Natural animal populations as model systems for understanding early life adversity effects on aging

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Adverse experiences in early life are associated with aging-related disease risk and mortality across many species. In humans, confounding factors, as well as the difficulty of directly measuring experiences and outcomes from birth till death, make it challenging to identify how early life adversity impacts aging and health. These challenges can be mitigated, in part, through the study of non-human animals, which are exposed to parallel forms of adversity and can age similarly to humans. Furthermore, studying the links between early life adversity and aging in natural populations of non-human animals provides an excellent opportunity to better understand the social and ecological pressures that shaped the evolution of early life sensitivities. Here, we highlight ongoing and future research directions that we believe will most effectively contribute to our understanding of the evolution of early life sensitivities and their repercussions.

Introduction

Early life is a sensitive period characterized by rapid growth and development, and, as a result, adverse early life experiences tend to produce longer-lasting consequences than similar experiences later in life (Walasek et al., 2022). As such, nutritional and psychosocial hardships experienced during childhood can have lifelong health repercussions, including increased risk of metabolic, cardiovascular, and neurological disease as observed in numerous human cohorts (Barker et al., 2002; S. Cohen et al., 2010; Cunningham et al., 2022; Felitti et al., 1998; Gluckman et al., 2008; Kittleson et al., 2006; Pollitt et al., 2007; Schilling et al., 2008; Short & Baram, 2019). For example, Indigenous adults who were exposed to violent acts of colonialism in early life, like forced attendance at American Indian residential schools, experience more chronic health conditions than individuals who did not attend these residential schools (Bear et al., 2019). Health disparities associated with early life adversity may be caused, in part, by an acceleration of the aging process, defined as the natural declines of somatic tissue and organ function that occur over time (Belsky, 2019; McCrory et al., 2022). For example, in humans, early life adversities are associated with accelerated biological aging (measured using “epigenetic clocks”), which strongly predicts aging-related health outcomes (Hamlat et al., 2021; Rampersaud et al., 2022). However, despite studies linking early life adversity to increased risk of mortality and age-associated disease (e.g., Aschbacher et al., 2021; Deighton et al., 2018; Gluckman et al., 2008; Miller et al., 2011), it is not well understood how early life adversity mechanistically influences these observed biological declines (Hawkley & Capitanio, 2020; Yang et al., 2017), or why,

from an evolutionary perspective, early life adversity has such long-lasting consequences (Lea et al., 2017; Lea & Rosenbaum, 2020).

Addressing this gap in knowledge is imperative for three reasons. First, based on an international survey spanning 21 countries, approximately 38% of surveyed adults experienced at least one form of early life adversity (Kessler et al., 2010). Studying both how and why early life environments impact later-life physiology is a crucial step in understanding how childhood experiences may contribute to the behavioral and health disparities present around the globe today (Lea et al., 2017; Lea & Rosenbaum, 2020). Second, there is a rapidly growing population of older individuals, so it is urgent to better understand how various factors, including early life environments, contribute to variation in aging phenotypes to improve the quality of life for older members of the population. Third, studies of early life adversity and aging are also of great interest to the field of evolutionary biology. Evolutionary approaches examine variation across species, life histories, and environments to better understand the conditions in which early life sensitivities arise and persist (Lea et al., 2017; Lea & Rosenbaum, 2020; Nettle & Bateson, 2015). Such perspectives are used to ask why health risks might vary across individuals, generations, geographic regions, cultures, and species. Evolutionary and mechanistic approaches complement one another to produce integrated insights into how intervention strategies might be adjusted across individuals and across populations (Bergman & Beehner, 2022; Gluckman et al., 2011; Williams & Nesse, 1991).

There are several inherent challenges associated with studying early life effects and aging health in humans. For example, exposure to early life adversity can co-occur with behavioral tendencies, such as smoking or drug use, providing an indirect means by which early life adversity can be associated with health (Anda et al., 2002; Felitti et al., 1998; Ford et al., 2011; Mersky et al., 2017; Snyder-Mackler et al., 2020). Due to systemic inequities, forms of adversity are typically correlated making it challenging to disentangle effects (e.g., Mersky et al., 2017). Further, childhood and adult environments are often similar, such that children who experienced adversity tend to face hardships in adulthood as well. These challenges are compounded by the fact that few studies are able to follow individuals from birth to death given long human lifespans (Snyder-Mackler et al., 2020). As a result, many studies rely on retrospective surveys and are vulnerable to reporting and recall biases. Finally, understanding the evolution of sensitivity to early life experiences is difficult without a comparative lens. By studying variation in traits across species, we can draw inferences about the evolution of traits (Nunn, 2011). Studies of non-human animals offer a tractable alternative path through which we may disentangle confounding and correlated variables, parse out direct and indirect effects of early life adversity on aging health across the body, and better understand selective pressures that may shape early life sensitivities.

Non-human animals as model systems

Similar to humans, adversity experienced during early life is a strong predictor of health proxies in non-human animals, impacting longevity, reproductive rate, and offspring survival (Burton & Metcalfe, 2014; Eyck et al., 2019). This has been well

described within experimental contexts, such as the effects of maternal separation on transcriptomic patterns in the brain in mice, which are in turn associated with increased stress susceptibility in adulthood (Kronman et al., 2021; Peña et al., 2017, 2019). Likewise, starlings (*Sturnus vulgaris*) that experience experimental food restrictions during early life have shorter telomeres and more inflammation than those which did not face this hardship (Nettle et al., 2017). Similar observations arise from wild animal studies. For example, increased mortality and accelerated reproductive aging are observed in both female red deer (*Cervus elaphus*) and tawny owls (*Strix aluco*) who are exposed early in life to a high population density or a low prey density, respectively (Millon et al., 2011; Nussey et al., 2007). In wild non-human primate studies, early life adversity shapes adult physiology, sociality, fecundity, and survival (Lange et al., 2022; Lea et al., 2015; Patterson et al., 2021, 2022; Rosenbaum et al., 2020; Tung et al., 2016; Weibel et al., 2020; Zipple et al., 2019, 2021). These parallel findings indicate that early life sensitivities are often conserved across taxa due to our shared evolutionary history, and as such, other animals may be suitable models for the study of the impact of early life adversity, as well as the evolution of early life sensitivity.

Studies of non-human animals can overcome many of the inherent challenges of studying early life effects in our species. Like humans, other animals are exposed to natural disasters, food shortages, and the loss of close family members. Many animals also establish dominance hierarchies which govern access to resources, similar to socioeconomic status in humans (Weibel et al., 2020), and close in age siblings may compete for parental care (Conde-Agudelo et al., 2012; Lee et al., 2019). While different

forms of adversity are highly correlated in humans, they tend to be more loosely correlated in non-human animals (Evans & Kim, 2010; Snyder-Mackler et al., 2020; Tung et al., 2016), creating the opportunity to disentangle the effects of different insults. The physiological mechanisms linking early life adversity to aging health may also be homologous across species. Aging is ubiquitous across animals (Nussey et al., 2013; Peters et al., 2019) and immunosenescence, or the dysregulation of the immune system that increases with age and contributes to age-related disease (Franceschi et al., 2018), is a process that is broadly shared between humans and non-human primates (Chiou et al., 2020). Additionally, most animals experience shorter lifespans than humans, aiding in longitudinal sampling across the lifecourse (Austad & Fischer, 1992; Bronikowski et al., 2011; Chiou et al., 2020; Emery Thompson, Rosati, et al., 2020).

Advantages of long-term studies of natural animal populations

Long-term animal field sites provide an exciting opportunity to explore the effects of different forms of early life adversity on aging in evolutionarily relevant contexts. Today, there are animal research sites that have been collecting systematic data for up to six decades (Hayes et al., 2017; Kappeler & Watts, 2012; Kerth, 2022; Mann & Karniski, 2017; Sheldon et al., 2022; Smith et al., 2017; Tung et al., 2010). Many research stations record births, deaths, and migrations; ecological data like temperature and food availability; and behavioral data like social interactions and dominance hierarchies. These data contribute to a wealth of information on social and ecological variables experienced across the life course. As such, researchers can quantify a multitude of forms of early life adversity including food scarcity, maternal death, low

parental social rank, and the degree of within-group competition over resources while also controlling for those same variables in adulthood.

Natural animal systems are particularly important because many key sources of early life adversity are difficult to recapitulate in captivity, and laboratory environments differ from the social and ecological environments animals experienced throughout evolutionary history. Further, the development of non-invasive methods for measuring hormone metabolites, which began in the late 1970s, ushered in a new era of studies on the physiology of free-ranging animals (Behringer & Deschner, 2017). Such tools allowed for the measurement of hormones such as glucocorticoids, and later expanded to include measurements of energetic markers such as the C-peptide of insulin and markers of cellular immune activation and inflammation, all of which provide information on individual health (Behringer & Deschner, 2017; Higham et al., 2020). Additionally, at some field stations, animals are trapped and released, allowing for the collection of blood and other biological samples (Anderson et al., 2021; Hoffman et al., 2011; Laubach et al., 2019; Massot et al., 2011; Nunes et al., 2006; Sapolsky, 1983). Thus, many field sites that collect long-term social and ecological data, in conjunction with biological samples and biomarkers of health, are well-poised to answer questions surrounding how early life environments shape life-long health.

Although natural animal populations have long been utilized as a resource to study physiological processes relevant to human health, only recently have they been used to quantify the relationship between early life adversity and aging-related processes. For example, while research on humans has long suggested a link between

early life adversity and mortality, only within the last 10 years has this been documented in wild long-lived mammals (yellow baboons*:* Tung et al., 2016; Weibel et al., 2020; spotted hyenas, *Crocuta crocuta:* Gicquel et al., 2022; Strauss et al., 2020). As data continue to accumulate and methods for biological sampling and analysis continue to advance, it is important to consider why long-term animal field sites are well-positioned to address questions about early life effects on health, and going forward, how research at these field sites can best contribute to our understanding of early life effects on aging in human populations. Here, we highlight why and how studies of non-human animals can advance our understanding of early life effects on aging by incorporating nuanced measurements of early life experiences and leveraging non-invasive biological samples to measure biomarkers of health (Figure 1). We suggest the need for more integrative approaches to studying early life effects, including how individuals adjust development in response to adversity, and the need to measure comprehensive biomarkers of aging within individuals across their lives.

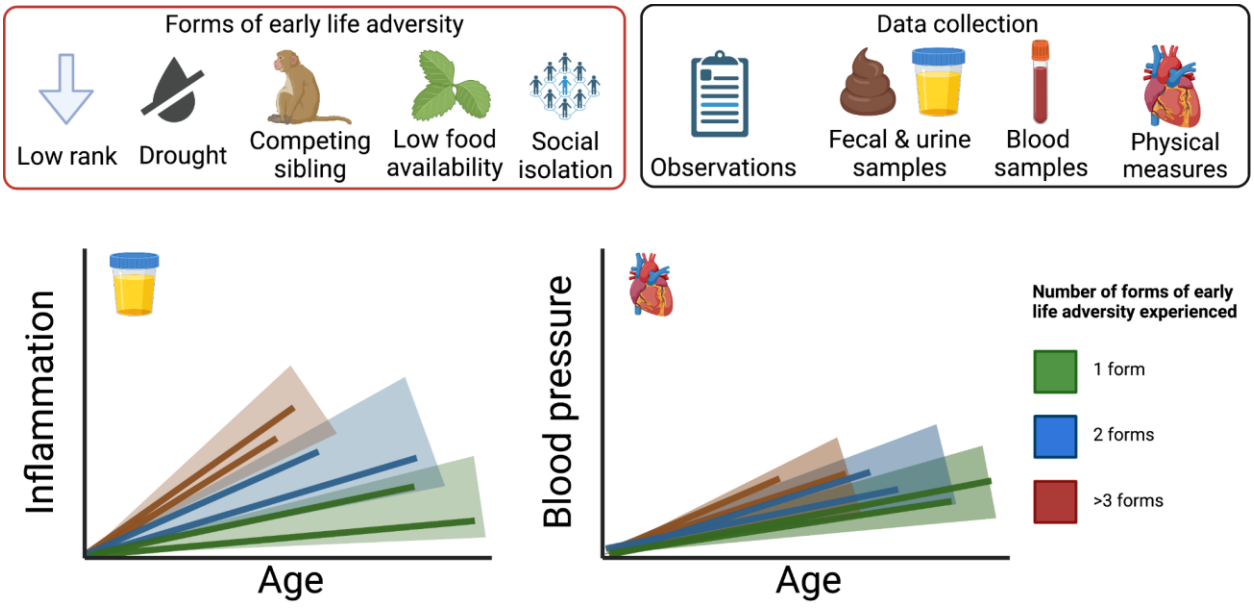

Figure 1. Socioecological and biological data can be used to identify how early life experiences contribute to variation in aging. Five potential forms of early life adversity are displayed as examples: low parental rank, drought, presence of a competing younger sibling, low food availability, and parental social isolation. Several methods for data collection are illustrated: observations (e.g., demographic records, ecology, behavior), non-invasive fecal and urine samples, and samples which can be collected during trap-and-release: blood samples and physical measures (e.g., body size, coloration, health exams). Three categories of exposure are displayed in the plots: green lines represent individuals which experienced one type of early life adversity, blue represents those which experienced two types of adversity, and red represents those which experienced three or more types of adversity. The shaded curves illustrate predicted effects for each category and the dark lines show individual aging trajectories. Fecal and urine samples collected from the same individuals over time are used to examine age-related changes in physiology, such as patterns of inflammation. Individuals in red show the most accelerated increase in inflammation while those in green show comparatively minimal changes in inflammation with age. Physical measures collected from the same individuals over time are used to examine age-related changes in blood pressure. Individuals in red, again, exhibit the most accelerated cardiovascular aging while those in green show slower aging. Those in red have the shortest lifespans and those in green have the longest lifespans. Importantly, the overlap among the categories of exposure indicate that there is variation among individuals in response to adversity. Variation in aging across systems is also observed: ID1 shows more accelerated cardiovascular aging than immune system aging. Early life

adversity here is linked to accelerated aging, however, age-related declines in health varied within individuals between the two biological systems illustrated. Created with BioRender.com

Considerations for using natural animal populations and evolutionary perspectives for studying the complexities of early life effects

Early life adversity is conceptualized and measured in various ways, and these methodologies have implications for our understanding of the health consequences stemming from adversity. A common approach to conceptualizing early life adversity, based on the concept that physiological wear-and-tear accumulates across the lifespan (i.e., allostatic load, McEwen & Stellar, 1993), is to tally exposures to different forms of adversity into a cumulative index. In support of this idea, cumulative early life adversity measures are strongly predictive of disease onset as well as lifespan in spotted hyenas, baboons, and humans (Ellis et al., 2022; Strauss et al., 2020; Tung et al., 2016; but see Gicquel et al., 2022). As such, cumulative indices might serve as valuable tools in predicting aging health trajectories.

Alternatively, one may also examine different forms of adversity independently, thereby gaining the ability to test how different types of adverse experiences shape later life outcomes. The same sources of adversity measured across different studies are not always associated with the same outcomes, and conversely, different sources of adversity can be associated with similar outcomes (Gunnar, 2020; Smith & Pollak,

2020). A comparative approach that examines the pathways by which different types of adversity (e.g., social, nutritional, temperature) across species and environmental contexts produce later life phenotypes will be important to distinguish how and why early life experiences result in diverse, systems-wide health, and aging-related disease (Lea & Rosenbaum, 2020).

Likewise, how we quantify attributes of early life adversity, such as the timing, intensity, duration, and predictability of exposure, will influence our understanding of the physiological responses associated with these exposures. Researchers aim to measure adversity during sensitive windows, which are periods during which individuals are particularly attuned to external cues and exhibit heightened phenotypic plasticity (Selevan et al., 2000). The timing of sensitive windows varies across species, within species, and among traits within individuals (Walasek et al., 2022; Wells, 2014). Importantly, studies that look at multiple developmental windows find that timing matters. For example, individuals exposed to the Dutch famine in utero during early gestation experienced much stronger declines in later life health than those exposed during mid or late gestation (Painter et al., 2005). Complexities like the duration and predictability of exposure have also proven important. A meta-analysis of 111 experimental laboratory studies across a broad range of animal taxa found that the duration and timing of adverse exposures interacted to best predict developmental outcomes (Eyck et al., 2019). For example, rat pups experimentally exposed to unpredictable electric shocks were more likely to develop symptoms of irritable bowel syndrome in adulthood than rat pups exposed to predictable shocks (Tyler et al., 2007).

Additional research is needed to identify the complex ways in which the timing, duration, and predictability of experiences intersect to identify time frames over which intervention efforts should be focused to promote healthy aging (Selevan et al., 2000).

The wealth of social and ecological information produced by long-term non-human animal field sites make these systems well poised to address some of the methodological uncertainties associated with quantifying the effects of early life adversity, such as untangling the effects of co-occurring adverse experiences and confounding variables. Because animals are observed regularly, data are collected systematically, and forms of adversity are often uncorrelated, studies of non-human animals can aid in identifying the relative effects of different adversity types (e.g., social versus ecological) as well as how timing, duration, and intensity of adverse exposures influences outcomes. For example, in baboons, cumulative early life adversity encompassing both social and ecological factors is a better predictor of survival than any individual measure of adversity; however, when analyzed individually, maternal loss and the presence of a competing sibling appear to have the greatest effect on longevity and offspring survival, suggesting that maternal social and nutritional support are particularly important for health and evolutionary fitness in this species (Tung et al., 2016; Zipple et al., 2019). Conversely, in wild Nazca boobies (*Sula granti*), social stress, but not nutritional stress, experienced during early life was associated with a hypersensitive stress response in adulthood (Grace & Anderson, 2018). Longitudinally followed animal populations clearly provide key opportunities to explore early life effects with a level of detail rarely available in humans (Ellis et al., 2022; Lea & Rosenbaum,

2020). These data will be useful not only in identifying links between exposures, biomarkers, and outcomes, but they will also allow researchers to untangle the relative influences of different types of exposures on aging phenotypes.

Work among non-human animals can further contribute to our understanding of early life effects on aging by considering developmental responses to adversity within an evolutionary life history framework. Evolutionary life history approaches can add important knowledge about how and why early life adversity sensitivities evolved. All organisms face trade-offs because a finite amount of resources (e.g., energy, nutrients, time) must be allocated across processes such as growth, reproduction, and maintenance of health (Stearns, 1992). Changes in development made in response to early life adversity may involve a trade-off in resource allocation that is necessary to survive the immediate developmental period, but which has long-term consequences for the pace of aging and longevity. In other words, accelerated aging in adulthood might arise from a reallocation of resources that is adaptive during adverse early life environments, but may become detrimental in later life (Lu et al., 2019). For example, infant Assamese macaques (*Macaca assamensis*) exposed to prenatal maternal stress and low food availability exhibited accelerated growth during early life, but decelerated motor skill development and reduced immune function (Berghänel et al., 2016). With long-term observation and longitudinally collected biomarkers of health, studies such as this could interpret whether reduced immune function among infants exposed to adversity might be predictive of accelerated immunosenescence and aging in other systems later in life. Identifying how early life environments shape developmental trade-

offs and trajectories will help uncover how these different environmental inputs translate into aging outcomes across life.

Biomarkers of aging across multiple biological systems

Early life adversity may impact adult health through an acceleration in the pace of aging (Deighton et al., 2018). Aging is complex, multi-faceted, and inherently difficult to study (Hayflick, 2007; Kirkwood, 2005; López-Otín et al., 2013). There is a clear definition of "chronological" age: the number of days lived since birth, however health can decline at varying chronological ages, indicating wide variation in the pace of "biological" aging (Belsky et al., 2015; Jazwinski & Kim, 2017; Moffitt et al., 2017; Sebastiani et al., 2017). Not only does the pace of aging vary across individuals, but it can also vary across biological systems within individuals (Demanelis et al., 2020; Fiorito et al., 2017; Moffitt et al., 2017; Tung et al., 2012). For example, an individual's cardiovascular system might start aging earlier than their immune system. While many studies are limited to one biomarker or several biomarkers from the same biological system (e.g. several biomarkers of immune function), evidence suggests that aging is best represented by complex networks (A. A. Cohen et al., 2015; Deighton et al., 2018), and should be measured across molecular, physiological, and physical systems (Aunan et al., 2016; López-Otín et al., 2013; Martin-Ruiz et al., 2011). Early life adversity is one factor that likely contributes to the timing of age-related health declines.

Researchers have only recently begun to use biomarkers to determine the biological underpinnings through which early life adversity is linked to negative health

outcomes later in life (Deighton et al., 2018). The majority of human studies are cross-sectional, collecting health measurements at one time point (usually older adulthood), and asking participants about their early life experiences at the time of collection (Deighton et al., 2018; Miller et al., 2011). However, the collection of repeated samples from individuals over time is preferred when possible because only longitudinal analyses can provide insight into within-individual aging trajectories (Newman et al., 2023; Siracusa et al., 2022). For example, a systematic review including 35 longitudinal studies of early life adversity in humans demonstrated that there is distinct variability in individual responses to adversity, some of which are already apparent across multiple biological systems during development (Oh et al., 2018). Further, impacts of early life adversity might not act uniformly across the lifespan. Sonu et al (2019) found that early life adversity substantially increases age-related disease risk among young adults, and that the effects of early life adversity are actually smaller among older adults. The smaller effects among older adults could be due to survival bias or the effects of early life adversity might be masked by other risk factors later in life (Sonu et al., 2019).

The growing number of animal field sites collecting non-invasive biological samples can aid in assessing how early life effects relate to physiological biomarkers of health, while reducing issues related to confounding variables and survivor bias. Research on the proximate mechanisms underlying early life adversity sensitivities in wild animals has mostly focused on glucocorticoids (Lu et al., 2019). Research on aging, specifically, has typically measured reproductive effort and survival (Lemaître et al., 2015; Nussey et al., 2008, 2013), although there has been a shift to measuring

aging across biological systems recently (e.g., see special issues: Emery Thompson et al., 2020; Newman et al., 2023). For example, a recent effort to document aging-related trajectories in chimpanzees (*Pan troglodytes*) has found that while activity levels, physical condition, and oxidative stress change minimally with age (Emery Thompson, Machanda, et al., 2020; González et al., 2020), older individuals experience an increase in both immunosenescence and glucocorticoid dysregulation (Emery Thompson et al., 2018; Emery Thompson, Fox, et al., 2020; Phillips et al., 2020). Work by the Amboseli Baboon Research Project, a long-term study of wild yellow baboons, has also begun to link early life adversity to biological mechanisms. Female baboons who experienced more early life adversity are characterized by high glucocorticoid levels in adulthood (Rosenbaum et al., 2020), which is also associated with a heightened risk of death (Campos et al., 2021). Interestingly, while a cumulative index of early life adversity is one of the biggest predictors of longevity in this population (Tung et al., 2016), it did not predict the pace of molecular aging using a DNA-methylation-based 'epigenetic clock' (Anderson et al., 2021). Further research is needed to identify if current environments or the accumulation of environments across the life course best predict epigenetic aging in yellow baboons (Anderson et al., 2021). By assessing non-invasive biomarkers of health, studies of non-human animals are beginning to add insight into how early life adversity affects variation in aging within and across individuals (Cohen et al., 2015; Nusslock & Miller, 2016). In Box 1, we describe research that we (the authors) are conducting on rhesus macaques at the Cayo Santiago field station as an example of how studies of non-human animals can integrate different data types to enrich our understanding of early life effects on health and aging.

Box 1. The Cayo Santiago Field Station

Cayo Santiago, an island off the coast of Puerto Rico, is home to a free-ranging population of rhesus macaques (Cooper, Brent, et al., 2022), which are descendents of 409 individuals transported to the island from India in 1938. The population is managed by the Caribbean Primate Research Center (CPRC) of the University of Puerto Rico. This is a provisioned, free-ranging population with minimal veterinary intervention. The macaques self-organize into social groups, form differentiated social relationships and dominance hierarchies, and compete over resources like space and food. Long-term demographic, behavioral, and ecological data extend back to the 1950s.

The Cayo Santiago Biobank Research Unit (CBRU), is a collaborative network of experts collecting behavioral data and biological samples from the rhesus macaques. Non-invasively collected samples, such as feces and urine, and observational data including behavioral interactions and gait speed, are collected throughout the year. These non-invasive samples are being used to measure markers such as inflammation, immune activation, and the HPA-axis. Additionally, a subset of the population is trapped and released annually allowing for the collection of a suite of data types, including blood and microbiome samples, as well as soft tissue morphology and eye exams (for additional details, see Newman et al., 2023). Samples collected during trap-and-release are being used to measure traits such as DNA methylation, telomere attrition, cardiovascular health, body condition, and physical range of motion. Because these samples are collected from the same individuals over time, within-individual aging profiles can be assessed. Additionally, to mitigate overpopulation on Cayo Santiago, the

CPRC formulated a plan to remove select social groups from the population. Since 2016, CBRU personnel have performed systematic collection of tissues spanning all major organ systems from the removed animals. These samples are being used to profile epigenomic and transcriptomic variation across all major organ systems (e.g., brain transcriptome: Chiou et al., 2022). Through collaborations between the CPRC and the CBRU, the Cayo Santiago field station illustrates the ability to collect numerous biological samples and use cutting-edge techniques to measure biomarkers across systems.

This type of multi-faceted data allows for the interrogation of early life adversity effects in novel and important ways. We now know that within this population, the presence of a competing sibling increases mortality risk among juveniles (Lee et al., 2019). Infants exposed to maternal maltreatment exhibit dysregulation of the stress response in juvenility (Petrullo et al., 2016), and increased vigilance can buffer these physiological changes(Mandalaywala et al., 2017). We are currently extending this work by comparing how different types of early life adversity shape health and survival across the lifespan. Furthermore, there is strong interest in studying the effects of aging in the Cayo Santiago population. Previous studies have examined age-related differences in multi-tissue epigenetic and transcriptomic patterns (Chiou et al., 2020, 2022; Watowich et al., 2022), ocular health (Fernandes et al., 2022), immunological measures (Cooper, Watowich, et al., 2022; Watowich et al., 2022), the oral, gut, and genital microbiome (Janiak et al., 2021), and behavior (Brent et al., 2017; Siracusa et al., 2022, 2023), paving the way for future studies to link early life experiences to declines in health

across systems and tissues. Ultimately, there is the potential to go beyond asking if early life adversity accelerates aging, and investigate more integrative questions like: Do the effects of early life adversity on aging vary across biological systems? And do the aging effects in some systems precede aging effects in others? The integrative data collection at this field site demonstrates the wide-ranging possibilities and potential of using natural animal populations to study early life effects on aging health trajectories within and across individuals.

Conclusion

Despite the importance of early life environments on later health, we have only begun to examine the complexities of adverse early life experiences, the pace of biological aging, and the underlying biological mechanisms governing the relationship between the two. Research on this topic has been complicated by the need for longitudinal data, availability of the most relevant biological samples, and integration of tools and analytical methods across disciplines. Long-term studies of non-human animals can help overcome some challenges and complement research on humans. Many animal field programs are well-suited to measure nuanced aspects of early life experiences and longitudinal health measures. The routine collection of non-invasive biological samples and socio-ecological data spanning birth until death are two additions to long-term research programs that can help elucidate similar processes in humans, as well as inform our understanding of the evolution of early life sensitivities and biological aging. Studies incorporating detailed measures of the early life environment as well as longitudinal data assessing physiology across biological systems will have the potential

to ask exciting new questions (Table 1). For example, does adversity accelerate aging differently across biological systems, and if so, which systems are most strongly affected? Do trade-offs in resource allocation during early life shape aging in adulthood? Does the time period in which an organism is particularly sensitive to their environment (i.e., sensitive windows) vary across biological systems and in response to different environmental insults? Taking a comparative perspective and using non-human animals as models can help establish how human aging patterns evolved and how early life environments shape aging, thus informing our understanding of the factors that increase vulnerability to age-related diseases (Emery Thompson, Rosati, et al., 2020; Snyder-Mackler et al., 2020). The prevalence of early life adversity and the rapidly growing aging population demonstrates the urgent need for comprehensive models of the long-term effects to guide social and medical interventions.

Table 1. **Outstanding research questions that can be addressed with long-term observational and biological data from non-human animals**

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