. Fixed phone and radio correlated negatively with the other items and had very weak loadings onto the factor. Since these are older market items that are rarely used in market economies, these variables were removed. No individuals had all or none of the items, allowing for maximum likelihood estimation of theta. 3PL, 2PL, and 1PL/Rasch models were compared using ANOVA, BIC, and log-likelihood which indicated that the 3PL model had a significantly better model fit than the 1PL ($\chi^2 = 2400.95$, $p < .001$) and 2PL model ($\chi^2 = 77.15$, $p < .001$; Table 2). The 3PL model takes item discrimination (a), item difficulty (b), and guessing probability (c) into account.

The first 3PL model provided a good fit for the data (RMSEA < .06), and this goodness of fit was moderately better than a baseline model (TLI < .95; (L. Hu & and Bentler, 1999)).

Water, motorcycle, electricity, microwave, cellphone, and cooling did not provide a good fit for the latent model (χ^2 = 12.90 to 34.83, $p < .05$; (Orlando & Thissen, 2000). However, person fit was good, with less than 10% of people falling outside of infit and outfit parameters. Bicycle loaded poorly onto the latent factor and had poor discrimination (Table 3; DeMars, 2010; Warner, 2012). Further, the item appeared entirely probabilistic (Figure 1). A revised 3PL model, excluding bicycle, provided a similar fit overall (χ^2 = 7213.25, p = 1.00) with slightly improved factor loadings (Table 4).

The c, or guessing, parameter was high for walls, floor, water, electricity, and TV. Most of these items are those that were provided by government, and TVs are common with the type of TV often indicating market integration (e.g., box TV vs. flat-screen TV). Discrimination (a parameter) is lower than is common in classical test theory. There is a higher range of theta, or market style of life, at which one can reasonably be expected to have an item. This is standard in the literature for IRT models of assets. However, some items, such as computer, washing machine, servants, and cooling, have really high discrimination (Table 4; Figure 2). This indicates that the IRT measure could likely be improved with the addition of more assets and characteristics that are theoretically close to a market-based culture.

The lower half of the MSOL index has low information value (Figure 3). This, along with the lack of discrimination in the items that fall in this range, indicates that the model is more probabilistic until you get to the asset items. This could indicate that market integration can only be measured well in a scalar manner once you have entered into a market economy. However, it could also be because low levels of a market economy are still highly overlapping with the former communist economy in Cambodia.

There is a gap in measurement between motorcycle (and housing assets) and TV, and another smaller gap in measurement between servants and VCR/DVD (Figure 4). The majority of people fall within this gap, having similar housing characteristics but no asset items. The measure is positively skewed, with dishwasher, heating, and VCR/DVD as outliers. The distribution deviates from normality, both because of the similarity among people due to communism and because measures that resemble wealth will be positively skewed.

The evaluation of market integration from IRT has similar limitations to the creation of other constructs using IRT (Reise & Rodriguez, 2016). The latent trait of market integration is highly skewed, in practice, because of its overlap with the skewed distribution of wealth. The latent construct produced should be closely considered, especially because of the close overlap of market integration and wealth. Ultimately, a latent construct more closely related to wealth had better item fit; however, one that seemed more similar to market style of life provided sufficient fit for the model as well. This poor item fit could cause an increase in error variance in the latent construct. A strength of the approach is that market integration is a bipolar construct with both high market integration (market lifestyle) and low market integration (subsistence lifestyle) having meaning. Further, it allows for an analysis of measurement validity and increases the amount of variation and reduces bias compared to the commonly used sum score (Frances & Solon, 2014; Neale et al., 2005). Although the measurement of market style of life using IRT offers some benefits and improvement, the underlying indicators still need to be reconsidered.

Tables and Figures

Table 1. List of Questions Included in the Initial Evaluation of Items

Number	Question	Levels
Q0502	How many rooms does this dwelling have in total, without counting the bathrooms or hallways?	*0. < 2 rooms* *1. ≥ 2 rooms*
Q0503	*What type of floor does your dwelling have?*	*0. Earth Floor* *1. Hard Floor (Tile, Cement, Brick, Wood)*
Q0504	What type of (exterior) walls does your dwelling have?	0. Mud/ Mud brick, Thatch and other, Plastic Sheet, Metal Sheet, Other 1. Cement, Brick, Stone or wood
Q0505 & Q0506	What is the main source of . . . water for members of your household?	0. Other 1. Piped into dwelling, compound, yard or plot
Q0701	A television?	0. No 1. Yes
Q0702	A motorcycle or motor scooter?	0. No 1. Yes
Q0703	A car or truck?	0. No 1. Yes
Q0704	Electricity?	0. No 1. Yes
Q0705	A bicycle?	0. No 1. Yes
Q0706	A microwave oven?	0. No 1. Yes
Q0707	Hot running water?	0. No 1. Yes
Q0708	A washing machine?	0. No 1. Yes
Q0709	A dishwasher?	0. No 1. Yes
Q0710	A refrigerator?	0. No 1. Yes
Q0711	A fixed-line telephone?	0. No 1. Yes
Q0712	A mobile / cellular telephone?	0. No 1. Yes
Q0713	A VCR (video) or DVD player?	0. No 1. Yes
Q0714	A computer?	0. No 1. Yes
Q0715	A radio?	0. No 1. Yes
Q0717	Internet access in the home?	0. No 1. Yes
Q0718	An air-condition (cooling) system in the home?	0. No 1. Yes
Q0719	A heating system in the home?	0. No 1. Yes
Q0720	Does your household have one or more domestic servants?	0. No 1. Yes

Table 2. Comparison of Model Fit and Convergent Validity Between One, Two, and Three Parameter Logistic IRT Models

	Model Fit				Convergent Validity	
					Urban/Rural	Total Score
Model	*AIC*	*RMSEA*	*LogLik*	*TLI*	*d*	*r*
Rasch/1PL	65528.82	.06	-32743.41	.85	.76***	1.00
2PL	63243.02	.03	-31581.51	.97	.74***	0.99
3PL	63205.86	.03	-31524.93	.97	.73***	0.95
3PL revised	55986.61	.02	-27936.31	.98	.73***	0.95

Note. *$p < .05$, ** $p < .01$, $p < .001$. PL = Parameter Logistic; AIC = Akaike Information Criterion; RMSEA = Root Mean Square Error of Approximation; LogLik = Log Likelihood; TLI = Tucker-Lewis Index.

Table 3. Means, Factor Loadings, and Item Response Theory (IRT) Model Parameters for the 3PL Model

Item	*M*	*95% CI*	F1	a	b	c
Walls	0.88	0.87 - 0.89	0.41	0.76	-2.76	0.11
Floor	0.96	0.95 - 0.96	0.46	0.89	-3.69	0.16
Water	0.32	0.30 - 0.33	0.69	1.62	1.19	0.14
TV	0.49	0.47 - 0.50	0.53	1.07	0.29	0.09
Motorcycle	0.89	0.88 - 0.90	0.63	1.39	-1.97	0.01
Car	0.18	0.17 - 0.19	0.79	2.21	1.25	0.01
Electricity	0.87	0.86 - 0.88	0.37	0.67	-2.93	0.09
Bicycle	0.54	0.53 - 0.56	0.15	0.26	-0.58	0.02
Microwave	0.04	0.03 - 0.04	0.88	3.08	2.04	0.00
Hot water	0.11	0.10 - 0.12	0.67	1.54	1.94	0.01
Washing machine	0.16	0.15 - 0.17	0.89	3.26	1.12	0.00
Dishwasher	0.00	0.00 – 0.00	0.53	1.06	6.44	0.00
Refrigerator	0.33	0.32 - 0.34	0.90	3.55	0.51	0.01
Cellphone	0.96	0.95 - 0.96	0.64	1.43	-2.80	0.02
VCR/DVD	0.08	0.07 - 0.08	0.35	0.63	4.22	0.00
Computer	0.10	0.09 - 0.11	0.76	2.01	1.71	0.00
Internet	0.10	0.09 - 0.11	0.85	2.72	1.68	0.02
Cooling	0.08	0.07 - 0.08	0.90	3.57	1.60	0.00
Heating	0.00	0.00 – 0.00	0.43	0.82	7.61	0.00
Servants	0.01	0.01 - 0.02	0.80	2.30	2.92	0.00

Note. F1 = factor loading, a = discrimination, b = difficulty, c = guessing.

Table 4. Means, Factor Loadings, and Item Response Theory (IRT) Model Parameters for the Revised 3PL Model

Item	F1	a	b	c
Walls	0.41	0.76	-2.86	0.06
Floor	0.47	0.90	-3.64	0.17
Water	0.69	1.60	1.19	0.13
TV	0.54	1.10	0.36	0.11
Motorcycle	0.64	1.41	-1.96	0.00
Car	0.79	2.21	1.25	0.01
Electricity	0.37	0.67	-2.89	0.11
Microwave	0.87	3.07	2.05	0.00
Hot water	0.68	1.58	1.93	0.01
Washing machine	0.89	3.26	1.12	0.00
Dishwasher	0.62	1.35	5.50	0.00
Refrigerator	0.90	3.58	0.51	0.01
Cellphone	0.64	1.43	-2.81	0.01
VCR/DVD	0.34	0.62	4.27	0.00
Computer	0.76	2.00	1.71	0.00
Internet	0.85	2.73	1.68	0.02
Cooling	0.90	3.57	1.60	0.00
Heating	0.70	1.67	4.78	0.00
Servants	0.80	2.29	2.93	0.00

Note. F1 = factor loading, a = discrimination, b = difficulty, c = guessing.

Figure 1. Item Characteristic Curves for 3 PL Model

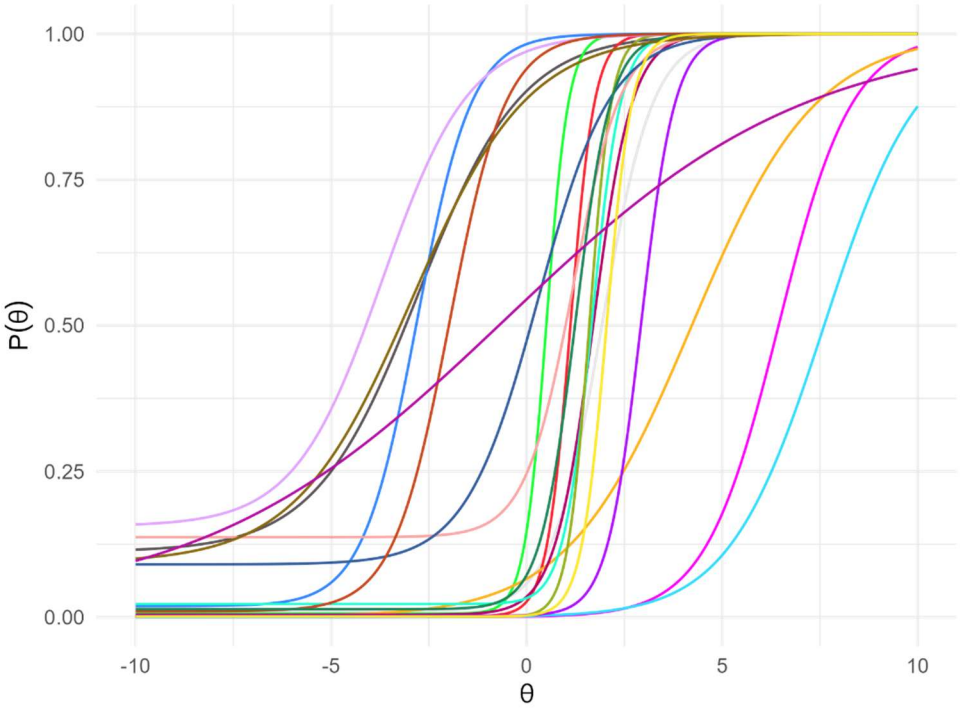


Figure 2. Item Characteristic Curves for 3PL Model Revised

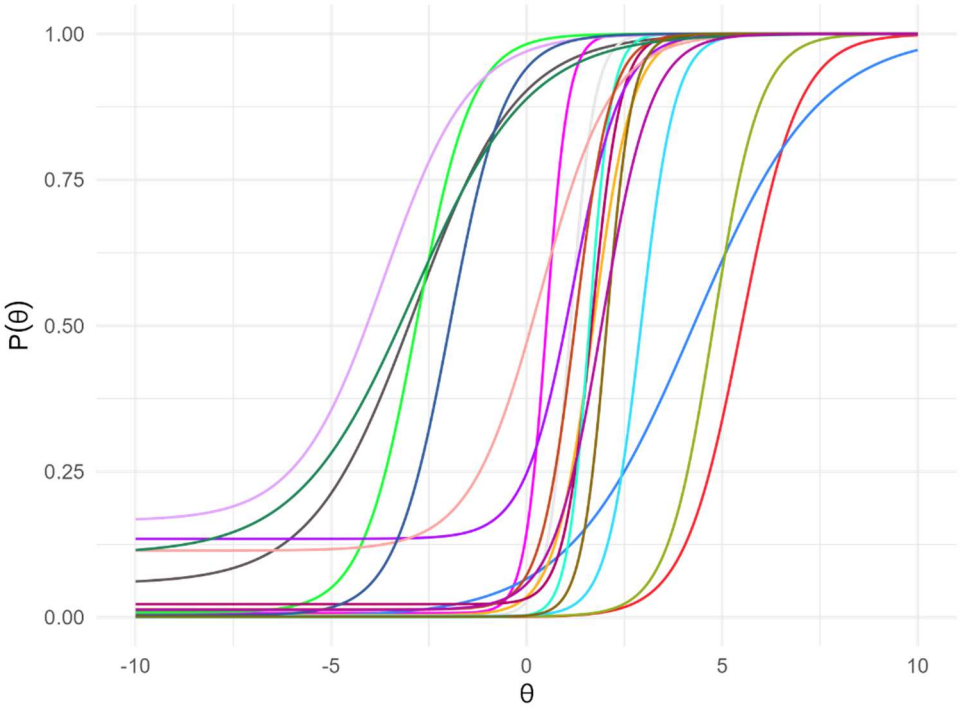


Figure 3. Test Information Curve

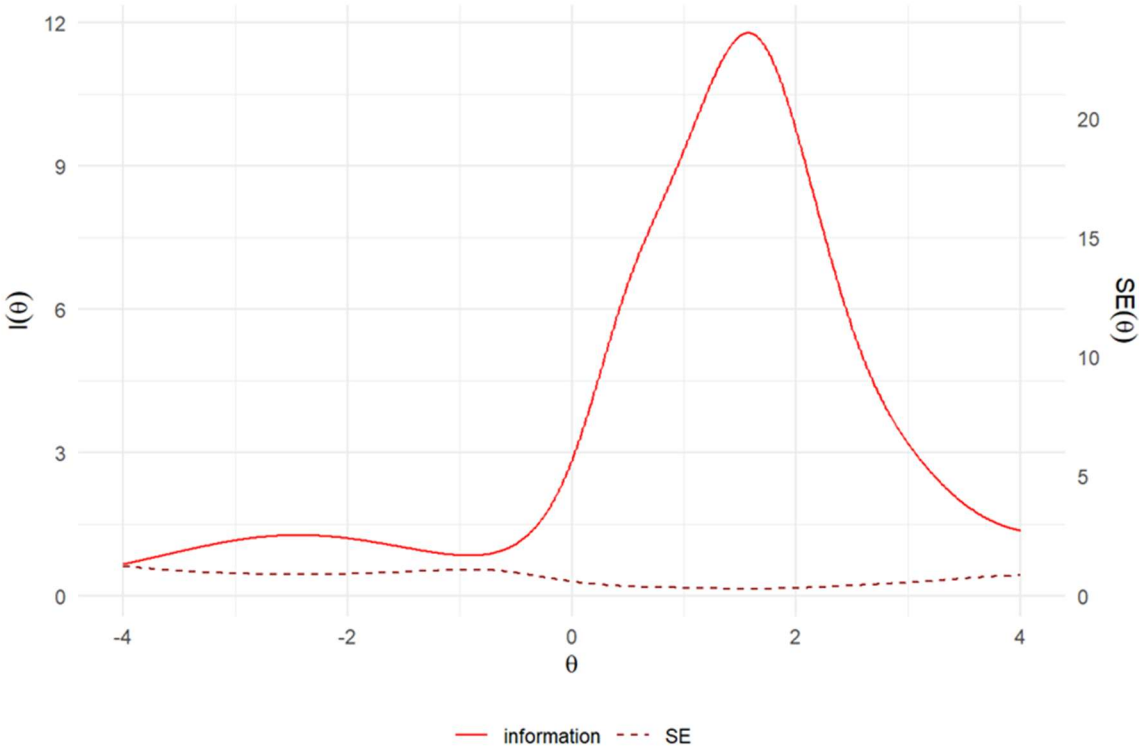
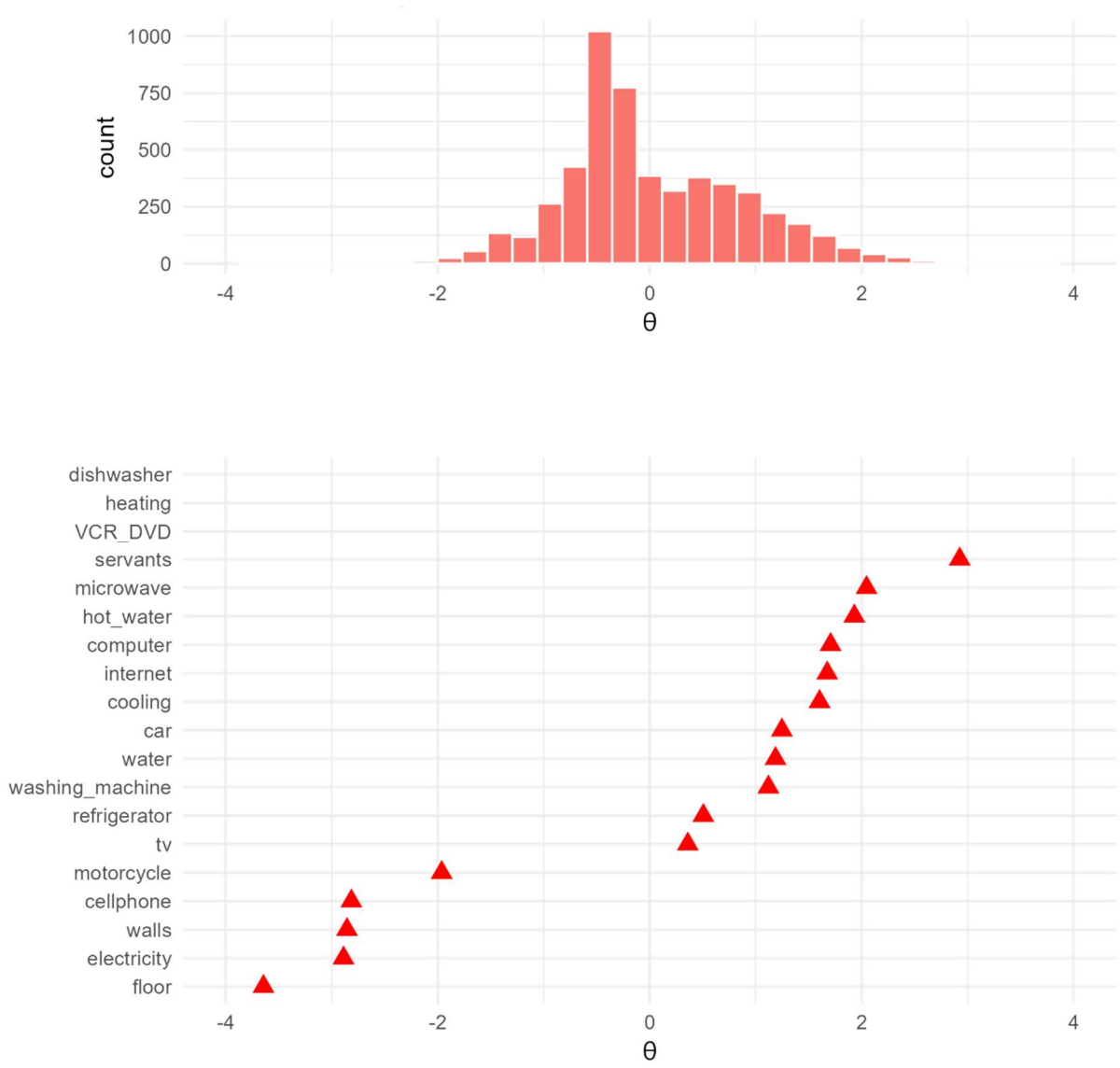


Figure 4. Item person (Wright) map



APPENDIX C

Variables Included in the WHS+ Frailty Index

Table 1. Variables and Criteria for the WHS+ Frailty Index

Variable Set	Variable Name	Survey Question	Criteria
General Health	Self-rated health	In general, how would you rate your health today?	0 = Very good, .25 = Good, .5 = Moderate, .75 = Bad, 1 = Very bad
		Overall in the last 30 days, how much difficulty did you have…	0 = None, .25 = Mild, .5 = Moderate, .75 = Severe, 1 = Extreme/Can not do
	Daily Activities	…with work or household activities?	
	Movement	…with moving around?	
	Vigorous Activities	… in vigorous activities ('vigorous activities require hard physical effort and cause large increases in breathing or heart rate)?	
	Self Care	… with self-care, such as bathing/washing or dressing yourself?	
	Grooming	… in taking care of and maintaining your general appearance (for example, grooming, looking neat and tidy)?	
	Independence	… in staying by yourself for a few days (3 to 7 days)?	
	Body Aches	…how much of bodily aches or pains did you have?	
	Discomfort	…how much bodily discomfort did you have?	
	Difficulty from Pain	… how much difficulty did you have in your daily life because of your pain?	
	Concentration & Memory	… did you have with concentrating or remembering things?	
	Learning	… did you have in learning a new task (for example, learning how to get to a new place, learning a new game, learning a new recipe)?	

Variable Set	Variable Name	Survey Question	Criteria
	Interpersonal	… with personal relationships or participation in the community?	
	Conflict	… in dealing with conflicts and tensions with others?	
	Friends	… with making new friendships or maintaining current friendships?	
	Strangers	…with dealing with strangers?	
	Sleep	… have with sleeping, such as falling asleep, waking up frequently during the night or waking up too early in the morning?	
	Energy	… have due to not feeling rested and refreshed during the day (for example, feeling tired, not having energy)?	
	Mood	…with feeling sad, low or depressed?	
	Anxiety	… with worry or anxiety?	
	Vision - Far	…In seeing and recognizing an object or a person you know across the road (from a distance of about 20 meters)?	
	Vision - Near	…In seeing and recognising an object at arm's length (for example, reading)?	
Medically Diagnosed Conditions			0 = No, 1 = Yes
	Arthritis	Have you ever been diagnosed with/told you have arthritis (sometimes called rheumatism or osteoarthritis)?	
	Stroke	Have you ever been diagnosed with stroke?	
	Angina	Have you ever been diagnosed with angina or angina pectoris (a heart disease) (chest pain)?	
	Diabetes	Have you ever been diagnosed with diabetes (high blood sugar)? (Not including diabetes associated with a pregnancy)	

Variable Set	Variable Name	Survey Question	Criteria
	Lung Disease	Have you ever been diagnosed with chronic lung disease (emphysema, bronchitis, COPD)?	
	Depression	Have you ever been diagnosed with depression?	
	Hypertension	Have you ever been diagnosed with hypertension?	
	Cataracts	In the last 5 years, were you diagnosed with a cataract in one or both of your eyes (cloudiness in the lens of the eye)?	
	Edentulism	Have you lost all of your natural teeth?	
Functional Activities Assessment		In the last 30 days how much difficulty did you have…?	0 = None, .25 = Mild, .5 = Moderate, .75 = Severe, 1 = Extreme/cannot do
	Standing	…In standing for long periods?	
	Household	… in taking care of your household responsibilities?	
	Community	… in joining in community activities (for example, festivities, religious or other activities) in the same way as anyone else can?	
	Concentration	… concentrating on doing something for 10 minutes?	
	Walking	… In walking a long distance such as a kilometer?	
	Bathing	… In bathing/washing your whole body?	
	Getting Dressed	… In getting dressed?	
	Work	… In your day to day work?	
	Carrying	… With carrying things?	
	Eating	… With eating (including cutting up your food)?	
	Getting Up	… With getting up from lying down?	

Variable Set	Variable Name	Survey Question	Criteria
	Toileting	… With getting to and using the toilet?	
	Incontinence	… with control of your bowel or bladder functions?	
	Travel	… With getting where you want to go, using private or public transport if needed?	
	Getting Out	… In getting out of your home?	
	Emotionally Affected	In the last 30 days, how much have you been emotionally affected by your health condition(s)?	
Functional Measurements		Grip Strength	Men: 1 =
			For BMI ≤ 24, GS ≤ 29
			For BMI 24.1–28, GS ≤ 30
			For BMI >28, GS ≤ 32
			Women: 1 =
			For BMI ≤ 23, GS ≤ 17
			For BMI 23.1–26, GS ≤ 17.3
			For BMI 26.1–29, GS ≤ 18
			For BMI>29, GS ≤ 21
		Normal walk	> 16s / 4m = 1
		Rapid walk	> 10s / 4m = 1

References

Ahmadi-Abhari, S., Luben, R. N., Wareham, N. J., & Khaw, K.-T. (2013). Distribution and determinants of C-reactive protein in the older adult population: European Prospective Investigation into Cancer-Norfolk study. *European Journal of Clinical Investigation*, *43*(9), 899–911. https://doi.org/10.1111/eci.12116

Ajayi, I. O., Adebamowo, C., Adami, H.-O., Dalal, S., Diamond, M. B., Bajunirwe, F., Guwatudde, D., Njelekela, M., Nankya-Mutyoba, J., Chiwanga, F. S., Volmink, J., Kalyesubula, R., Laurence, C., Reid, T. G., Dockery, D., Hemenway, D., Spiegelman, D., & Holmes, M. D. (2016). Urban–rural and geographic differences in overweight and obesity in four sub-Saharan African adult populations: A multi-country cross-sectional study. *BMC Public Health*, *16*(1), 1126. https://doi.org/10.1186/s12889-016-3789-z

Aktipis, C. A., Boddy, A. M., Jansen, G., Hibner, U., Hochberg, M. E., Maley, C. C., & Wilkinson, G. S. (2015). Cancer across the tree of life: Cooperation and cheating in multicellularity. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *370*(1673), 20140219. https://doi.org/10.1098/rstb.2014.0219

Alberro, A., Iribarren-Lopez, A., Sáenz-Cuesta, M., Matheu, A., Vergara, I., & Otaegui, D. (2021). Inflammaging markers characteristic of advanced age show similar levels with frailty and dependency. *Scientific Reports*, *11*(1), 4358. https://doi.org/10.1038/s41598-021-83991-7

Alberti, K. G. M., Zimmet, P., & Shaw, J. (2005). The metabolic syndrome—A new worldwide definition. *The Lancet*, *366*(9491), 1059–1062. https://doi.org/10.1016/S0140-6736(05)67402-8

Allender, S., Wickramasinghe, K., Goldacre, M., Matthews, D., & Katulanda, P. (2011). Quantifying urbanization as a risk factor for noncommunicable disease. *Journal of Urban Health*, *88*(5), 906–918. https://doi.org/10.1007/s11524-011-9586-1

Almeida, O. P., Pirkis, J., Kerse, N., Sim, M., Flicker, L., Snowdon, J., Draper, B., Byrne, G., Lautenschlager, N. T., Stocks, N., Alfonso, H., & Pfaff, J. J. (2012). Socioeconomic disadvantage increases risk of prevalent and persistent depression in later life. *Journal of Affective Disorders*, *138*(3), 322–331. https://doi.org/10.1016/j.jad.2012.01.021

Ameisen, J. C. (2002). On the origin, evolution, and nature of programmed cell death: A timeline of four billion years. *Cell Death & Differentiation*, *9*(4), Article 4. https://doi.org/10.1038/sj.cdd.4400950

Amer, O. E., Sabico, S., Khattak, M. N. K., Alnaami, A. M., Aljohani, N. J., Alfawaz, H., AlHameidi, A., & Al-Daghri, N. M. (2021). Increasing prevalence of pediatric metabolic syndrome and its components among Arab youth: A time-series study from 2010–2019. *Children*, *8*(12), Article 12. https://doi.org/10.3390/children8121129

Angel, J. L., Vega, W., & López-Ortega, M. (2017). Aging in Mexico: Population trends and emerging issues. The Gerontologist, 57(2), 153-162. doi:10.1093/geront/gnw136

Angkurawaranon, C., Jiraporncharoen, W., Chenthanakij, B., Doyle, P., & Nitsch, D. (2014). Urbanization and non-communicable disease in Southeast Asia: A review of current evidence. *Public Health*, *128*(10), 886–895. https://doi.org/10.1016/j.puhe.2014.08.003

Angleman, S. B., Harris, T. B., & Melzer, D. (2006). The role of waist circumference in predicting disability in periretirement age adults. *International Journal of Obesity*, *30*(2), Article 2. https://doi.org/10.1038/sj.ijo.0803130

Arai, Y., Martin-Ruiz, C. M., Takayama, M., Abe, Y., Takebayashi, T., Koyasu, S., Suematsu, M., Hirose, N., & von Zglinicki, T. (2015). Inflammation, but not telomere length, predicts successful ageing at extreme old age: A longitudinal study of semi-supercentenarians. *EBioMedicine*, *2*(10), 1549–1558.

Arima, H., Kubo, M., Yonemoto, K., Doi, Y., Ninomiya, T., Tanizaki, Y., Hata, J., Matsumura, K., Iida, M., & Kiyohara, Y. (2008). High-sensitivity c-reactive protein and coronary heart disease in a general population of Japanese. *Arteriosclerosis, Thrombosis, and Vascular Biology, 28*(7), 1385–1391. https://doi.org/10.1161/ATVBAHA.107.157164

Ashwell, M., & Hsieh, S. D. (2005). Six reasons why the waist-to-height ratio is a rapid and effective global indicator for health risks of obesity and how its use could simplify the international public health message on obesity. *International Journal of Food Sciences and Nutrition, 56*(5), 303-307. doi:10.1080/09637480500195066

Assmann, G., & Schulte, H. (1988). The Prospective Cardiovascular Münster (PROCAM) study: Prevalence of hyperlipidemia in persons with hypertension and/or diabetes mellitus and the relationship to coronary heart disease. *American Heart Journal*, *116*(6, Part 2), 1713–1724. https://doi.org/10.1016/0002-8703(88)90220-7

Auro, K., Joensuu, A., Fischer, K., Kettunen, J., Salo, P., Mattsson, H., Niironen, M., Kaprio, J., Eriksson, J. G., Lehtimäki, T., Raitakari, O., Jula, A., Tiitinen, A., Jauhiainen, M., Soininen, P., Kangas, A. J., Kähönen, M., Havulinna, A. S., Ala-Korpela, M., … Perola, M. (2014). A metabolic view on menopause and ageing. *Nature Communications*, *5*(1), 4708. https://doi.org/10.1038/ncomms5708

Azevedo, L. B. D., Cucato, G. G., & Morseth, B. (2024). Editorial: Sedentary behaviour and cardiometabolic health. *Frontiers in Cardiovascular Medicine*, *11*. https://doi.org/10.3389/fcvm.2024.1498410

Bacon, S. (2013). Central Adiposity. In M. D. Gellman & J. R. Turner (Eds.), *Encyclopedia of Behavioral Medicine* (pp. 368–369). Springer. https://doi.org/10.1007/978-1-4419-1005-9_1108

Baeza, I., De Castro, N. M., Giménez-Llort, L., & De la Fuente, M. (2010). Ovariectomy, a model of menopause in rodents, causes a premature aging of the nervous and immune

systems. *Journal of Neuroimmunology*, *219*(1), 90–99. https://doi.org/10.1016/j.jneuroim.2009.12.008

Ballou, S. P., Lozanski, G. B., Hodder, S., Rzewnicki, D. L., Mion, L. C., Sipe, J. D., Ford, A. B., & Kushner, I. (1996). Quantitative and qualitative alterations of acute-phase proteins in healthy elderly persons. *Age and Ageing, 25*(3), 224–230. https://doi.org/10.1093/ageing/25.3.224

Banait, T., Wanjari, A., Danade, V., Banait, S., & Jain, J. (2022). Role of high-sensitivity c-reactive protein (Hs-CRP) in non-communicable diseases: A review. *Cureus, 14*(10), e30225. https://doi.org/10.7759/cureus.30225

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting linear mixed-effects models using lme4. *Journal of Statistical Software*, *67*(1), 1–48. https://doi.org/10.18637/jss.v067.i01

Bauman, A., Bull, F., Chey, T., Craig, C. L., Ainsworth, B. E., Sallis, J. F., Bowles, H. R., Hagstromer, M., Sjostrom, M., & Pratt, M. (2009). the international prevalence study on physical activity: Results from 20 countries. *The International Journal of Behavioral Nutrition and Physical Activity*, *6*, 21. https://doi.org/10.1186/1479-5868-6-21

Bell, K., Salmon, A., & McNaughton, D. (2011). Alcohol, tobacco, obesity and the new public health. *Critical Public Health, 21*(1), 1–8.

Bermingham, K. M., Linenberg, I., Hall, W. L., Kadé, K., Franks, P. W., Davies, R., Wolf, J., Hadjigeorgiou, G., Asnicar, F., Segata, N., Manson, J. E., Newson, L. R., Delahanty, L. M., Ordovas, J. M., Chan, A. T., Spector, T. D., Valdes, A. M., & Berry, S. E. (2022). Menopause is associated with postprandial metabolism, metabolic health and lifestyle: The ZOE PREDICT study. *eBioMedicine*, *85*. https://doi.org/10.1016/j.ebiom.2022.104303

Bernabeu-Wittel, M., Gómez-Díaz, R., González-Molina, Á., Vidal-Serrano, S., Díez-Manglano, J., Salgado, F., Soto-Martín, M., Ollero-Baturone, M., & on behalf of the PROTEO RESEARCHERS. (2020). Oxidative stress, telomere shortening, and apoptosis associated to sarcopenia and frailty in patients with multimorbidity. *Journal of Clinical Medicine*, *9*(8), Article 8. https://doi.org/10.3390/jcm9082669

Bischops, A. C., De Neve, J.-W., Awasthi, A., Vollmer, S., Bärnighausen, T., & Geldsetzer, P. (2020). A cross-sectional study of cardiovascular disease risk clustering at different socio-geographic levels in India. *Nature Communications*, *11*(1), 5891.

Blackwell, A. D., Pryor III, G., Pozo, J., Tiwia, W., & Sugiyama, L. S. (2009). Growth and market integration in Amazonia: A comparison of growth indicators between Shuar, Shiwiar, and nonindigenous school children. *American Journal of Human Biology*, *21*(2), 161–171. https://doi.org/10.1002/ajhb.20838

Blackwell, A. D., Snodgrass, J. J., Madimenos, F. C., & Sugiyama, L. S. (2010). Life history, immune function, and intestinal helminths: Trade-offs among immunoglobulin E, C-reactive protein, and growth in an Amazonian population. *American Journal of Human Biology*, *22*(6), 836–848. https://doi.org/10.1002/ajhb.21092

Blagosklonny, M. V. (2008). Aging: Ros or tor. *Cell Cycle*, *7*(21), 3344–3354.

Blagosklonny, M. V. (2010). Calorie restriction: Decelerating mTOR-driven aging from cells to organisms (including humans). *Cell Cycle, 9*(4), 683–688. https://doi.org/10.4161/cc.9.4.10766

Blake, G. J., Rifai, N., Buring, J. E., & Ridker, P. M. (2003). Blood pressure, c-reactive protein, and risk of future cardiovascular events. *Circulation, 108*(24), 2993–2999. https://doi.org/10.1161/01.CIR.0000104566.10178.AF

Blasco, M. A. (2005). Telomeres and human disease: Ageing, cancer and beyond. *Nature Reviews Genetics*, *6*(8), 611–622. https://doi.org/10.1038/nrg1656

Bobbioni-Harsch, E., Habicht, F., Lehmann, T., James, R. W., Rohner-Jeanrenaud, F., & Golay, A. (1997). Energy expenditure and substrates oxidative patterns, after glucose, fat or mixed load in normal weight subjects. *European Journal of Clinical Nutrition*, *51*(6), Article 6. https://doi.org/10.1038/sj.ejcn.1600413

Boersma, B., & Wit, J. M. (1997). Catch-up Growth. *Endocrine Reviews*, *18*(5), 646–661. https://doi.org/2019041123293483000

Boffetta, P. (2006). Human cancer from environmental pollutants: The epidemiological evidence. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis*, *608*(2), 157–162. https://doi.org/10.1016/j.mrgentox.2006.02.015

Bonafè, M., Barbieri, M., Marchegiani, F., Olivieri, F., Ragno, E., Giampieri, C., Mugianesi, E., Centurelli, M., Franceschi, C., & Paolisso, G. (2003). Polymorphic variants of Insulin-Like Growth Factor I (IGF-I) receptor and phosphoinositide 3-kinase genes affect IGF-I plasma levels and human longevity: Cues for an evolutionarily conserved mechanism of life span control. *The Journal of Clinical Endocrinology & Metabolism*, *88*(7), 3299–3304. https://doi.org/10.1210/jc.2002-021810

Bosy-Westphal, A., Eichhorn, C., Kutzner, D., Illner, K., Heller, M., & Müller, M. J. (2003). The age-related decline in resting energy expenditure in humans is due to the loss of fat-free mass and to alterations in its metabolically active components. *The Journal of Nutrition*, *133*(7), 2356–2362. https://doi.org/10.1093/jn/133.7.2356

Braveman, P. A., Cubbin, C., Egerter, S., Chideya, S., Marchi, K. S., Metzler, M., & Posner, S. (2005). Socioeconomic status in health research: One size does not fit all. *JAMA*, *294*(22), 2879–2888. https://doi.org/10.1001/jama.294.22.2879

Bridevaux, P.-O., Gerbase, M. W., Schindler, C., Felber Dietrich, D., Curjuric, I., Dratva, J., . . . Rochat, T. (2009). Sex-specific effect of body weight gain on systemic inflammation in subjects with COPD: results from the SAPALDIA cohort study. *European Respiratory Journal, 34*(2), 332-339. doi:10.1183/09031936.00162608

Brindle, E., Fujita, M., Shofer, J., & O'Connor, K. A. (2010). Serum, plasma, and dried blood spot high-sensitivity C-reactive protein enzyme immunoassay for population research. *Journal of Immunological Methods*, *362*(1), 112–120. https://doi.org/10.1016/j.jim.2010.09.014

Brown, L. L., Zhang, Y. S., Mitchell, C., & Ailshire, J. (2018). Does telomere length indicate biological, physical, and cognitive health among older adults? Evidence from the Health and Retirement Study. *The Journals of Gerontology: Series A*, *73*(12), 1626–1632. https://doi.org/10.1093/gerona/gly001

Brunet, T., & King, N. (2017). The origin of animal multicellularity and cell differentiation. *Developmental Cell*, *43*(2), 124–140.

Bruunsgaard, H., Pedersen, M., & Pedersen, B. K. (2001). Aging and proinflammatory cytokines. *Current Opinion in Hematology, 8*(3), 131-136.

Bull, F. C., Al-Ansari, S. S., Biddle, S., Borodulin, K., Buman, M. P., Cardon, G., Carty, C., Chaput, J.-P., Chastin, S., & Chou, R. (2020). World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *British Journal of Sports Medicine*, *54*(24), 1451–1462.

Caballero, B. (2007). The global epidemic of obesity: an overview. *Epidemiologic Reviews, 29,* 1–5. https://doi.org/10.1093/epirev/mxm012

Calabrò, A., Accardi, G., Aiello, A., Caruso, C., & Candore, G. (2023). Sex and gender affect immune aging. *Frontiers in Aging*, *4*. https://doi.org/10.3389/fragi.2023.1272118

Caldwell, J. C. (2001). Population health in transition. *Bulletin of the World Health Organization*, *79*(2), 159–160.

Caldwell, J., & Caldwell, P. (1991). What have we learnt about the cultural, social and behavioural determinants of health? From Selected Readings to the first Health Transition Workshop. *Health Transition Review*, *1*(1), 3–19.

Cambodia: Impacts of the nutrition transition on urban and rural mothers and children | ENN. (2024, April 11). https://www.ennonline.net/fex/72/cambodia-impacts-of-the-nutrition-transition

Campisi, J. (2001). Cellular senescence as a tumor-suppressor mechanism. *Trends in Cell Biology*, *11*(11), S27-31. https://doi.org/10.1016/s0962-8924(01)02151-1

Campisi, J. (2003). Cellular senescence and apoptosis: How cellular responses might influence aging phenotypes. *Experimental Gerontology*, *38*(1), 5–11. https://doi.org/10.1016/S0531-5565(02)00152-3

Carapeto, P. V., & Aguayo-Mazzucato, C. (2021). Effects of exercise on cellular and tissue aging. *Aging (Albany NY)*, *13*(10), 14522–14543. https://doi.org/10.18632/aging.203051

Carr, M. C. (2003). The emergence of the metabolic syndrome with menopause. *The Journal of Clinical Endocrinology & Metabolism*, *88*(6), 2404–2411. https://doi.org/10.1210/jc.2003-030242

Carrasco, E., Gómez de las Heras, M. M., Gabandé-Rodríguez, E., Desdín-Micó, G., Aranda, J. F., & Mittelbrunn, M. (2022). The role of T cells in age-related diseases. *Nature Reviews Immunology*, *22*(2), 97–111. https://doi.org/10.1038/s41577-021-00557-4

Carrasco-Escobar, G., Schwalb, A., Tello-Lizarraga, K., Vega-Guerovich, P., & Ugarte-Gil, C. (2020). Spatio-temporal co-occurrence of hotspots of tuberculosis, poverty and air pollution in Lima, Peru. *Infectious Diseases of Poverty*, *9*(02), 84–89.

Caselli, G., Meslé, F., & Vallin, J. (2002). Epidemiologic transition theory exceptions. *Genus, 58*(1), 9–51.

Caspersen, C. J., Pereira, M. A., & Curran, K. M. (2000). Changes in physical activity patterns in the United States, by sex and cross-sectional age. *Medicine & Science in Sports & Exercise, 32*(9), 1601-1609.

Cepon-Robins, T. J., Gildner, T. E., Schrock, J., Eick, G., Bedbury, A., Liebert, M. A., Urlacher, S. S., Madimenos, F. C., Harrington, C. J., Amir, D., Bribiescas, R. G., Sugiyama, L. S., & Snodgrass, J. J. (2019). Soil-transmitted helminth infection and intestinal inflammation among the Shuar of Amazonian Ecuador. *American Journal of Physical Anthropology*, *170*(1), 65–74. https://doi.org/10.1002/ajpa.23897

Chakravarti, D., LaBella, K. A., & DePinho, R. A. (2021). Telomeres: History, health, and hallmarks of aging. *Cell*, *184*(2), 306–322. https://doi.org/10.1016/j.cell.2020.12.028

Chalmers, R. P. (2012). mirt: A multidimensional item response theory package for the R environment. *Journal of Statistical Software*, *48*(6), 1–29.

Chavakis, T., Alexaki, V. I., & Ferrante, A. W. (2023). Macrophage function in adipose tissue homeostasis and metabolic inflammation. *Nature Immunology*, *24*(5), 757–766. https://doi.org/10.1038/s41590-023-01479-0

Chen, C., Akiyama, K., Wang, D., Xu, X., Li, B., Moshaverinia, A., Brombacher, F., Sun, L., & Shi, S. (2014). mTOR inhibition rescues osteopenia in mice with systemic sclerosis. *Journal of Experimental Medicine*, *212*(1), 73–91. https://doi.org/10.1084/jem.20140643

Chen, G., & Yung, R. (2019). Meta-inflammaging at the crossroad of geroscience. *Aging Medicine*, *2*(3), 157–161. https://doi.org/10.1002/agm2.12078

Chong, B., Kong, G., Shankar, K., Chew, H. S. J., Lin, C., Goh, R., Chin, Y. H., Tan, D. J. H., Chan, K. E., Lim, W. H., Syn, N., Chan, S. P., Wang, J.-W., Khoo, C. M., Dimitriadis, G. K., Wijarnpreecha, K., Sanyal, A., Noureddin, M., Siddiqui, M. S., … Chew, N. W. S. (2023). The global syndemic of metabolic diseases in the young adult population: A consortium of trends and projections from the Global Burden of Disease 2000–2019. *Metabolism*, *141*, 155402. https://doi.org/10.1016/j.metabol.2023.155402

Cohen, A. A., Kennedy, B. K., Anglas, U., Bronikowski, A. M., Deelen, J., Dufour, F., Ferbeyre, G., Ferrucci, L., Franceschi, C., Frasca, D., Friguet, B., Gaudreau, P., Gladyshev, V. N., Gonos, E. S., Gorbunova, V., Gut, P., Ivanchenko, M., Legault, V., Lemaître, J.-F., … Fülöp, T. (2020). Lack of consensus on an aging biology paradigm? A global survey reveals an agreement to disagree, and the need for an interdisciplinary framework. *Mechanisms of Ageing and Development*, *191*, 111316. https://doi.org/10.1016/j.mad.2020.111316

Cohen, J., Cohen, P., West, S. G., & Aiken, L. S. (2002). Applied multiple regression/correlation analysis for the behavioral sciences. Routledge.

Colman, R. J., Anderson, R. M., Johnson, S. C., Kastman, E. K., Kosmatka, K. J., Beasley, T. M., Allison, D. B., Cruzen, C., Simmons, H. A., Kemnitz, J. W., & Weindruch, R. (2009). Caloric restriction delays disease onset and mortality in rhesus monkeys. *Science*, *325*(5937), 201–204. https://doi.org/10.1126/science.1173635

Comfort, A. (1964). *Ageing, the Biology of Senescence*. Holt, Rinehart and Winston. https://books.google.com/books?id=CpIIAAAAMAAJ

Cong, Y.-S., Wright, W. E., & Shay, J. W. (2002). Human telomerase and its regulation. *Microbiology and Molecular Biology Reviews*, *66*(3), 407–425. https://doi.org/10.1128/mmbr.66.3.407-425.2002

Congdon, J. D., Nagle, R. D., Osentoski, M. F., Kinney, O. M., & van Loben Sels, R. C. (2003). Life history and demographic aspects of aging in the long-lived turtle (Emydoidea blandingii). In C. E. Finch, J.-M. Robine, & Y. Christen (Eds.), *Brain and Longevity* (pp. 15–31). Springer. https://doi.org/10.1007/978-3-642-59356-7_2

Connolly, V., & Kesson, C. (1996). Socioeconomic status and clustering of cardiovascular disease risk factors in diabetic patients. *Diabetes Care*, *19*(5), 419–422.

Coppé, J.-P., Desprez, P.-Y., Krtolica, A., & Campisi, J. (2010). The senescence-associated secretory phenotype: The dark side of tumor suppression. Annual Review of Pathology: Mechanisms of Disease, 5(1), 99–118. https://doi.org/10.1146/annurev-pathol-121808-102144

Cordain, L., Eaton, S. B., Miller, J. B., Mann, N., & Hill, K. (2002). The paradoxical nature of hunter-gatherer diets: Meat-based, yet non-atherogenic. *European Journal of Clinical Nutrition*, *56*(1), S42–S52. https://doi.org/10.1038/sj.ejcn.1601353

Cornu, M., Albert, V., & Hall, M. N. (2013). mTOR in aging, metabolism, and cancer. *Current Opinion in Genetics & Development*, *23*(1), 53–62. https://doi.org/10.1016/j.gde.2012.12.005

Cornu, M., Oppliger, W., Albert, V., Robitaille, A. M., Trapani, F., Quagliata, L., Fuhrer, T., Sauer, U., Terracciano, L., & Hall, M. N. (2014). Hepatic mTORC1 controls locomotor activity, body temperature, and lipid metabolism through FGF21. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(32), 11592–11599. https://doi.org/10.1073/pnas.1412047111

CRS, Congressional Research Service (2023). *National Institutes of Health (NIH) Funding: FY1996-FY2024*. https://sgp.fas.org/crs/misc/R43341.pdf

Cruz-Góngora, V. D. la, Martínez-Tapia, B., Cuevas-Nasu, L., Flores-Aldana, M., & Shamah-Levy, T. (2017). Dietary intake and adequacy of energy and nutrients in Mexican older adults: Results from two National Health and Nutrition Surveys. *Salud Pública de México*, *59*, 285–298. https://doi.org/10.21149/7851

Cuthbertson, D. J., Steele, T., Wilding, J. P., Halford, J. C., Harrold, J. A., Hamer, M., & Karpe, F. (2017). What have human experimental overfeeding studies taught us about adipose tissue expansion and susceptibility to obesity and metabolic complications? *International Journal of Obesity*, *41*(6), 853–865. https://doi.org/10.1038/ijo.2017.4

Darikwa, T. B., & Manda, S. O. (2020). Spatial co-clustering of cardiovascular diseases and select risk factors among adults in South Africa. *International Journal of Environmental Research and Public Health*, *17*(10), Article 10. https://doi.org/10.3390/ijerph17103583

Darmon, N., & Drewnowski, A. (2008). Does social class predict diet quality?1. *The American Journal of Clinical Nutrition*, *87*(5), 1107–1117. https://doi.org/10.1093/ajcn/87.5.1107

DeCaro, J. A., & Helfrecht, C. (2022). Applying minimally invasive biomarkers of chronic stress across complex ecological contexts. *American Journal of Human Biology*, *34*(11), e23814. https://doi.org/10.1002/ajhb.23814

Delanerolle, G., Phiri, P., Elneil, S., Talaulikar, V., Eleje, G. U., Kareem, R., Shetty, A., Saraswath, L., Kurmi, O., Benetti-Pinto, C. L., Muhammad, I., Rathnayake, N., Toh, T.-H., Aggarwal, I. M., Shi, J. Q., Taylor, J., Riach, K., Potocnik, K., Litchfield, I., … Lee, J. Y.-S. (2025). Menopause: A global health and wellbeing issue that needs urgent attention. *The Lancet Global Health*, *13*(2), e196–e198. https://doi.org/10.1016/S2214-109X(24)00528-X

DeMars, C. (2010). Item Response Theory. Oxford University Press. https://doi.org/10.1093/acprof:oso/9780195377033.001.0001

Desdín-Micó, G., Soto-Heredero, G., Aranda, J. F., Oller, J., Carrasco, E., Gabandé-Rodríguez, E., Blanco, E. M., Alfranca, A., Cussó, L., Desco, M., Ibañez, B., Gortazar, A. R., Fernández-Marcos, P., Navarro, M. N., Hernaez, B., Alcamí, A., Baixauli, F., & Mittelbrunn, M. (2020). T cells with dysfunctional mitochondria induce multimorbidity and premature senescence. *Science*, *368*(6497), 1371–1376. https://doi.org/10.1126/science.aax0860

DiPietro, L. (2001). Physical activity in aging: Changes in patterns and their relationship to health and function. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *56*(suppl_2), 13–22.

Dregan, A., Charlton, J., Chowienczyk, P., & Gulliford, M. C. (2014). Chronic inflammatory disorders and risk of type 2 diabetes mellitus, coronary heart disease, and stroke: A population-based cohort study. *Circulation*, 130, 837-844. doi:10.1161/circulationaha.114.009990

Drewnowski, A., & Darmon, N. (2005). The economics of obesity: Dietary energy density and energy cost. *The American Journal of Clinical Nutrition*, *82*(1), 265S-273S. https://doi.org/10.1093/ajcn/82.1.265S

Drouard, G., Mykkänen, J., Heiskanen, J., Pohjonen, J., Ruohonen, S., Pahkala, K., Lehtimäki, T., Wang, X., Ollikainen, M., Ripatti, S., Pirinen, M., Raitakari, O., & Kaprio, J. (2024). Exploring machine learning strategies for predicting cardiovascular disease risk factors from multi-omic data. *BMC Medical Informatics and Decision Making*, *24*(1), Article 1. https://doi.org/10.1186/s12911-024-02521-3

Du, H., Zhang, X., Zeng, Y., Huang, X., Chen, H., Wang, S., Wu, J., Li, Q., Zhu, W., Li, H., Liu, T., Yu, Q., Wu, Y., & Jie, L. (2019). A novel phytochemical, DIM, inhibits proliferation, migration, invasion and TNF-α induced inflammatory cytokine production of synovial fibroblasts from rheumatoid arthritis patients by targeting MAPK and AKT/mTOR Signal Pathway. *Frontiers in Immunology*, *10*. https://www.frontiersin.org/articles/10.3389/fimmu.2019.01620

Earp, B. D., & Trafimow, D. (2015). Replication, falsification, and the crisis of confidence in social psychology. *Frontiers in Psychology*, *6*, 621.

Eaton, S. B., Konner, M., & Shostak, M. (1988). Stone agers in the fast lane: Chronic degenerative diseases in evolutionary perspective. *The American Journal of Medicine*, *84*(4), 739–749. https://doi.org/10.1016/0002-9343(88)90113-1

Edelman, G. M., & Gally, J. A. (2001). Degeneracy and complexity in biological systems. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(24), 13763–13768. https://doi.org/10.1073/pnas.231499798

Engelmann, F., Barron, A., Urbanski, H., Neuringer, M., Kohama, S. G., Park, B., & Messaoudi, I. (2011). Accelerated immune senescence and reduced response to vaccination in

ovariectomized female rhesus macaques. *Age*, *33*(3), 275–289. https://doi.org/10.1007/s11357-010-9178-0

Engström, G., Hedblad, B., Stavenow, L., Lind, P., Janzon, L., & Lindgärde, F. (2003). Inflammation-sensitive plasma proteins are associated with future weight gain. *Diabetes, 52*(8), 2097-2101. doi:10.2337/diabetes.52.8.2097

Estruch, R., Martínez-González, M. A., Corella, D., Salas-Salvadó, J., Ruiz-Gutiérrez, V., Covas, M. I., Fiol, M., Gómez-Gracia, E., López-Sabater, M. C., & Vinyoles, E. (2006). Effects of a Mediterranean-style diet on cardiovascular risk factors: A randomized trial. *Annals of Internal Medicine*, *145*(1), 1–11. https://doi.org/10.7326/0003-4819-145-1-200607040-00004

Fedewa, M. V., Hathaway, E. D., & Ward-Ritacco, C. L. (2017). Effect of exercise training on C reactive protein: A systematic review and meta-analysis of randomised and non-randomised controlled trials. *British Journal of Sports Medicine*, *51*(8), 670–676. https://doi.org/10.1136/bjsports-2016-095999

Fiedler, J. L., Lividini, K., Bermudez, O. I., & Smitz, M.-F. (2012). Household Consumption and Expenditures Surveys (HCES): A primer for food and nutrition analysts in low- and middle-income countries. *Food and Nutrition Bulletin*, *33*(3_suppl2), S170–S184. https://doi.org/10.1177/15648265120333S205

Finch, C. E. (2007). CHAPTER 3—Energy Balance, Inflammation, and Aging. In C. E. Finch (Ed.), *The Biology of Human Longevity* (pp. 175–232). Academic Press. https://doi.org/10.1016/B978-012373657-4/50004-0

Finkel, T. (2015). The metabolic regulation of aging. *Nature Medicine*, *21*(12), 1416–1423. https://doi.org/10.1038/nm.3998

Fisher, R. A. (1930). *The genetical theory of natural selection.* (pp. xiv, 272). Clarendon Press. https://doi.org/10.5962/bhl.title.27468

Forrester, S. N., Taylor, J. L., Whitfield, K. E., & Thorpe, R. J. (2020). Advances in understanding the causes and consequences of health disparities in aging minorities. *Current Epidemiology Reports*, *7*, 59–67.

Frances, M. Y., & Solon, T. K. (2014). Item response theory for measurement validity. *Shanghai Archives of Psychiatry*, *26*(3), 171.

Franceschi, C., & Bonafè, M. (2003). Centenarians as a model for healthy aging. *Biochemical Society Transactions*, *31*(2), 457–461. https://doi.org/10.1042/bst0310457

Franceschi, C., & Campisi, J. (2014). Chronic inflammation (Inflammaging) and its potential contribution to age-associated diseases. *The Journals of Gerontology: Series A, 69*(Suppl_1), S4-S9. doi:10.1093/gerona/glu057

Franceschi, C., Bonafè, M., Valensin, S., Olivieri, F., Luca, M. D., Ottaviani, E., & Benedictis, G. D. (2000). Inflamm-aging: An evolutionary perspective on immunosenescence. *Annals of the New York Academy of Sciences*, *908*(1), 244–254. https://doi.org/10.1111/j.1749-6632.2000.tb06651.x

Franceschi, C., Garagnani, P., Parini, P., Giuliani, C., & Santoro, A. (2018). Inflammaging: A new immune–metabolic viewpoint for age-related diseases. *Nature Reviews Endocrinology*, *14*(10), 576–590. https://doi.org/10.1038/s41574-018-0059-4

Franceschi, C., Garagnani, P., Vitale, G., Capri, M., & Salvioli, S. (2017). Inflammaging and 'Garb-aging.' *Trends in Endocrinology & Metabolism*, *28*(3), 199–212. https://doi.org/10.1016/j.tem.2016.09.005

Franceschi, C., Monti, D., Sansoni, P., & Cossarizza, A. (1995). The immunology of exceptional individuals: The lesson of centenarians. *Immunology Today*, *16*(1), 12–16. https://doi.org/10.1016/0167-5699(95)80064-6

Freedman, V. A., Grafova, I. B., & Rogowski, J. (2011). Neighborhoods and chronic disease onset in later life. *American Journal of Public Health*, *101*(1), 79–86. https://doi.org/10.2105/AJPH.2009.178640

Freitas, A. A., & de Magalhães, J. P. (2011). A review and appraisal of the DNA damage theory of ageing. *Mutation Research/Reviews in Mutation Research*, *728*(1), 12–22. https://doi.org/10.1016/j.mrrev.2011.05.001

Fuller, R., Rahona, E., Fisher, S., Caravanos, J., Webb, D., Kass, D., Matte, T., & Landrigan, P. J. (2018). Pollution and non-communicable disease: Time to end the neglect. *The Lancet Planetary Health*, *2*(3), e96–e98. https://doi.org/10.1016/S2542-5196(18)30020-2

Fulop, T., & Larbi, A. (2018). Biology of aging: Paving the way for healthy aging. *Experimental Gerontology, 107*, 1-3. doi:https://doi.org/10.1016/j.exger.2018.03.014

Furman, D., Campisi, J., Verdin, E., Carrera-Bastos, P., Targ, S., Franceschi, C., Ferrucci, L., Gilroy, D. W., Fasano, A., Miller, G. W., Miller, A. H., Mantovani, A., Weyand, C. M., Barzilai, N., Goronzy, J. J., Rando, T. A., Effros, R. B., Lucia, A., Kleinstreuer, N., & Slavich, G. M. (2019). Chronic inflammation in the etiology of disease across the life span. *Nature Medicine*, *25*(12), 1822–1832. https://doi.org/10.1038/s41591-019-0675-0

Gaal, L. F. V., Mertens, I. L., & Block, C. E. D. (2006). Mechanisms linking obesity with cardiovascular disease. *Nature*, *444*(7121), 875. https://doi.org/10.1038/nature05487

Gage, T. B. (2005). Are modern environments really bad for us?: Revisiting the demographic and epidemiologic transitions. *American Journal of Physical Anthropology*, *128*(S41), 96–117. https://doi.org/10.1002/ajpa.20353

Ganasegeran, K., Abdul Manaf, M. R., Safian, N., Waller, L. A., Mustapha, F. I., Abdul Maulud, K. N., & Mohd Rizal, M. F. (2024). how socio-economic inequalities cluster people with

diabetes in Malaysia: Geographic evaluation of area disparities using a non-parameterized unsupervised learning method. *Journal of Epidemiology and Global Health*, *14*(1), 169–183. https://doi.org/10.1007/s44197-023-00185-2

Gao, Z., Wyman, M. J., Sella, G., & Przeworski, M. (2016). Interpreting the dependence of mutation rates on age and time. *PLOS Biology*, *14*(1), e1002355. https://doi.org/10.1371/journal.pbio.1002355

Gibson, J., Russ, T. C., Clarke, T.-K., Howard, D. M., Hillary, R. F., Evans, K. L., Walker, R. M., Bermingham, M. L., Morris, S. W., Campbell, A., Hayward, C., Murray, A. D., Porteous, D. J., Horvath, S., Lu, A. T., McIntosh, A. M., Whalley, H. C., & Marioni, R. E. (2019). A meta-analysis of genome-wide association studies of epigenetic age acceleration. *PLOS Genetics*, *15*(11), e1008104. https://doi.org/10.1371/journal.pgen.1008104

Giglio, T., Imro, M. A., Filaci, G., Scudeletti, M., Puppo, F., De Cecco, L., Indiveri, F., & Costantini, S. (1994). Immune cell circulating subsets are affected by gonadal function. *Life Sciences*, *54*(18), 1305–1312. https://doi.org/10.1016/0024-3205(94)00508-7

Gildner, T. E., Cepon-Robins, T. J., Liebert, M. A., Urlacher, S. S., Madimenos, F. C., Snodgrass, J. J., & Sugiyama, L. S. (2016). Regional variation in Ascaris lumbricoides and Trichuris trichiura infections by age cohort and sex: Effects of market integration among the indigenous Shuar of Amazonian Ecuador. *Journal of Physiological Anthropology*, *35*(1), 28. https://doi.org/10.1186/s40101-016-0118-2

Gildner, T. E., Cepon-Robins, T. J., Liebert, M. A., Urlacher, S. S., Schrock, J. M., Harrington, C. J., Madimenos, F. C., Snodgrass, J. J., & Sugiyama, L. S. (2020). Market integration and soil-transmitted helminth infection among the Shuar of Amazonian Ecuador. *PLOS ONE, 15*(7), e0236924. https://doi.org/10.1371/journal.pone.0236924

Giollabhui, N. M., Ellman, L. M., Coe, C. L., Byrne, M. L., Abramson, L. Y., & Alloy, L. B. (2020). To exclude or not to exclude: Considerations and recommendations for C-Reactive Protein values higher than 10 mg/L. *Brain, Behavior, and Immunity, 87*, 898–900. https://doi.org/10.1016/j.bbi.2020.01.023

Glazer, H. P., Osipov, R. M., Clements, R. T., Sellke, F. W., & Bianchi, C. (2009). Hypercholesterolemia is associated with hyperactive cardiac mTORC1 and mTORC2 signaling. *Cell Cycle*, *8*(11), 1738–1746. https://doi.org/10.4161/cc.8.11.8619

Gluckman, P. D., Low, F. M., Buklijas, T., Hanson, M. A., & Beedle, A. S. (2011). How evolutionary principles improve the understanding of human health and disease. *Evolutionary Applications*, *4*(2), 249–263.

Gocmez, S. S., Yazir, Y., Gacar, G., Demirtaş Şahin, T., Arkan, S., Karson, A., & Utkan, T. (2020). Etanercept improves aging-induced cognitive deficits by reducing inflammation and vascular dysfunction in rats. *Physiology & Behavior*, *224*, 113019. https://doi.org/10.1016/j.physbeh.2020.113019

Goldberg, X., Espelt, C., Porta-Casteràs, D., Palao, D., Nadal, R., & Armario, A. (2021). Non-communicable diseases among women survivors of intimate partner violence: Critical review from a chronic stress framework. *Neuroscience & Biobehavioral Reviews*, *128*, 720–734. https://doi.org/10.1016/j.neubiorev.2021.06.045

Gomez-Cabrero, D., Walter, S., Abugessaisa, I., Miñambres-Herraiz, R., Palomares, L. B., Butcher, L., Erusalimsky, J. D., Garcia-Garcia, F. J., Carnicero, J., Hardman, T. C., Mischak, H., Zürbig, P., Hackl, M., Grillari, J., Fiorillo, E., Cucca, F., Cesari, M., Carrie, I., Colpo, M., … Rodriguez-Mañas, L. (2021). A robust machine learning framework to identify signatures for frailty: A nested case-control study in four aging European cohorts. *GeroScience*, *43*(3), 1317–1329. https://doi.org/10.1007/s11357-021-00334-0

Gravlee, C. C. (2009). How race becomes biology: Embodiment of social inequality. *American Journal of Physical Anthropology*, *139*(1), 47–57.

Grizzi, F., & Chiriva-Internati, M. (2006). Cancer: Looking for simplicity and finding complexity. *Cancer Cell International*, *6*(1), Article 1. https://doi.org/10.1186/1475-2867-6-4

Gruenewald, T. L., Seeman, T. E., Karlamangla, A. S., & Sarkisian, C. A. (2009). Allostatic load and frailty in older adults. *Journal of the American Geriatrics Society*, *57*(9), 1525–1531. https://doi.org/10.1111/j.1532-5415.2009.02389.x

Guerrero-López, C. M., Serván-Mori, E., Miranda, J. J., Jan, S., Orozco-Núñez, E., Downey, L., Feeny, E., Heredia-Pi, I., Flamand, L., Nigenda, G., & Norton, R. (2023). Burden of non-communicable diseases and behavioural risk factors in Mexico: Trends and gender observational analysis. *Journal of Global Health*, *13*, 04054. https://doi.org/10.7189/jogh.13.04054

Guo, Y.-Z., Pan, L., Du, C.-J., Ren, D.-Q., & Xie, X.-M. (2013). Association between C-reactive protein and risk of cancer: a meta-analysis of prospective cohort studies. Asian Pacific Journal of Cancer Prevention, 14(1), 243-248.

Gurven, M. D., & Lieberman, D. E. (2020). WEIRD bodies: Mismatch, medicine and missing diversity. *Evolution and Human Behavior*, *41*(5), 330–340. https://doi.org/10.1016/j.evolhumbehav.2020.04.001

Gurven, M. D., Trumble, B. C., Stieglitz, J., Blackwell, A. D., Michalik, D. E., Finch, C. E., & Kaplan, H. S. (2016). Cardiovascular disease and type 2 diabetes in evolutionary perspective: A critical role for helminths? *Evolution, Medicine, and Public Health*, *2016*(1), 338–357. https://doi.org/10.1093/emph/eow028

Gurven, M., Jaeggi, A. V., Kaplan, H., & Cummings, D. (2013). Physical activity and modernization among Bolivian Amerindians. *PLOS ONE*, *8*(1), e55679. https://doi.org/10.1371/journal.pone.0055679

Gurven, M., Kaplan, H., Winking, J., Eid Rodriguez, D., Vasunilashorn, S., Kim, J. K., . . . Crimmins, E. (2009). Inflammation and infection do not promote arterial aging and cardiovascular disease risk factors among lean horticulturalists. PloS one, 4(8), e6590. doi:10.1371/journal.pone.0006590

Gurven, M., Kaplan, H., Winking, J., Finch, C., & Crimmins, E. M. (2008). Aging and Inflammation in two epidemiological worlds. *The Journals of Gerontology: Series A*, *63*(2), 196–199. https://doi.org/10.1093/gerona/63.2.196

Gurven, M., Kaplan, H., Winking, J., Rodriguez, D. E., Vasunilashorn, S., Kim, J. K., Finch, C., & Crimmins, E. (2009). Inflammation and infection do not promote arterial aging and cardiovascular disease risk factors among lean horticulturalists. *PLOS ONE*, *4*(8), e6590. https://doi.org/10.1371/journal.pone.0006590

Guthold, R., Stevens, G. A., Riley, L. M., & Bull, F. C. (2018). Worldwide trends in insufficient physical activity from 2001 to 2016: A pooled analysis of 358 population-based surveys with 1·9 million participants. *The Lancet Global Health*, *6*(10), e1077–e1086. https://doi.org/10.1016/S2214-109X(18)30357-7

Gutiérrez Robledo, L. M., López Ortega, M., & Arango Lopera, V. E. (2012). The state of elder care in Mexico. *Current Geriatrics Reports, 1*(4), 183-189. doi:10.1007/s13670-012-0028-z

Halbreich, U., Lumley, L. A., Palter, S., Manning, C., Gengo, F., & Joe, S.-H. (1995). Possible acceleration of age effects on cognition following menopause. *Journal of Psychiatric Research*, *29*(3), 153–163. https://doi.org/10.1016/0022-3956(95)00005-P

Hall, R. L. (2004). An energetics-based approach to understanding the menstrual cycle and menopause. *Human Nature*, *15*(1), 83–99. https://doi.org/10.1007/s12110-004-1005-9

Hammen, C. (2005). Stress and Depression. *Annual Review of Clinical Psychology*, *1*(Volume 1, 2005), 293–319. https://doi.org/10.1146/annurev.clinpsy.1.102803.143938

Han, T. S., Seidell, J. C., Currall, J. E. P., Morrison, C. E., Deurenberg, P., & Lean, M. E. J. (1997). The influences of height and age on waist circumference as an index of adiposity in adults. *International Journal of Obesity*, *21*(1), Article 1. https://doi.org/10.1038/sj.ijo.0800371

Harman, D. (2001). Aging: Overview. *Annals of the New York Academy of Sciences*, *928*(1), 1–21. https://doi.org/10.1111/j.1749-6632.2001.tb05631.x

Hassen, C. B., Machado-Fragua, M. D., Landré, B., Fayosse, A., Dumurgier, J., Kivimaki, M., Sabia, S., & Singh-Manoux, A. (2023). Change in lipids before onset of dementia, coronary heart disease, and mortality: A 28-year follow-up Whitehall II prospective cohort study. *Alzheimer's & Dementia*. https://doi.org/10.1002/alz.13140

Hawkes, C. (2006). Uneven dietary development: Linking the policies and processes of globalization with the nutrition transition, obesity and diet-related chronic diseases. *Globalization and Health*, *2*(1), 4. https://doi.org/10.1186/1744-8603-2-4

Hawkes, K., & Coxworth, J. E. (2013). Grandmothers and the evolution of human longevity: A review of findings and future directions. *Evolutionary Anthropology: Issues, News, and Reviews*, *22*(6), 294–302. https://doi.org/10.1002/evan.21382

Hawkes, K., O'Connell, J. F., Jones, N. G. B., Alvarez, H., & Charnov, E. L. (1998). Grandmothering, menopause, and the evolution of human life histories. *Proceedings of the National Academy of Sciences*, *95*(3), 1336–1339. https://doi.org/10.1073/pnas.95.3.1336

Hayflick, L., & Moorhead, P. S. (1961). The serial cultivation of human diploid cell strains. *Experimental Cell Research*, *25*(3), 585–621. https://doi.org/10.1016/0014-4827(61)90192-6

He, F. J., & MacGregor, G. A. (2009). A comprehensive review on salt and health and current experience of worldwide salt reduction programmes. *Journal of Human Hypertension*, *23*(6), 363–384.

Herrmann, S. D., Heumann, K. J., Der Ananian, C. A., & Ainsworth, B. E. (2013). validity and reliability of the Global Physical Activity Questionnaire (GPAQ). *Measurement in Physical Education and Exercise Science*, *17*(3), 221–235. https://doi.org/10.1080/1091367X.2013.805139

Higgins-Chen, A. T., Thrush, K. L., Wang, Y., Minteer, C. J., Kuo, P.-L., Wang, M., Niimi, P., Sturm, G., Lin, J., & Moore, A. Z. (2022). A computational solution for bolstering reliability of epigenetic clocks: Implications for clinical trials and longitudinal tracking. *Nature Aging*, *2*(7), 644–661.

Ho, E., Qualls, C., & Villareal, D. T. (2022). Effect of diet, exercise, or both on biological age and healthy aging in older adults with obesity: Secondary analysis of a randomized controlled trial. *The Journal of Nutrition, Health & Aging*, *26*(6), 552–557. https://doi.org/10.1007/s12603-022-1812-x

Hoadley, K. A., Yau, C., Hinoue, T., Wolf, D. M., Lazar, A. J., Drill, E., Shen, R., Taylor, A. M., Cherniack, A. D., Thorsson, V., Akbani, R., Bowlby, R., Wong, C. K., Wiznerowicz, M., Sanchez-Vega, F., Robertson, A. G., Schneider, B. G., Lawrence, M. S., Noushmehr, H., … Laird, P. W. (2018). Cell-of-origin patterns dominate the molecular classification of 10,000 tumors from 33 types of cancer. *Cell*, *173*(2), 291-304.e6. https://doi.org/10.1016/j.cell.2018.03.022

Hodes, R. J. (2024). *Keynote Address* [President's Opening Plenary Session]. Gerontology Society of America, Portland, OR.

Hoogendijk, E. O., Rijnhart, J. J. M., Kowal, P., Pérez-Zepeda, M. U., Cesari, M., Abizanda, P., Flores Ruano, T., Schop-Etman, A., Huisman, M., & Dent, E. (2018). Socioeconomic inequalities in frailty among older adults in six low- and middle-income countries: Results from the WHO Study on global AGEing and adult health (SAGE). *Maturitas*, *115*, 56–63. https://doi.org/10.1016/j.maturitas.2018.06.011

Horvath, S., & Raj, K. (2018). DNA methylation-based biomarkers and the epigenetic clock theory of ageing. *Nature Reviews Genetics*, *19*(6), Article 6. https://doi.org/10.1038/s41576-018-0004-3

Hotamisligil, G. S. (2006). Inflammation and metabolic disorders. *Nature, 444*(7121), Article 7121. https://doi.org/10.1038/nature05485

Houck, K., Sorensen, M. V., Lu, F., Alban, D., Alvarez, K., Hidobro, D., Doljanin, C., & Ona, A. I. (2013). The effects of market integration on childhood growth and nutritional status: The dual burden of under- and over-nutrition in the Northern Ecuadorian Amazon. *American Journal of Human Biology*, *25*(4), 524–533. https://doi.org/10.1002/ajhb.22404

Hu, L., & and Bentler, P. M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling: A Multidisciplinary Journal, 6*(1), 1–55. https://doi.org/10.1080/10705519909540118

Hu, P., Herningtyas, E. H., Kale, V., Crimmins, E. M., Risbud, A. R., McCreath, H., … Seeman, T. E. (2015). External quality control for dried blood spot based c-reactive protein assay: Experience from the Indonesia family life survey and the longitudinal aging study in India. *Biodemography and Social Biology,* 61, 111–120. https://doi.org/10.1080/19485565.2014.1001886

Hu, X. F., Kenny, T.-A., & Chan, H. M. (2018). Inuit country food diet pattern is associated with lower risk of coronary heart disease. *Journal of the Academy of Nutrition and Dietetics*, *118*(7), 1237-1248.e1. https://doi.org/10.1016/j.jand.2018.02.004

Hui-Fang, L., Cai, L., Wang, X.-M., & Golden, A. R. (2019). Ethnic disparities in prevalence and clustering of cardiovascular disease risk factors in rural Southwest China. *BMC Cardiovascular Disorders*, *19*(1), Article 1. https://doi.org/10.1186/s12872-019-1185-1

Iyer, R. R., Pluciennik, A., Burdett, V., & Modrich, P. L. (2006). DNA Mismatch Repair: Functions and Mechanisms. *Chemical Reviews*, *106*(2), 302–323. https://doi.org/10.1021/cr0404794

Jaeggi, A. V., Blackwell, A. D., von Rueden, C., Trumble, B. C., Stieglitz, J., Garcia, A. R., Kraft, T. S., Beheim, B. A., Hooper, P. L., Kaplan, H., & Gurven, M. (2021). Do wealth and inequality associate with health in a small-scale subsistence society? *eLife*, *10*, e59437. https://doi.org/10.7554/eLife.59437

Jafarinasabian, P., Inglis, J. E., Reilly, W., Kelly, O. J., & Ilich, J. Z. (2017). Aging human body: changes in bone, muscle and body fat with consequent changes in nutrient intake. *Journal of Endocrinology,* 234, R37-R51. doi:10.1530/joe-16-0603

Janssen, I. (2009). Influence of age on the relation between waist circumference and cardiometabolic risk markers. *Nutrition, Metabolism and Cardiovascular Diseases*, *19*(3), 163–169. https://doi.org/10.1016/j.numecd.2008.06.013

Jia, G., Aroor, A. R., Martinez-Lemus, L. A., & Sowers, J. R. (2014). Overnutrition, mTOR signaling, and cardiovascular diseases. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *307*(10), R1198–R1206. https://doi.org/10.1152/ajpregu.00262.2014

Johnson, R. K., Appel, L. J., Brands, M., Howard, B. V., Lefevre, M., Lustig, R. H., Sacks, F., Steffen, L. M., & Wylie-Rosett, J. (2009). dietary sugars intake and cardiovascular health. *Circulation*, *120*(11), 1011–1020. https://doi.org/10.1161/CIRCULATIONAHA.109.192627

Johnson, S. C., Rabinovitch, P. S., & Kaeberlein, M. (2013). mTOR is a key modulator of ageing and age-related disease. *Nature*, *493*(7432), Article 7432. https://doi.org/10.1038/nature11861

Kalani, R., Judge, S., Carter, C., Pahor, M., & Leeuwenburgh, C. (2006). Effects of caloric restriction and exercise on age-related, chronic inflammation assessed by c-reactive protein and interleukin-6. *The Journals of Gerontology: Series A*, *61*(3), 211–217. https://doi.org/10.1093/gerona/61.3.211

Kallestrup-Lamb, M., Marin, A. O. K., Menon, S., & Søgaard, J. (2024). Aging populations and expenditures on health. *The Journal of the Economics of Ageing*, *29*, 100518. https://doi.org/10.1016/j.jeoa.2024.100518

Kaplan, H., Thompson, R. C., Trumble, B. C., Wann, L. S., Allam, A. H., Beheim, B., Frohlich, B., Sutherland, M. L., Sutherland, J. D., Stieglitz, J., Rodriguez, D. E., Michalik, D. E., Rowan, C. J., Lombardi, G. P., Bedi, R., Garcia, A. R., Min, J. K., Narula, J., Finch, C. E., … Thomas, G. S. (2017). Coronary atherosclerosis in indigenous South American Tsimane: A cross-sectional cohort study. *The Lancet*, *389*(10080), 1730–1739. https://doi.org/10.1016/S0140-6736(17)30752-3

Karastergiou, K., Smith, S. R., Greenberg, A. S., & Fried, S. K. (2012). Sex differences in human adipose tissues–the biology of pear shape. Biology of Sex Differences, 3, 13.

Keating, X. D., Zhou, K., Liu, X., Hodges, M., Liu, J., Guan, J., Phelps, A., & Castro-Piñero, J. (2019). Reliability and concurrent validity of Global Physical Activity Questionnaire (GPAQ): A systematic review. *International Journal of Environmental Research and Public Health*, *16*(21), Article 21. https://doi.org/10.3390/ijerph16214128

Kehler, D. S., & Theou, O. (2019). The impact of physical activity and sedentary behaviors on frailty levels. *Mechanisms of Ageing and Development*, *180*, 29–41. https://doi.org/10.1016/j.mad.2019.03.004

Kelly, T., Yang, W., Chen, C.-S., Reynolds, K., & He, J. (2008). Global burden of obesity in 2005 and projections to 2030. *International Journal of Obesity, 32*(9), 1431–1437. https://doi.org/10.1038/ijo.2008.102

Kendler, K. S., Karkowski, L. M., & Prescott, C. A. (1999). Causal relationship between stressful life events and the onset of major depression. *American Journal of Psychiatry*, *156*(6), 837–841. https://doi.org/10.1176/ajp.156.6.837

Kennedy, B. K., Berger, S. L., Brunet, A., Campisi, J., Cuervo, A. M., Epel, E. S., Franceschi, C., Lithgow, G. J., Morimoto, R. I., & Pessin, J. E. (2014). Geroscience: Linking aging to chronic disease. *Cell*, *159*(4), 709–713.

Khera, A., Vega, G. L., Das, S. R., Ayers, C., McGuire, D. K., Grundy, S. M., & de Lemos, J. A. (2009). Sex differences in the relationship between c-reactive protein and body fat. *The Journal of Clinical Endocrinology & Metabolism*, *94*(9), 3251–3258. https://doi.org/10.1210/jc.2008-2406

Kim, S. H., Arora, I., Hsia, D. S., Knowler, W. C., LeBlanc, E., Mylonakis, E., Pratley, R., & Pittas, A. G. (2023). New-onset diabetes after COVID-19. *The Journal of Clinical Endocrinology & Metabolism*, *108*(11), e1164–e1174. https://doi.org/10.1210/clinem/dgad284

Kirkwood, T. B. L. (1977). Evolution of ageing. *Nature*, *270*(5635), Article 5635. https://doi.org/10.1038/270301a0

Klöting, N., & Blüher, M. (2005). Extended longevity and insulin signaling in adipose tissue. *Experimental Gerontology*, *40*(11), 878–883. https://doi.org/10.1016/j.exger.2005.07.004

Kopp, H. P., Kopp, C. W., Festa, A., Krzyzanowska, K., Kriwanek, S., Minar, E., . . . Schernthaner, G. (2003). Impact of weight loss on inflammatory proteins and their association with the insulin resistance syndrome in morbidly obese patients. *Arteriosclerosis, Thrombosis, and Vascular Biology, 23*(6), 1042-1047. doi:10.1161/01.atv.0000073313.16135.21

Kowal, P., Chatterji, S., Naidoo, N., Biritwum, R., Fan, W., Lopez Ridaura, R., Maximova, T., Arokiasamy, P., Phaswana-Mafuya, N., Williams, S., Snodgrass, J. J., Minicuci, N., D'Este, C., Peltzer, K., & Boerma, J. T. (2012). Data Resource Profile: The World Health Organization Study on global AGEing and adult health (SAGE). *International Journal of Epidemiology*, *41*(6), 1639–1649. https://doi.org/10.1093/ije/dys210

Kowal, P., Kahn, K., Ng, N., Naidoo, N., Abdullah, S., Bawah, A., Binka, F., Chuc, N. T. K., Debpuur, C., Ezeh, A., Xavier Gómez-Olivé, F., Hakimi, M., Hirve, S., Hodgson, A., Juvekar, S., Kyobutungi, C., Menken, J., Van Minh, H., Mwanyangala, M. A., …

Tollman, S. M. (2010). Ageing and adult health status in eight lower-income countries: The INDEPTH WHO-SAGE collaboration. *Global Health Action*, *3*(1), 5302. https://doi.org/10.3402/gha.v3i0.5302

Kraus, W. E., Bhapkar, M., Huffman, K. M., Pieper, C. F., Das, S. K., Redman, L. M., Villareal, D. T., Rochon, J., Roberts, S. B., & Ravussin, E. (2019). 2 years of calorie restriction and cardiometabolic risk (CALERIE): Exploratory outcomes of a multicentre, phase 2, randomised controlled trial. *The Lancet Diabetes & Endocrinology*, *7*(9), 673–683.

Krenz, A., & Strulik, H. (2023). Physiological aging in India: The role of the epidemiological transition. *PLOS ONE*, *18*(7), e0287259. https://doi.org/10.1371/journal.pone.0287259

Kuk, J. L., Lee, S., Heymsfield, S. B., & Ross, R. (2005). Waist circumference and abdominal adipose tissue distribution: Influence of age and sex. *The American Journal of Clinical Nutrition*, *81*(6), 1330–1334. https://doi.org/10.1093/ajcn/81.6.1330

Kuo, H.-K., Yen, C.-J., Chang, C.-H., Kuo, C.-K., Chen, J.-H., & Sorond, F. (2005). Relation of C-reactive protein to stroke, cognitive disorders, and depression in the general population: systematic review and meta-analysis. *The Lancet Neurology, 4*(6), 371-380.

Kuuire, V., Atuoye, K., Bisung, E., & Braimah, J. A. (2023). A multilevel analysis of neighborhood inequalities and non-communicable disease multimorbidity in Ghana. In *Health Geography in Sub-Saharan Africa* (pp. 13–34). Springer, Cham. https://doi.org/10.1007/978-3-031-37565-1_2

Kyu, H. H., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., Abbastabar, H., Abd-Allah, F., Abdela, J., Abdelalim, A., Abdollahpour, I., Abdulkader, R. S., Abebe, M., Abebe, Z., Abil, O. Z., Aboyans, V., Abrham, A. R., Abu-Raddad, L. J., Abu-Rmeileh, N. M. E., … Murray, C. J. L. (2018). Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*, *392*(10159), 1859–1922. https://doi.org/10.1016/S0140-6736(18)32335-3

Lai, G. (1995). Work and family roles and psychological well-being in urban China. Journal of Health and Social Behavior, 36, 11-37. doi:10.2307/2137285

Laland, K. N., Uller, T., Feldman, M. W., Sterelny, K., Müller, G. B., Moczek, A., Jablonka, E., & Odling-Smee, J. (2015). The extended evolutionary synthesis: Its structure, assumptions and predictions. *Proceedings of the Royal Society B: Biological Sciences*, *282*(1813), 20151019. https://doi.org/10.1098/rspb.2015.1019

Landrigan, P. J., Fuller, R., Acosta, N. J. R., Adeyi, O., Arnold, R., Basu, N. (Nil), Baldé, A. B., Bertollini, R., Bose-O'Reilly, S., Boufford, J. I., Breysse, P. N., Chiles, T., Mahidol, C., Coll-Seck, A. M., Cropper, M. L., Fobil, J., Fuster, V., Greenstone, M., Haines, A., … Zhong, M. (2018). The Lancet Commission on pollution and health. *The Lancet*, *391*(10119), 462–512. https://doi.org/10.1016/S0140-6736(17)32345-0

Landsbergis, P. A., Dobson, M., Koutsouras, G., & Schnall, P. (2013). Job strain and ambulatory blood pressure: A meta-analysis and systematic review. *American Journal of Public Health*, *103*(3), e61–e71. https://doi.org/10.2105/AJPH.2012.301153

Lassale, C., Batty, G. D., Steptoe, A., Cadar, D., Akbaraly, T. N., Kivimäki, M., & Zaninotto, P. (2019). Association of 10-Year c-reactive protein trajectories with markers of healthy aging: Findings from the English Longitudinal Study of Aging. *The Journals of Gerontology: Series A*, *74*(2), 195–203. https://doi.org/10.1093/gerona/gly028

Lathe, R., & St. Clair, D. (2023). Programmed ageing: Decline of stem cell renewal, immunosenescence, and Alzheimer's disease. *Biological Reviews*, *98*(4), 1424–1458. https://doi.org/10.1111/brv.12959

Law, M. R. (1997). Epidemiologic evidence on salt and blood pressure. *American Journal of Hypertension*, *10*(S4), 42S-45S. https://doi.org/10.1016/S0895-7061(97)00073-3

Lea, A. J., Clark, A. G., Dahl, A. W., Devinsky, O., Garcia, A. R., Golden, C. D., Kamau, J., Kraft, T. S., Lim, Y. A. L., Martins, D. J., Mogoi, D., Pajukanta, P., Perry, G. H., Pontzer, H., Trumble, B. C., Urlacher, S. S., Venkataraman, V. V., Wallace, I. J., Gurven, M., … Ayroles, J. F. (2023). Applying an evolutionary mismatch framework to understand disease susceptibility. *PLOS Biology*, *21*(9), e3002311. https://doi.org/10.1371/journal.pbio.3002311

Lea, A. J., Martins, D., Kamau, J., Gurven, M., & Ayroles, J. F. (2020). Urbanization and market integration have strong, nonlinear effects on cardiometabolic health in the Turkana. *Science Advances*, *6*(43), eabb1430. https://doi.org/10.1126/sciadv.abb1430

Lee, H., Lee, E., & Jang, I.-Y. (2020). Frailty and Comprehensive Geriatric Assessment. *Journal of Korean Medical Science*, *35*(3). https://doi.org/10.3346/jkms.2020.35.e16

Lee, W.-S., Monaghan, P., & Metcalfe, N. B. (2013). Experimental demonstration of the growth rate–lifespan trade-off. *Proceedings of the Royal Society B: Biological Sciences, 280*(1752), 20122370. https://doi.org/10.1098/rspb.2012.2370

Leonard, W. R., & Robertson, M. L. (1997). Comparative primate energetics and hominid evolution. *American Journal of Physical Anthropology, 102*(2), 265-281.

Leonard, W. R., & Ulijaszek, S. J. (2002). Energetics and evolution: An emerging research domain. *American Journal of Human Biology*, *14*(5), 547–550. https://doi.org/10.1002/ajhb.10068

Levine, M. E. (2020). Assessment of epigenetic clocks as biomarkers of aging in basic and population research. *The Journals of Gerontology: Series A*, *75*(3), 463–465. https://doi.org/10.1093/gerona/glaa021

Levine, M. E., Lu, A. T., Chen, B. H., Hernandez, D. G., Singleton, A. B., Ferrucci, L., Bandinelli, S., Salfati, E., Manson, J. E., & Quach, A. (2016). Menopause accelerates biological aging. *Proceedings of the National Academy of Sciences*, *113*(33), 9327–9332.

Li, Y., Zhong, X., Cheng, G., Zhao, C., Zhang, L., Hong, Y., Wan, Q., He, R., & Wang, Z. (2017). Hs-CRP and all-cause, cardiovascular, and cancer mortality risk: A meta-analysis. *Atherosclerosis*, *259*, 75–82. https://doi.org/10.1016/j.atherosclerosis.2017.02.003

Li, Z., Zhang, Z., Ren, Y., Wang, Y., Fang, J., Yue, H., Ma, S., & Guan, F. (2021). Aging and age-related diseases: From mechanisms to therapeutic strategies. *Biogerontology*, *22*(2), 165–187. https://doi.org/10.1007/s10522-021-09910-5

Liebert, M. A., Snodgrass, J. J., Madimenos, F. C., Cepon, T. J., Blackwell, A. D., & Sugiyama, L. S. (2013). Implications of market integration for cardiovascular and metabolic health among an indigenous Amazonian Ecuadorian population. *Annals of Human Biology*, *40*(3), 228–242. https://doi.org/10.3109/03014460.2012.759621

Liebert, M., Cepon, T., Madimenos, F., Mathur , A., Williams, S., Naidoo, N., & Snodgrass, J. (2013). SAGE Working Paper No. 7: Self-reported physical activity and measured energy expenditure using accelerometers: Results of a SAGE sub-study in India. Retrieved from http://www.who.int/healthinfo/sage/SAGEWorkingPaper7_Liebert_SAGEAccelerometry_Nov13.pdf?ua=1.

Ligthart, G. J., Corberand, J. X., Fournier, C., Galanaud, P., Hijmans, W., Kennes, B., Müller-Hermelink, H. K., & Steinmann, G. G. (1984). Admission criteria for immunogerontological studies in man: The SENIEUR protocol. *Mechanisms of Ageing and Development*, *28*(1), 47–55.

Lin, J. E., Neylan, T. C., Epel, E., & O'Donovan, A. (2016). Associations of childhood adversity and adulthood trauma with C-reactive protein: A cross-sectional population-based study. *Brain, Behavior, and Immunity*, *53*, 105–112. https://doi.org/10.1016/j.bbi.2015.11.015

Lind, M. I., Chen, H., Meurling, S., Guevara Gil, A. C., Carlsson, H., Zwoinska, M. K., Andersson, J., Larva, T., & Maklakov, A. A. (2017). Slow development as an evolutionary cost of long life. *Functional Ecology*, *31*(6), 1252–1261. https://doi.org/10.1111/1365-2435.12840

Liu, G. Y., & Sabatini, D. M. (2020). mTOR at the nexus of nutrition, growth, ageing and disease. *Nature Reviews Molecular Cell Biology*, *21*(4), Article 4. https://doi.org/10.1038/s41580-019-0199-y

Liu, Z., Liang, Q., Ren, Y., Guo, C., Ge, X., Wang, L., Cheng, Q., Luo, P., Zhang, Y., & Han, X. (2023). Immunosenescence: Molecular mechanisms and diseases. *Signal Transduction and Targeted Therapy*, *8*(1), Article 1. https://doi.org/10.1038/s41392-023-01451-2

López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M., & Kroemer, G. (2013). The hallmarks of aging. *Cell*, *153*(6), 1194–1217.

López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M., & Kroemer, G. (2023). Hallmarks of aging: An expanding universe. *Cell*, 186(2), 243–278. https://doi.org/10.1016/j.cell.2022.11.001

Lord, F. M. (2012). *Applications of item response theory to practical testing problems*. Routledge.

Lorenzo-López, L., Maseda, A., de Labra, C., Regueiro-Folgueira, L., Rodríguez-Villamil, J. L., & Millán-Calenti, J. C. (2017). Nutritional determinants of frailty in older adults: A systematic review. *BMC Geriatrics*, *17*(1), Article 1. https://doi.org/10.1186/s12877-017-0496-2

Lu, F. (2007). Integration into the market among indigenous peoples: A cross-cultural perspective from the Ecuadorian Amazon. *Current Anthropology*, *48*(4), 593–602. https://doi.org/10.1086/519806

Luan, Y., & Yao, Y. (2018). The clinical significance and potential role of c-reactive protein in chronic inflammatory and neurodegenerative diseases. *Frontiers in Immunology*, *9*. https://doi.org/10.3389/fimmu.2018.01302

Lund Håheim, L., Nafstad, P., Olsen, I., Schwarze, P., & Rønningen, K. S. (2009). C-reactive protein variations for different chronic somatic disorders. *Scandinavian Journal of Public Health, 37*(6), 640-646. doi:10.1177/1403494809104358

Luxton, J. J., & Bailey, S. M. (2021). Twins, telomeres, and aging—In space! *Plastic and Reconstructive Surgery*, *147*(1S-2), 7S. https://doi.org/10.1097/PRS.0000000000007616

Luxton, J. J., McKenna, M. J., Lewis, A., Taylor, L. E., George, K. A., Dixit, S. M., Moniz, M., Benegas, W., Mackay, M. J., Mozsary, C., Butler, D., Bezdan, D., Meydan, C., Crucian, B. E., Zwart, S. R., Smith, S. M., Mason, C. E., & Bailey, S. M. (2020). Telomere length dynamics and DNA damage responses associated with long-duration spaceflight. *Cell Reports*, *33*(10). https://doi.org/10.1016/j.celrep.2020.108457

Maciejowski, J., & de Lange, T. (2017). Telomeres in cancer: Tumour suppression and genome instability. *Nature Reviews Molecular Cell Biology*, *18*(3), Article 3. https://doi.org/10.1038/nrm.2016.171

Madimenos, F. C., Snodgrass, J. J., Blackwell, A. D., Liebert, M. A., & Sugiyama, L. S. (2011). Physical activity in an indigenous Ecuadorian forager-horticulturalist population as measured using accelerometry. *American Journal of Human Biology, 23*(4), 488–497. https://doi.org/10.1002/ajhb.21163

Madimenos, F. C., Snodgrass, J. J., Liebert, M. A., Cepon, T. J., & Sugiyama, L. S. (2012). Reproductive effects on skeletal health in Shuar women of Amazonian Ecuador: A life

history perspective. *American Journal of Human Biology*, *24*(6), 841–852. https://doi.org/10.1002/ajhb.22329

Maiese, K. (2015). mTOR: Driving apoptosis and autophagy for neurocardiac complications of diabetes mellitus. *World Journal of Diabetes*, *6*(2), 217–224. https://doi.org/10.4239/wjd.v6.i2.217

Majcherek, D., Weresa, M. A., & Ciecierski, C. (2020). Understanding regional risk factors for cancer: A cluster analysis of lifestyle, environment and socio-economic status in Poland. *Sustainability*, *12*(21), Article 21. https://doi.org/10.3390/su12219080

Malekzadeh, A., Michels, K., Wolfman, C., Anand, N., & Sturke, R. (2020). Strengthening research capacity in LMICs to address the global NCD burden. *Global Health Action*, *13*(1), 1846904. https://doi.org/10.1080/16549716.2020.1846904

Man, S., Connett, J. E., Anthonisen, N. R., Wise, R. A., Tashkin, D. P., & Sin, D. D. (2006). C-reactive protein and mortality in mild to moderate chronic obstructive pulmonary disease. Thorax, 61(10), 849-853.

Marlowe, F. (2000). The patriarch hypothesis. *Human Nature*, *11*(1), 27–42. https://doi.org/10.1007/s12110-000-1001-7

Marzetti, E., Calvani, R., Bernabei, R., & Leeuwenburgh, C. (2011). Apoptosis in skeletal myocytes: A potential target for interventions against sarcopenia and physical frailty – a mini-review. *Gerontology*, *58*(2), 99–106. https://doi.org/10.1159/000330064

Mattison, S. M., Hare, D., MacLaren, N. G., Reynolds, A. Z., Sum, C.-Y., Liu, R., Shenk, M. K., Blumenfield, T., Su, M., Li, H., & Wander, K. (2022). Context specificity of "market integration" among the matrilineal mosuo of southwest china. *Current Anthropology*. https://doi.org/10.1086/719266

McCarthy, E. M., & Rinella, M. E. (2012). The role of diet and nutrient composition in nonalcoholic fatty liver disease. *Journal of the Academy of Nutrition and Dietetics*, *112*(3), 401–409. https://doi.org/10.1016/j.jada.2011.10.007

McDade, T. W., Burhop, J., & Dohnal, J. (2004). High-sensitivity enzyme immunoassay for c-reactive protein in dried blood spots. *Clinical Chemistry*, *50*(3), 652–654. https://doi.org/10.1373/clinchem.2003.029488

McDade, T. W., Hawkley, L. C., & Cacioppo, J. T. (2006). Psychosocial and behavioral predictors of inflammation in middle-aged and older Adults: The Chicago health, aging, and social relations study. *Psychosomatic Medicine*, *68*(3), 376. https://doi.org/10.1097/01.psy.0000221371.43607.64

McDade, T. W., Tallman, P. S., Madimenos, F. C., Liebert, M. A., Cepon, T. J., Sugiyama, L. S., & Snodgrass, J. J. (2012). Analysis of variability of high sensitivity C-reactive protein in

lowland Ecuador reveals no evidence of chronic low-grade inflammation. *American Journal of Human Biology, 24*(5), 675–681. https://doi.org/10.1002/ajhb.22296

McDade, T. W., Williams, S., & Snodgrass, J. J. (2007). What a drop can do: dried blood spots as a minimally invasive method for integrating biomarkers into population-based research. *Demography, 44*(4), 899-925.

McKee, P., & Barber, C. E. (2001). *Plato's theory of aging*. *6*(2).

Medawar, P. B. (1952). *An Unsolved Problem of Biology*. H. K. Lewis.

Medina, C., Barquera, S., & Janssen, I. (2013). Validity and reliability of the International Physical Activity Questionnaire among adults in Mexico. *Revista Panamericana de Salud Pública*, *34*, 21–28.

Melanson, K. J., Greenberg, A. S., Ludwig, D. S., Saltzman, E., Dallal, G. E., & Roberts, S. B. (1998). Blood glucose and hormonal responses to small and large meals in healthy young and older women. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *53*(4), B299–B305. https://doi.org/10.1093/gerona/53A.4.B299

Mendall, M. A., Patel, P., Ballam, L., Strachan, D., & Northfield, T. C. (1996). C Reactive protein and its relation to cardiovascular risk factors: A population based cross sectional study. *BMJ*, *312*(7038), 1061–1065. https://doi.org/10.1136/bmj.312.7038.1061

Mercken, E. M., Carboneau, B. A., Krzysik-Walker, S. M., & de Cabo, R. (2012). Of mice and men: The benefits of caloric restriction, exercise, and mimetics. *Ageing Research Reviews, 11*(3), 390–398. https://doi.org/10.1016/j.arr.2011.11.005

Metcalfe, N. B., & Monaghan, P. (2003). Growth versus lifespan: Perspectives from evolutionary ecology. *Experimental Gerontology*, *38*(9), 935–940. https://doi.org/10.1016/S0531-5565(03)00159-1

Mete, B., Keskin, L., Demirhindi, H., Şahin, C. K., Mete, E. D., & Bayram, E. (2024). the role of hedonic hunger as a moderator and mediator in older adults Obesity. *European Journal of Geriatrics and Gerontology*, *12*(1).

Meydani, S. N., Das, S. K., Pieper, C. F., Lewis, M. R., Klein, S., Dixit, V. D., Gupta, A. K., Villareal, D. T., Bhapkar, M., & Huang, M. (2016). Long-term moderate calorie restriction inhibits inflammation without impairing cell-mediated immunity: A randomized controlled trial in non-obese humans. *Aging*, *8*(7), 1416.

Milan-Mattos, J. C., Anibal, F. F., Perseguini, N. M., Minatel, V., Rehder-Santos, P., Castro, C. A., Vasilceac, F. A., Mattiello, S. M., Faccioli, L. H., & Catai, A. M. (2019). Effects of natural aging and gender on pro-inflammatory markers. *Brazilian Journal of Medical and Biological Research*, *52*, e8392. https://doi.org/10.1590/1414-431X20198392

Mitnitski, A., Song, X., & Rockwood, K. (2013). Assessing biological aging: The origin of deficit accumulation. *Biogerontology*, *14*(6), 709–717. https://doi.org/10.1007/s10522-013-9446-3

Mitteldorf, J. (2001). Can experiments on caloric restriction be reconciled with the disposable soma theory for the evolution of senescence? *Evolution*, *55*(9), 1902–1905. https://doi.org/10.1111/j.0014-3820.2001.tb00841.x

Moriarty, B. M. (1974). Socioeconomic status and residential locational choice. *Environment and Behavior*, *6*(4), 448–469. https://doi.org/10.1177/001391657400600402

Morrisette-Thomas, V., Cohen, A. A., Fülöp, T., Riesco, É., Legault, V., Li, Q., Milot, E., Dusseault-Bélanger, F., & Ferrucci, L. (2014). Inflamm-aging does not simply reflect increases in pro-inflammatory markers. *Mechanisms of Ageing and Development*, *139*, 49–57. https://doi.org/10.1016/j.mad.2014.06.005

Muñoz-Espín, D., & Serrano, M. (2014). Cellular senescence: From physiology to pathology. *Nature Reviews Molecular Cell Biology*, *15*(7), Article 7. https://doi.org/10.1038/nrm3823

Muntner, P., Shimbo, D., Carey, R. M., Charleston, J. B., Gaillard, T., Misra, S., Myers, M. G., Ogedegbe, G., Schwartz, J. E., & Townsend, R. R. (2019). Measurement of blood pressure in humans: A scientific statement from the American Heart Association. *Hypertension*, *73*(5), e35–e66.

Najjar, S. S., Scuteri, A., & Lakatta, E. G. (2005). Arterial aging. *Hypertension*, *46*(3), 454–462. https://doi.org/10.1161/01.HYP.0000177474.06749.98

Naska, A., Lagiou, A., & Lagiou, P. (2017). Dietary assessment methods in epidemiological research: Current state of the art and future prospects. *F1000Research*, *6*, 926. https://doi.org/10.12688/f1000research.10703.1

Naveed, T. A., Gordon, D., Ullah, S., & Zhang, M. (2021). The construction of an asset index at household level and measurement of economic disparities in Punjab (Pakistan) by using MICS-Micro Data. *Social Indicators Research*, *155*(1), 73–95. https://doi.org/10.1007/s11205-020-02594-3

Neale, M. C., Lubke, G., Aggen, S. H., & Dolan, C. V. (2005). Problems with using sum scores for estimating variance components: Contamination and measurement noninvariance. *Twin Research and Human Genetics*, *8*(6), 553–568.

Nelson, P., & Masel, J. (2017). Intercellular competition and the inevitability of multicellular aging. *Proceedings of the National Academy of Sciences*, *114*(49), 12982–12987. https://doi.org/10.1073/pnas.1618854114

Nesse, R. M., & Stearns, S. C. (2008). The great opportunity: Evolutionary applications to medicine and public health. *Evolutionary Applications*, *1*(1), 28–48.

Nestel, P. J., Carroll, K. F., & Havenstein, N. (1970). Plasma triglyceride response to carbohydrates, fats and caloric intake. *Metabolism*, *19*(1), 1–18. https://doi.org/10.1016/0026-0495(70)90112-5

Newby, P. K., Muller, D., Hallfrisch, J., Qiao, N., Andres, R., & Tucker, K. L. (2003). Dietary patterns and changes in body mass index and waist circumference in adults. *The American Journal of Clinical Nutrition, 77*(6), 1417–1425. https://doi.org/10.1093/ajcn/77.6.1417

Nicklas, B. J., Ambrosius, W., Messier, S. P., Miller, G. D., Penninx, B. W. J. H., Loeser, R. F., . . . Pahor, M. (2004). Diet-induced weight loss, exercise, and chronic inflammation in older, obese adults: a randomized controlled clinical trial. *The American Journal of Clinical Nutrition, 79*(4), 544-551. doi:10.1093/ajcn/79.4.544

Nishiyama, A. (2011). Economic growth and infant mortality in developing countries. *The European Journal of Development Research*, *23*, 630–647.

Noubiap, J. J., Nansseu, J. R., Lontchi-Yimagou, E., Nkeck, J. R., Nyaga, U. F., Ngouo, A. T., Tounouga, D. N., Tianyi, F. L., Foka, A. J., & Ndoadoumgue, A. L. (2022). Global, regional, and country estimates of metabolic syndrome burden in children and adolescents in 2020: A systematic review and modelling analysis. *The Lancet Child & Adolescent Health*, *6*(3), 158–170.

O' Neill, C. (2013). PI3-kinase/Akt/mTOR signaling: Impaired on/off switches in aging, cognitive decline and Alzheimer's disease. *Experimental Gerontology*, *48*(7), 647–653. https://doi.org/10.1016/j.exger.2013.02.025

O'Keefe, J. H., Gheewala, N. M., & O'Keefe, J. O. (2008). Dietary strategies for improving post-prandial glucose, lipids, inflammation, and cardiovascular health. *Journal of the American College of Cardiology*, *51*(3), 249–255. https://doi.org/10.1016/j.jacc.2007.10.016

Oda, K., Matsuoka, Y., Funahashi, A., & Kitano, H. (2005). A comprehensive pathway map of epidermal growth factor receptor signaling. *Molecular Systems Biology*, *1*(1), 2005.0010. https://doi.org/10.1038/msb4100014

Oh, C., Kim, H.-S., & No, J.-K. (2015). Impact of dining out on nutritional intake and metabolic syndrome risk factors: Data from the 2011 Korean National Health and Nutrition Examination Survey. *British Journal of Nutrition*, *113*(3), 473–478. https://doi.org/10.1017/S0007114514003870

Olfson, M., Wall, M., Liu, S.-M., Schoenbaum, M., & Blanco, C. (2018). Declining health-related quality of life in the US. *American Journal of Preventive Medicine*, *54*(3), 325–333.

Omran, A. R. (2005). The Epidemiologic Transition: A Theory of the Epidemiology of Population Change. *The Milbank Quarterly*, *83*(4), 731–757. https://doi.org/10.1111/j.1468-0009.2005.00398.x

Orlando, M., & Thissen, D. (2000). Likelihood-based item-fit indices for dichotomous Item Response Theory models. *Applied Psychological Measurement, 24*(1), 50–64. https://doi.org/10.1177/01466216000241003

Orr, M. E., Salinas, A., Buffenstein, R., & Oddo, S. (2014). Mammalian target of rapamycin hyperactivity mediates the detrimental effects of a high sucrose diet on Alzheimer's disease pathology. *Neurobiology of Aging*, *35*(6), 1233–1242. https://doi.org/10.1016/j.neurobiolaging.2013.12.006

Pagidipati, N. J., Taub, P. R., Ostfeld, R. J., & Kirkpatrick, C. F. (2025). Dietary patterns to promote cardiometabolic health. *Nature Reviews Cardiology*, *22*(1), 38–46. https://doi.org/10.1038/s41569-024-01061-7

Palma-Gudiel, H., Fañanás, L., Horvath, S., & Zannas, A. S. (2020). Psychosocial stress and epigenetic aging. *International Review of Neurobiology, 150*, 107–128.

Paradies, Y., Ben, J., Denson, N., Elias, A., Priest, N., Pieterse, A., Gupta, A., Kelaher, M., & Gee, G. (2015). Racism as a determinant of health: A systematic review and meta-analysis. *PloS One*, *10*(9), e0138511.

Park, S. I., Suh, J., Lee, H. S., Song, K., Choi, Y., Oh, J. S., Choi, H. S., Kwon, A., Kim, H.-S., Kim, J. H., & Chae, H. W. (2021). Ten-year trends of metabolic syndrome prevalence and nutrient intake among Korean children and adolescents: A population-based study. *Yonsei Medical Journal*, *62*(4), 344–351. https://doi.org/10.3349/ymj.2021.62.4.344

Pearson, T. A., Mensah, G. A., Alexander, R. W., Anderson, J. L., Cannon, R. O., Criqui, M., Fadl, Y. Y., Fortmann, S. P., Hong, Y., Myers, G. L., Rifai, N., Smith, S. C., Taubert, K., Tracy, R. P., Vinicor, F., Centers for Disease Control and Prevention, & American Heart Association. (2003). Markers of inflammation and cardiovascular disease: Application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*, *107*(3), 499–511.

Perazza, L. R., Brown-Borg, H. M., & Thompson, L. V. (2022). Physiological systems in promoting frailty. *Comprehensive Physiology*, *12*(3), 3575–3620.

Perry, C. A., Van Guilder, G. P., Hossain, M., & Kauffman, A. (2021). cardiometabolic changes in response to a calorie-restricted DASH diet in obese older adults. *Frontiers in Nutrition*, *8*. https://doi.org/10.3389/fnut.2021.647847

Pessa, J. E., Nguyen, H., John, G. B., & Scherer, P. E. (2014). The anatomical basis for wrinkles. *Aesthetic Surgery Journal*, *34*(2), 227–234. https://doi.org/10.1177/1090820X13517896

Peters, R., Ee, N., Peters, J., Booth, A., Mudway, I., & Anstey, K. J. (2019). Air pollution and dementia: A systematic review. *Journal of Alzheimer's Disease*, *70*(s1), S145–S163. https://doi.org/10.3233/JAD-180631

Phillips, D. R., & Gyasi, R. M. (2021). Global aging in a comparative context. *The Gerontologist, 61*(3), 476–477. https://doi.org/10.1093/geront/gnaa155

Pifferi, F., Terrien, J., Perret, M., Epelbaum, J., Blanc, S., Picq, J.-L., Dhenain, M., & Aujard, F. (2019). Promoting healthspan and lifespan with caloric restriction in primates. *Communications Biology*, *2*(1), Article 1. https://doi.org/10.1038/s42003-019-0348-z

Pitsavos, C., Panagiotakos, D. B., Tzima, N., Lentzas, Y., Chrysohoou, C., Das, U. N., & Stefanadis, C. (2007). Diet, exercise, and c-reactive protein levels in people with abdominal obesity: The ATTICA epidemiological study. *Angiology*, *58*(2), 225–233. https://doi.org/10.1177/0003319707300014

Poehlman, E. T., Toth, M. J., Bunyard, L. B., Gardner, A. W., Donaldson, K. E., Colman, E., Fonong, T., & Ades, P. A. (1995). Physiological predictors of increasing total and central adiposity in aging men and women. *Archives of Internal Medicine*, *155*(22), 2443–2448. https://doi.org/10.1001/archinte.1995.00430220101011

Polak, P., Cybulski, N., Feige, J. N., Auwerx, J., Rüegg, M. A., & Hall, M. N. (2008). Adipose-specific knockout of raptor results in lean mice with enhanced mitochondrial respiration. *Cell Metabolism*, *8*(5), 399–410.

Pontzer, H. (2018). Energy constraint as a novel mechanism linking exercise and health. *Physiology*. https://doi.org/10.1152/physiol.00027.2018

Popkin, B. M. (2015). Nutrition transition and the global diabetes epidemic. *Current Diabetes Reports*, *15*, 1–8.

Popkin, B. M., Adair, L. S., & Ng, S. W. (2012). Global nutrition transition and the pandemic of obesity in developing countries. *Nutrition Reviews*, *70*(1), 3–21.

Powell, K. E., Paluch, A. E., & Blair, S. N. (2011). Physical activity for health: What kind? How much? How intense? On top of what? *Annual Review of Public Health*, *32*(32), 349–365. https://doi.org/10.1146/annurev-publhealth-031210-101151

Poznyak, A., Grechko, A. V., Poggio, P., Myasoedova, V. A., Alfieri, V., & Orekhov, A. N. (2020). The Diabetes Mellitus–Atherosclerosis Connection: The Role of Lipid and Glucose Metabolism and Chronic Inflammation. *International Journal of Molecular Sciences*, *21*(5), Article 5. https://doi.org/10.3390/ijms21051835

Pressler, M., Devinsky, J., Duster, M., Lee, J. H., Glick, C. S., Wiener, S., Laze, J., Friedman, D., Roberts, T., & Devinsky, O. (2022). Dietary transitions and health outcomes in four populations – Systematic review. *Frontiers in Nutrition*, *9*. https://doi.org/10.3389/fnut.2022.748305

Pu, D., Tan ,R., Yu ,Q., & and Wu, J. (2017). Metabolic syndrome in menopause and associated factors: A meta-analysis. *Climacteric*, *20*(6), 583–591. https://doi.org/10.1080/13697137.2017.1386649

Puzianowska-Kuźnicka, M., Owczarz, M., Wieczorowska-Tobis, K., Nadrowski, P., Chudek, J., Slusarczyk, P., Skalska, A., Jonas, M., Franek, E., & Mossakowska, M. (2016a). Interleukin-6 and C-reactive protein, successful aging, and mortality: The PolSenior study. *Immunity & Ageing*, *13*(1), 21. https://doi.org/10.1186/s12979-016-0076-x

Pyrkov, T. V., & Fedichev, P. O. (2019). Biological age is a universal marker of aging, stress, and frailty. *Biomarkers of Human Aging*, 23–36.

Ramasubbu, K., & Devi Rajeswari, V. (2023). Impairment of insulin signaling pathway PI3K/Akt/mTOR and insulin resistance induced AGEs on diabetes mellitus and neurodegenerative diseases: A perspective review. *Molecular and Cellular Biochemistry*, *478*(6), 1307–1324. https://doi.org/10.1007/s11010-022-04587-x

Ramey, E. R., & Goldstein, M. (1957). The adrenal cortex and the sympathetic nervous system. *Physiological Reviews*, *37*(2), 155–195.

Randall, Z. D., Brouillard, A. M., Deych, E., & Rich, M. W. (2022). Demographic, behavioral, dietary, and clinical predictors of high-sensitivity C-reactive protein: The National Health and Nutrition Examination Surveys (NHANES). *American Heart Journal Plus: Cardiology Research and Practice*, *21*, 100196. https://doi.org/10.1016/j.ahjo.2022.100196

Reardon, T., Tschirley, D., Dolislager, M., Snyder, J., Hu, C., & White, S. (2014). Urbanization, diet change, and transformation of food supply chains in Asia. *Michigan: Global Center for Food Systems Innovation*, *46*.

Reise, S. P., & Rodriguez, A. (2016). Item response theory and the measurement of psychiatric constructs: Some empirical and conceptual issues and challenges. Psychological *Medicine, 46*(10), 2025–2039. https://doi.org/10.1017/S0033291716000520

Ren, P., Dong, X., & Vijg, J. (2022). Age-related somatic mutation burden in human tissues. *Frontiers in Aging*, *3*. https://doi.org/10.3389/fragi.2022.1018119

Reuben, D. B., Judd-Hamilton, L., Harris, T. B., & Seeman, T. E. (2003). The associations between physical activity and inflammatory markers in high-functioning older persons: MacArthur studies of successful aging. *Journal of the American Geriatrics Society, 51*(8), 1125-1130. doi:doi:10.1046/j.1532-5415.2003.51380.x

Rezende, L. F. M. de, Lopes, M. R., Rey-López, J. P., Matsudo, V. K. R., & Luiz, O. do C. (2014). Sedentary behavior and health outcomes: An overview of systematic reviews. *PLOS ONE*, *9*(8), e105620. https://doi.org/10.1371/journal.pone.0105620

Ridker, P. M., Buring, J. E., Shih, J., Matias, M., & Hennekens, C. H. (1998). Prospective study of c-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation, 98*(8), 731–733. https://doi.org/10.1161/01.CIR.98.8.731

Rigamonti, A. E., Cicolini, S., Tamini, S., Caroli, D., Cella, S. G., & Sartorio, A. (2021). The age-dependent increase of metabolic syndrome requires more extensive and aggressive non-pharmacological and pharmacological interventions: A cross-sectional study in an Italian cohort of obese women. *International Journal of Endocrinology*, *2021*(1), 5576286. https://doi.org/10.1155/2021/5576286

Roberts, S. B., & Rosenberg, I. (2006). Nutrition and aging: Changes in the regulation of energy metabolism with aging. *Physiological Reviews*, *86*(2), 651–667. https://doi.org/10.1152/physrev.00019.2005

Rockwood, K., & Mitnitski, A. (2007). Frailty in relation to the accumulation of deficits. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *62*(7), 722–727. https://doi.org/10.1093/gerona/62.7.722

Rockwood, K., Song, X., MacKnight, C., Bergman, H., Hogan, D. B., McDowell, I., & Mitnitski, A. (2005). A global clinical measure of fitness and frailty in elderly people. *CMAJ : Canadian Medical Association Journal*, *173*(5), 489–495. https://doi.org/10.1503/cmaj.050051

Rode, L., Nordestgaard, B. G., & Bojesen, S. E. (2016). Long telomeres and cancer risk among 95 568 individuals from the general population. *International Journal of Epidemiology*, *45*(5), 1634–1643. https://doi.org/10.1093/ije/dyw179

Rolls, B. J., Dimeo, K. A., & Shide, D. J. (1995). Age-related impairments in the regulation of food intake. *The American Journal of Clinical Nutrition*, *62*(5), 923–931. https://doi.org/10.1093/ajcn/62.5.923

Rönnbäck, C., & Hansson, E. (2019). The importance and control of low-grade inflammation due to damage of cellular barrier systems that may lead to systemic inflammation. *Frontiers in Neurology*, *10*. https://doi.org/10.3389/fneur.2019.00533

Rook, G. A. W. (2023). The old friends hypothesis: Evolution, immunoregulation and essential microbial inputs. *Frontiers in Allergy*, *4*, 1220481. https://doi.org/10.3389/falgy.2023.1220481

Rosseel, Y. (2012). lavaan: An R Package for Structural Equation Modeling. *Journal of Statistical Software*, *48*(2), 1–36. https://doi.org/10.18637/jss.v048.i02

Rutledge, J., Oh, H., & Wyss-Coray, T. (2022). Measuring biological age using omics data. *Nature Reviews Genetics*, *23*(12), 715–727. https://doi.org/10.1038/s41576-022-00511-7

Sahyoun, N. R., Serdula, M. K., Galuska, D. A., Zhang, X. L., & Pamuk, E. R. (2004). The epidemiology of recent involuntary weight loss in the United States population. *The Journal of Nutrition, Health & Aging*, *8*(6), 510–517.

Salgado, M., Madureira, J., Mendes, A. S., Torres, A., Teixeira, J. P., & Oliveira, M. D. (2020). Environmental determinants of population health in urban settings. A systematic review. *BMC Public Health*, *20*(1), 853. https://doi.org/10.1186/s12889-020-08905-0

Salvioli, S., Monti, D., Lanzarini, C., Conte, M., Pirazzini, C., Giulia Bacalini, M., . . . Franceschi, C. (2013). Immune system, cell senescence, aging and longevity - Inflamm-aging reappraised. *Current Pharmaceutical Design, 19*(9), 1675-1679.

Samson, S. L., & Garber, A. J. (2014). Metabolic Syndrome. *Endocrinology and Metabolism Clinics*, *43*(1), 1–23. https://doi.org/10.1016/j.ecl.2013.09.009

Sanders, J. L., & Newman, A. B. (2013). Telomere Length in Epidemiology: A Biomarker of Aging, Age-Related Disease, Both, or Neither? *Epidemiologic Reviews*, *35*(1), 112–131. https://doi.org/10.1093/epirev/mxs008

Sandri, M., Barberi, L., Bijlsma, A. Y., Blaauw, B., Dyar, K. A., Milan, G., Mammucari, C., Meskers, C. G., M, Pallafacchina, G., Paoli, A., Pion, D., Roceri, M., Romanello, V., Serrano, A. L., Toniolo, L., Larsson, L., Maier, A. B., Muñoz-cánoves, P., … Schiaffino, S. (2013). Signalling pathways regulating muscle mass in ageing skeletal muscle. The role of the IGF1-Akt-mTOR-FoxO pathway. *Biogerontology; Dordrecht*, *14*(3), 303–323. http://dx.doi.org/10.1007/s10522-013-9432-9

Sansone, A., & Romanelli, F. (2021). Chapter 11—Hormones in aging. In C. Caruso & G. Candore (Eds.), *Human Aging* (pp. 207–217). Academic Press. https://doi.org/10.1016/B978-0-12-822569-1.00007-X

Santosa, A., Wall, S., Fottrell, E., Högberg, U., & Byass, P. (2014). The development and experience of epidemiological transition theory over four decades: A systematic review. *Global Health Action*, *7*(1), 23574. https://doi.org/10.3402/gha.v7.23574

Sapolsky, R. M., Krey, L. C., & McEwen, B. S. (1983). The adrenocortical stress-response in the aged male rat: Impairment of recovery from stress. *Experimental Gerontology*, *18*(1), 55–64. https://doi.org/10.1016/0531-5565(83)90051-7

Saxton, R. A., & Sabatini, D. M. (2017). mTOR signaling in growth, metabolism, and disease. *Cell*, *168*(6), 960–976. https://doi.org/10.1016/j.cell.2017.02.004

Schmidt, R., Schmidt, H., Curb, J. D., Masaki, K., White, L. R., & Launer, L. J. (2002). Early inflammation and dementia: A 25-year follow-up of the Honolulu-Asia aging study. *Annals of Neurology*, 52(2), 168-174.

Schoen, R. E., Tangen, C. M., Kuller, L. H., Burke, G. L., Cushman, M., Tracy, R. P., Dobs, A., & Savage, P. J. (1999). Increased blood glucose and insulin, body size, and incident

colorectal cancer. *Journal of the National Cancer Institute*, *91*(13), 1147–1154. https://doi.org/10.1093/jnci/91.13.1147

Schrock, J. M., McClure, H. H., Snodgrass, J. J., Liebert, M. A., Charlton, K. E., Arokiasamy, P., Naidoo, N., & Kowal, P. (2017). Food insecurity partially mediates associations between social disadvantage and body composition among older adults in India: Results from the Study on global AGEing and adult health (SAGE). *American Journal of Human Biology*, *29*(6). https://doi.org/10.1002/ajhb.23033

Schwarz, P. E. H., Timpel, P., Harst, L., Greaves, C. J., Ali, M. K., Lambert, J., Weber, M. B., Almedawar, M. M., & Morawietz, H. (2018). Blood sugar regulation as a key focus for cardiovascular health promotion and prevention: An umbrella review. *Journal of the American College of Cardiology*, *72*(15), 1829–1844. https://doi.org/10.1016/j.jacc.2018.07.081

Sciorati, C., Gamberale, R., Monno, A., Citterio, L., Lanzani, C., Lorenzo, R. D., Ramirez, G. A., Esposito, A., Manunta, P., Manfredi, A. A., & Rovere-Querini, P. (2020). Pharmacological blockade of TNFα prevents sarcopenia and prolongs survival in aging mice. *Aging*, *12*(23), 23497–23508. https://doi.org/10.18632/aging.202200

Sciubba, J. D. (2020). Population Aging as a Global Issue. In *Oxford Research Encyclopedia of International Studies*.

Searle, S. D., Mitnitski, A., Gahbauer, E. A., Gill, T. M., & Rockwood, K. (2008). A standard procedure for creating a frailty index. *BMC Geriatrics*, *8*, 1–10.

Seeman, T. E., Singer, B. H., Rowe, J. W., Horwitz, R. I., & McEwen, B. S. (1997). Price of adaptation—Allostatic load and its health consequences: MacArthur studies of successful aging. *Archives of Internal Medicine*, *157*(19), 2259–2268. https://doi.org/10.1001/archinte.1997.00440400111013

Seo, J. W., & Park, S. B. (2021). The association of hemoglobin A1c and fasting glucose levels with hs-CRP in adults not diagnosed with diabetes from the NHANES, 2017. *Journal of Diabetes Research*, *2021*, 5585938. https://doi.org/10.1155/2021/5585938

Shaikh, A., Khan, S. D., Baloch, F., Virani, S. S., & Samad, Z. (2023). The COVID-19 pandemic and coronary heart disease: The next surge. *Current Atherosclerosis Reports*, *25*(9), 559–569. https://doi.org/10.1007/s11883-023-01131-0

Shakya, S., Bajracharya, R., Ledbetter, L., & Cary, M. P., Jr. (2022). The association between cardiometabolic risk factors and frailty in older adults: A systematic review. *Innovation in Aging*, *6*(5), igac032. https://doi.org/10.1093/geroni/igac032

Shakya, S., Silva, S. G., McConnell, E. S., McLaughlin, S. J., & Cary Jr, M. P. (2024). Psychosocial stressors associated with frailty in community-dwelling older adults in the United States. *Journal of the American Geriatrics Society*, *72*(4), 1088–1099. https://doi.org/10.1111/jgs.18821

Shammas, M. (2011). Telomeres, lifestyle, cancer, and aging. *Current Opinion in Clinical Nutrition and Metabolic Care*, *14*(1), 28–34. https://doi.org/10.1097/MCO.0b013e32834121b1

Sharma, S., Malarcher, A. M., Giles, W. H., & Myers, G. (2004). Racial, ethnic and socioeconomic disparities in the clustering of cardiovascular disease risk factors. *Ethnicity & Disease*, *14*(1), 43–48.

Shekar, M., & Popkin, B. (2020). *Obesity: Health and Economic Consequences of an Impending Global Challenge*. Washington, DC: World Bank. https://doi.org/10.1596/978-1-4648-1491-4

Shi, H., Hu, F. B., Huang, T., Schernhammer, E. S., Willett, W. C., Sun, Q., & Wang, M. (2024). Sedentary behaviors, light-intensity physical activity, and healthy aging. *JAMA Network Open, 7*(6), e2416300. https://doi.org/10.1001/jamanetworkopen.2024.16300

Simons, J. W. I. M. (1967). The use of frequency distributions of cell diameters to characterize cell populations in tissue culture. *Experimental Cell Research*, *45*(2), 336–350. https://doi.org/10.1016/0014-4827(67)90184-X

Singer, B., & Grunberger, D. (2012). *Molecular biology of mutagens and carcinogens*. Springer Science & Business Media.

Singer, B., Ryff, C. D., & Seeman, T. (2004). Operationalizing allostatic load. *Allostasis, Homeostasis, and the Costs of Physiological Adaptation*, 113–149.

Slopien, R., Wender-Ozegowska, E., Rogowicz-Frontczak, A., Meczekalski, B., Zozulinska-Ziolkiewicz, D., Jaremek, J. D., Cano, A., Chedraui, P., Goulis, D. G., Lopes, P., Mishra, G., Mueck, A., Rees, M., Senturk, L. M., Simoncini, T., Stevenson, J. C., Stute, P., Tuomikoski, P., Paschou, S. A., … Lambrinoudaki, I. (2018). Menopause and diabetes: EMAS clinical guide. *Maturitas*, *117*, 6–10. https://doi.org/10.1016/j.maturitas.2018.08.009

Snodgrass, J. J. (2012). Human Energetics. In *Human Biology* (pp. 325–384). John Wiley & Sons, Ltd. https://doi.org/10.1002/9781118108062.ch8

Snodgrass, J. J., Leonard, W. R., Tarskaia, L. A., & Schoeller, D. A. (2006). Total energy expenditure in the Yakut (Sakha) of Siberia as measured by the doubly labeled water method2. *The American Journal of Clinical Nutrition*, *84*(4), 798–806. https://doi.org/10.1093/ajcn/84.4.798

Sofi, F., Cesari, F., Abbate, R., Gensini, G. F., & Casini, A. (2008). Adherence to Mediterranean diet and health status: Meta-analysis. *BMJ*, *337*, a1344. https://doi.org/10.1136/bmj.a1344

Soysal, P., Stubbs, B., Lucato, P., Luchini, C., Solmi, M., Peluso, R., Sergi, G., Isik, A. T., Manzato, E., Maggi, S., Maggio, M., Prina, A. M., Cosco, T. D., Wu, Y.-T., & Veronese,

N. (2016). Inflammation and frailty in the elderly: A systematic review and meta-analysis. *Ageing Research Reviews*, *31*, 1–8. https://doi.org/10.1016/j.arr.2016.08.006

Spazzafumo, L., Olivieri, F., Abbatecola, A. M., Castellani, G., Monti, D., Lisa, R., Galeazzi, R., Sirolla, C., Testa, R., Ostan, R., Scurti, M., Caruso, C., Vasto, S., Vescovini, R., Ogliari, G., Mari, D., Lattanzio, F., & Franceschi, C. (2013). Remodelling of biological parameters during human ageing: Evidence for complex regulation in longevity and in type 2 diabetes. *Age*, *35*(2), 419–429. https://doi.org/10.1007/s11357-011-9348-8

Speakman, J. R., & Mitchell, S. E. (2011). Caloric restriction. *Molecular Aspects of Medicine*, *32*(3), 159–221. https://doi.org/10.1016/j.mam.2011.07.001

Stam, R. (2007). PTSD and stress sensitisation: A tale of brain and body: Part 1: Human studies. *Neuroscience & Biobehavioral Reviews*, *31*(4), 530–557. https://doi.org/10.1016/j.neubiorev.2006.11.010

Stampfer, M. J., Colditz, G. A., & Willett, W. C. (1990). Menopause and heart disease. A review. *Annals of the New York Academy of Sciences*, *592*, 193–203; discussion 257-62. https://doi.org/10.1111/j.1749-6632.1990.tb30329.x

Stanciu, S. M., Jinga, M., Miricescu, D., Stefani, C., Nica, R. I., Stanescu-Spinu, I.-I., Vacaroiu, I. A., Greabu, M., & Nica, S. (2024). mTOR dysregulation, insulin resistance, and hypertension. *Biomedicines*, *12*(8), Article 8. https://doi.org/10.3390/biomedicines12081802

Stanhope, K. L. (2016). Sugar consumption, metabolic disease and obesity: The state of the controversy. *Critical Reviews in Clinical Laboratory Sciences*, *53*(1), 52–67. https://doi.org/10.3109/10408363.2015.1084990

Stanifer, J. W., Egger, J. R., Turner, E. L., Thielman, N., Patel, U. D., & for the Comprehensive Kidney Disease Assessment for Risk factors, epidemiology, Knowledge, and Attitudes (CKD AFRiKA) Study. (2016). Neighborhood clustering of non-communicable diseases: Results from a community-based study in Northern Tanzania. *BMC Public Health*, *16*(1), 226. https://doi.org/10.1186/s12889-016-2912-5

Stevens, J., Katz, E., & Huxley, R. (2010). Associations between gender, age and waist circumference. *European Journal of Clinical Nutrition*, *64*(1), 6–15. https://doi.org/10.1038/ejcn.2009.101

Stieglitz, J., Schniter, E., von Rueden, C., Kaplan, H., & Gurven, M. (2015). Functional disability and social conflict increase risk of depression in older adulthood among Bolivian forager-farmers. *The Journals of Gerontology: Series B*, *70*(6), 948–956. https://doi.org/10.1093/geronb/gbu080

Strain, T., Flaxman, S., Guthold, R., Semenova, E., Cowan, M., Riley, L. M., Bull, F. C., Stevens, G. A., Raheem, R. A., Agoudavi, K., Anderssen, S. A., Alkhatib, W., Aly, E. A. H., Anjana, R. M., Bauman, A., Bovet, P., Moniz, T. B., Bulotaitė, G., Caixeta, R., …

Zoma, L. R. (2024). National, regional, and global trends in insufficient physical activity among adults from 2000 to 2022: A pooled analysis of 507 population-based surveys with 5·7 million participants. *The Lancet Global Health*, *12*(8), e1232–e1243. https://doi.org/10.1016/S2214-109X(24)00150-5

Strassmann, B. I. (1996). Energy economy in the evolution of menstruation. *Evolutionary Anthropology*, *5*(5), 157–164. https://doi.org/10.1002/(SICI)1520-6505(1996)5:5<157::AID-EVAN4>3.0.CO;2-C

Strassmann, B. I. (1999). Menstrual cycling and breast cancer: An evolutionary perspective. *Journal of Women's Health*, *8*(2), 193–202. https://doi.org/10.1089/jwh.1999.8.193

Tan, P., Wang, Y.-J., Li, S., Wang, Y., He, J.-Y., Chen, Y.-Y., Deng, H.-Q., Huang, W., Zhan, J.-K., & Liu, Y.-S. (2016). The PI3K/Akt/mTOR pathway regulates the replicative senescence of human VSMCs. *Molecular and Cellular Biochemistry*, *422*(1), 1–10. https://doi.org/10.1007/s11010-016-2796-9

Tang, D., Kang, R., Coyne, C. B., Zeh, H. J., & Lotze, M. T. (2012). PAMPs and DAMPs: Signal 0s that spur autophagy and immunity. *Immunological Reviews*, *249*(1), 158–175. https://doi.org/10.1111/j.1600-065X.2012.01146.x

The Biomarker Network (2025). *The Biomarker Network*. https://gero.usc.edu/cbph/network/

Thomas, T. L., DiClemente, R., & Snell, S. (2014). Overcoming the triad of rural health disparities: How local culture, lack of economic opportunity, and geographic location instigate health disparities. *Health Education Journal*, *73*(3), 285–294. https://doi.org/10.1177/0017896912471049

Thompson, A. L., Koehler, E., Herring, A. H., Paynter, L., Du, S., Zhang, B., Popkin, B., & Gordon-Larsen, P. (2016). Weight gain trajectories associated with elevated c-reactive protein levels in Chinese adults. *Journal of the American Heart Association*, *5*(9), e003262. https://doi.org/10.1161/JAHA.116.003262

Tomasetti, C., & Vogelstein, B. (2015). Variation in cancer risk among tissues can be explained by the number of stem cell divisions. *Science*, *347*(6217), 78–81. https://doi.org/10.1126/science.1260825

Tomasetti, C., Li, L., & Vogelstein, B. (2017). Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. *Science*, *355*(6331), 1330–1334. https://doi.org/10.1126/science.aaf9011

Traynor, A., & Raykov, T. (2013). Household Possessions Indices as Wealth Measures: A Validity Evaluation. *Comparative Education Review*, *57*(4), 662–688. https://doi.org/10.1086/671423

Trevathan, W. R. (2007). Evolutionary medicine. *Annual Review of Anthropology*, *36*(1), 139–154. https://doi.org/10.1146/annurev.anthro.36.081406.094321

Trøseid, M., Arnesen, H., Hjerkinn, E. M., & Seljeflot, I. (2009). Serum levels of interleukin-18 are reduced by diet and n-3 fatty acid intervention in elderly high-risk men. *Metabolism*, *58*(11), 1543–1549. https://doi.org/10.1016/j.metabol.2009.04.031

Tuljapurkar, S. D., Puleston, C. O., & Gurven, M. D. (2007). Why Men Matter: Mating Patterns Drive Evolution of Human Lifespan. *PLOS ONE*, *2*(8), e785. https://doi.org/10.1371/journal.pone.0000785

Turner, C., Aggarwal, A., Walls, H., Herforth, A., Drewnowski, A., Coates, J., Kalamatianou, S., & Kadiyala, S. (2018). Concepts and critical perspectives for food environment research: A global framework with implications for action in low- and middle-income countries. *Global Food Security*, *18*, 93–101. https://doi.org/10.1016/j.gfs.2018.08.003

Urlacher, S. S., Ellison, P. T., Sugiyama, L. S., Pontzer, H., Eick, G., Liebert, M. A., Cepon-Robins, T. J., Gildner, T. E., & Snodgrass, J. J. (2018). Tradeoffs between immune function and childhood growth among Amazonian forager-horticulturalists. *Proceedings of the National Academy of Sciences*, *115*(17), E3914–E3921. https://doi.org/10.1073/pnas.1717522115

Urlacher, S. S., Liebert, M. A., Snodgrass, J. J., Blackwell, A. D., Cepon-Robins, T. J., Gildner, T. E., Madimenos, F. C., Amir, D., Bribiescas, R. G., & Sugiyama, L. S. (2016). Heterogeneous effects of market integration on subadult body size and nutritional status among the Shuar of Amazonian Ecuador. *Annals of Human Biology*, *43*(4), 316–329. https://doi.org/10.1080/03014460.2016.1192219

Valentine, R. J., Vieira, V. J., Woods, J. A., & Evans, E. M. (2009). Stronger relationship between central adiposity and C-reactive protein in older women than men. *Menopause*, *16*(1), 84. https://doi.org/10.1097/gme.0b013e31817fcb8f

Vasunilashorn, S., Crimmins, E. M., Kim, J. K., Winking, J., Gurven, M., Kaplan, H., & Finch, C. E. (2010). Blood lipids, infection, and inflammatory markers in the Tsimane of Bolivia. *American Journal of Human Biology*, *22*(6), 731–740. https://doi.org/10.1002/ajhb.21074

Vineis, P., & Xun, W. (2009). The emerging epidemic of environmental cancers in developing countries. *Annals of Oncology*, *20*(2), 205–212. https://doi.org/10.1093/annonc/mdn596

Vlachakis, D., Zacharaki, E. I., Tsiamaki, E., Koulouri, M., Raftopoulou, S., Papageorgiou, L., Chrousos, G. P., Ellul, J., & Megalooikonomou, V. (2017). Insights into the molecular mechanisms of stress and inflammation in ageing and frailty of the elderly. *Journal of Molecular Biochemistry*, *6*, 41.

Walker, R., Gurven, M., Hill, K., Migliano, A., Chagnon, N., Souza, R. D., Djurovic, G., Hames, R., Hurtado, A. M., Kaplan, H., Kramer, K., Oliver, W. J., Valeggia, C., & Yamauchi, T. (2006). Growth rates and life histories in twenty-two small-scale societies. *American Journal of Human Biology*, *18*(3), 295–311. https://doi.org/10.1002/ajhb.20510

Wang, J., & Hulme, C. (2021). Frailty and Socioeconomic Status: A Systematic Review. *Journal of Public Health Research*, *10*(3), jphr.2021.2036. https://doi.org/10.4081/jphr.2021.2036

Wang, M., Yang, M., Liang, S., Wang, N., Wang, Y., Sambou, M. L., Qin, N., Zhu, M., Wang, C., Jiang, Y., & Dai, J. (2024). Association between sleep traits and biological aging risk: A Mendelian randomization study based on 157 227 cases and 179 332 controls. *Sleep*, *47*(3), zsad299. https://doi.org/10.1093/sleep/zsad299

Wang, Q., Ferreira, D. L. S., Nelson, S. M., Sattar, N., Ala-Korpela, M., & Lawlor, D. A. (2018). Metabolic characterization of menopause: Cross-sectional and longitudinal evidence. *BMC Medicine*, *16*(1), 17. https://doi.org/10.1186/s12916-018-1008-8

Wannamethee, S. G., Shaper, A. G., Lennon, L., & Whincup, P. H. (2007). Decreased muscle mass and increased central adiposity are independently related to mortality in older men. *The American Journal of Clinical Nutrition, 86*(5), 1339-1346. doi:10.1093/ajcn/86.5.1339

Warburton, D. E. R., Nicol, C. W., & Bredin, S. S. D. (2006). Health benefits of physical activity: The evidence. *CMAJ*, *174*(6), 801–809. https://doi.org/10.1503/cmaj.051351

Ward-Caviness, C. K., Nwanaji-Enwerem, J. C., Wolf, K., Wahl, S., Colicino, E., Trevisi, L., Kloog, I., Just, A. C., Vokonas, P., & Cyrys, J. (2016). Long-term exposure to air pollution is associated with biological aging. *Oncotarget*, *7*(46), 74510.

Warner, R. M. (2012). Applied statistics: From bivariate through multivariate techniques. Sage publications.

Weaver, A. M., McGuinn, L. A., Neas, L., Devlin, R. B., Dhingra, R., Ward-Caviness, C. K., Cascio, W. E., Kraus, W. E., Hauser, E. R., & Diaz-Sanchez, D. (2022). Associations between neighborhood socioeconomic cluster and hypertension, diabetes, myocardial infarction, and coronary artery disease within a cohort of cardiac catheterization patients. *American Heart Journal*, *243*, 201–209. https://doi.org/10.1016/j.ahj.2021.09.013

Wei, Y., Qin, Z., Liao, X., Zhou, X., Huang, H., Lan, C., Qin, W., Zhu, G., Su, H., & Peng, T. (2024). Pancreatic cancer mortality trends attributable to high fasting blood sugar over the period 1990–2019 and projections up to 2040. *Frontiers in Endocrinology*, *15*. https://doi.org/10.3389/fendo.2024.1302436

Weichhart, T. (2018). mTOR as regulator of lifespan, aging, and cellular senescence: A mini-review. *Gerontology*, *64*(2), 127–134. https://doi.org/10.1159/000484629

Weindruch, R., & Sohal, R. S. (1997). Caloric intake and aging. *The New England Journal of Medicine*, *337*(14), 986–994.

Wellons, M., Ouyang, P., Schreiner, P. J., Herrington, D. M., & Vaidya, D. (2012). Early menopause predicts future coronary heart disease and stroke: The Multi-Ethnic Study of

Atherosclerosis (MESA). *Menopause, 19*(10), 1081–1087. https://doi.org/10.1097/gme.0b013e3182517bd0

Wener, M. H., Daum, P. R., & McQuillan, G. M. (2000). The influence of age, sex, and race on the upper reference limit of serum C-reactive protein concentration. *The Journal of Rheumatology*, *27*(10), 2351–2359.

Whitacre, J. M. (2010). Degeneracy: A link between evolvability, robustness and complexity in biological systems. *Theoretical Biology and Medical Modelling*, *7*(1), 6. https://doi.org/10.1186/1742-4682-7-6

WHO, World Health Organization (2004). Global Physical Activity Questionnaire Analysis Guide. Geneva, Switzerland. Retrieved from https://www.who.int/ncds/surveillance/steps/resources/GPAQ_Analysis_Guide.pdf

WHO, World Health Organization (2006). WHO SAGE Survey Manual: The WHO Study on Global AGEing and Adult Health (SAGE). Geneva, Switzerland. Retrieved from www.who.int/healthinfo/survey/SAGESurveyManualFinal.pdf

WHO, World Health Organization (2014). World health statistics 2014. Retrieved from https://www.who.int/gho/publications/world_health_statistics/2014/en/

WHO, World Health Organization (2015). China country assessment report on ageing and health. Geneva, Switzerland. Retrieved from http://apps.who.int/iris/bitstream/handle/10665/194271/9789241509312_eng.pdf

WHO, World Health Organization (2023, September 16). *Non communicable diseases*. https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases

WHO, World Health Organization. (2024). Ageing and health. https://www.who.int/news-room/fact-sheets/detail/ageing-and-health

WHO, World Health Organization. (2024). Non communicable diseases. https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases

Williams, G. C. (1957). Pleiotropy, natural selection, and the evolution of senescence. *Evolution*, *11*(4), 398–411. https://doi.org/10.1111/j.1558-5646.1957.tb02911.x

Williams, J., Allen, L., Wickramasinghe, K., Mikkelsen, B., Roberts, N., & Townsend, N. (2018). A systematic review of associations between non-communicable diseases and socioeconomic status within low-and lower-middle-income countries. *Journal of Global Health*, *8*(2), 020409.

Willis, M. W., Ketter, T. A., Kimbrell, T. A., George, M. S., Herscovitch, P., Danielson, A. L., Benson, B. E., & Post, R. M. (2002). Age, sex and laterality effects on cerebral glucose metabolism in healthy adults. *Psychiatry Research: Neuroimaging*, *114*(1), 23–37. https://doi.org/10.1016/S0925-4927(01)00126-3

Woods, J. A., Wilund, K. R., Martin, S. A., & Kistler, B. M. (2011). Exercise, Inflammation and Aging. *Aging and Disease*, *3*(1), 130–140.

World Bank Group, Aug. 2024. The World Bank in Cambodia: Overview. Accessed 01/03/25. https://www.worldbank.org/en/country/cambodia/overview

Wu, P.-Y., Chen, K.-M., & Tsai, W.-C. (2021). The Mediterranean Dietary Pattern and Inflammation in Older Adults: A Systematic Review and Meta-analysis. *Advances in Nutrition*, *12*(2), 363–373. https://doi.org/10.1093/advances/nmaa116

Xu, S., Cai, Y., & Wei, Y. (2013). mTOR signaling from cellular senescence to organismal aging. *Aging and Disease*, *5*(4), 263–273. https://doi.org/10.14336/AD.2014.0500263

Yamada, S., Gotoh, T., Nakashima, Y., Kayaba, K., Ishikawa, S., Nago, N., Nakamura, Y., Itoh, Y., & Kajii, E. (2001). Distribution of Serum C-Reactive Protein and Its Association with Atherosclerotic Risk Factors in a Japanese Population: Jichi Medical School Cohort Study. *American Journal of Epidemiology*, *153*(12), 1183–1190. https://doi.org/10.1093/aje/153.12.1183

Yang, X., Zhou, J., Shao, H., Huang, B., Kang, X., Wu, R., Bian, F., Hu, M., & Liu, D. (2023). Effect of an intermittent calorie-restricted diet on Type 2 Diabetes remission: A randomized controlled trial. *The Journal of Clinical Endocrinology & Metabolism*, *108*(6), 1415–1424. https://doi.org/2023051701091874000

Yeh, E. T. H. (2004). CRP as a Mediator of Disease. *Circulation*, *109*(21_suppl_1), II–11. https://doi.org/10.1161/01.CIR.0000129507.12719.80

Yehuda, R., Hoge, C. W., McFarlane, A. C., Vermetten, E., Lanius, R. A., Nievergelt, C. M., Hobfoll, S. E., Koenen, K. C., Neylan, T. C., & Hyman, S. E. (2015). Post-traumatic stress disorder. *Nature Reviews Disease Primers*, *1*(1), 1–22. https://doi.org/10.1038/nrdp.2015.57

Yin, P., Qi, J., Liu, Y., Liu, J., You, J., Wang, L., & Zhou, M. (2019). Incidence, Prevalence, and Mortality of Four Major Chronic Non-communicable Diseases—China, 1990-2017. *China CDC Weekly*, *1*(3), 32–37. https://doi.org/10.46234/ccdcw2019.012

Yousefzadeh, M. J., Flores, R. R., Zhu, Y., Schmiechen, Z. C., Brooks, R. W., Trussoni, C. E., Cui, Y., Angelini, L., Lee, K.-A., McGowan, S. J., Burrack, A. L., Wang, D., Dong, Q., Lu, A., Sano, T., O'Kelly, R. D., McGuckian, C. A., Kato, J. I., Bank, M. P., … Niedernhofer, L. J. (2021). An aged immune system drives senescence and ageing of solid organs. *Nature*, *594*(7861), 100–105. https://doi.org/10.1038/s41586-021-03547-7

Yusuf, S., Reddy, S., Ôunpuu, S., & Anand, S. (2001). Global Burden of Cardiovascular Diseases. *Circulation*, *104*(22), 2746–2753. https://doi.org/10.1161/hc4601.099487

Zhang, B., Ma, S., Rachmin, I., He, M., Baral, P., Choi, S., Gonçalves, W. A., Shwartz, Y., Fast, E. M., Su, Y., Zon, L. I., Regev, A., Buenrostro, J. D., Cunha, T. M., Chiu, I. M., Fisher,

D. E., & Hsu, Y.-C. (2020). Hyperactivation of sympathetic nerves drives depletion of melanocyte stem cells. *Nature*, *577*(7792), Article 7792. https://doi.org/10.1038/s41586-020-1935-3

Zhang, Y., Liu, N., Li, Y., Long, Y., Baumgartner, J., Adamkiewicz, G., Bhalla, K., Rodriguez, J., & Gemmell, E. (2023). Neighborhood infrastructure-related risk factors and non-communicable diseases: A systematic meta-review. *Environmental Health*, *22*(1), Article 1. https://doi.org/10.1186/s12940-022-00955-8

Zheng, F., Yan, L., Yang, Z., Zhong, B., & Xie, W. (2018). HbA1c, diabetes and cognitive decline: The English Longitudinal Study of Ageing. *Diabetologia*, *61*(4), 839–848. https://doi.org/10.1007/s00125-017-4541-7

Zuckerman, M., Harper, K., Barrett, R., & Armelagos, G. (2014). The evolution of disease: Anthropological perspectives on epidemiologic transitions. *Global Health Action*, *7*(1), 23303. https://doi.org/10.3402/gha.v7.23303