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Review

The Hunger Games as the Key to Happily Ever After?

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Abstract: The world's human population is reaching record longevities. Consequently, our societies are experiencing the impacts of prolonged longevity, such as increased retirement age. A major hypothesised influence on ageing patterns is resource limitation, formalised under calorie restriction theory. This theory predicts extended organismal longevity due to reduced calorie intake without malnutrition. However, several challenges face current calorie restriction (CR) research and, although several attempts have been made to overcome these challenges, there is still a lack of holistic understanding of how CR shapes organismal vitality. Here, we conduct a literature review of 222 CR peer-reviewed publications to summarise the state-of-the-art in the field. We use this summary to highlight challenges of CR research in our understanding of its impacts on longevity. Our review demonstrates that experimental research in this field is biased towards short-lived species (98.2% of studies examine species with <5 years of mean life expectancy) and lacks realism in key areas, such as stochastic environments or interactions with other environmental drivers such as temperature. We argue that only by considering a range of short- and long-lived species and by taking more realistic approaches can the impacts of CR on longevity be examined and validated in natural settings. We conclude by proposing experimental designs and study species that will allow the discipline to gain a much-needed understanding of how restricting caloric intake affects long-lived species in realistic settings. Through incorporating more experimental realism, we anticipate crucial insights that will ultimately shape the myriad of socio-bio-economic impacts of senescence in humans and other species across the Tree of Life.

Keywords: life history; longevity; senescence; stochastic environments

1. Calorie restriction and senescence

Senescence is at the forefront of social, economic, and biological research (1–4). This biological phenomenon is characterised by the physiological decline of an organism's vitality with age after reaching maturity. Ultimately, senescence results in reduced reproductive output and increased mortality risk with age. Exploring the implications of senescence is urgent because the world's population of older adults, aged 65 and above, is projected to increase from the current 12% to 16% by 2050, doubling the old-age dependency ratio (5). Indeed, some human societies are reaching record longevities, including Japan and Sweden, where the number of women aged 100 and above has increased over six-fold in only 25 years (6). Human societies are already experiencing the tangible impacts of prolonged longevity, such as increasing age at retirement and economic consequent policies seeking to increase employment among people in their late 50's and early 60's (6,7). Perhaps less widely appreciated is the fact that our societies depend directly on the productivity accrued throughout the longevity of non-human species. This dependence is materialised via nature's crucial ecosystem services (8,9). Key examples include carbon sequestration, which is a function of the vitality and survival of forest trees (8), or crop production, which is sustained via reproduction (9). Thus, beyond focusing only on humans, investigating why some species senesce but others do not (2) will ultimately provide a fundamental and translational framework of understanding and predicting performance implications of ageing in humans (10) and across the whole Tree of Life. This knowledge is glaringly lacking (2).

Out of the over 300 existing theories on the evolution of senescence (11), resource availability has been suggested as a major influence on ageing patterns. This idea was first proposed by Aristotle (12) and is currently formalised in the Calorie Restriction (CR) model. The CR model predicts that the onset of senescence is delayed and life expectancy prolonged due to the ultimate effects of restricted food intake without malnutrition (13). The benefits of CR may be mediated at the molecular and cellular level by lowering molecular oxidative damage (*e.g.*, decreased production of mitochondrial reactive oxygen species) (14,15) and reducing free radical-induced cellular damage (*i.e.*, to cellular macromolecules such as proteins and lipids) (16,17). Benefits of CR can also be mediated by activating pathways that lead to renewal of older/low-functioning cellular components. These pathways include autophagy through the modulation of hormonal signals that switch metabolic pathways (18). A further mechanism hypothesised for the benefits of CR is metabolic stability, whereby calorie restriction is associated with an organism's ability to maintain steady state values of redox couples which are a determinant of longevity (19). CR may also result in some species in behavioural changes, such as a shifts in activity levels to a state of torpor, which in itself can expand lifespan (20).

Identifying the benefits of CR has been the focus of researchers since the early 20th century. The positive effects of limiting calories by manipulating diet were first observed in 1935 in a study on rats by McCay et al. (21). Since then, positive effects of CR have been reported in several species, ranging from yeast, to invertebrates, and other mammals (13,22–25). However, several challenges exist in CR research: (i) the effects of CR are seemingly inconsistent across species, with some controversy over its positive or negative effects on organismal performance (26) (Figure 1); (ii) the ongoing variation in protocols and limitations of studies confounds the interpretation of the outcomes of CR research within and across species (27,28); (iii) CR studies have been conducted mostly under constant laboratory conditions (29); and (iv) the range of species studied is still rather limited to infer CR general effects (Figure 1). Together, these challenges limit our ability to unequivocally test predictions of the CR model. Indeed, several reviews highlighting these challenges discuss ways forward in CR research to understand its role senescence (28,29).

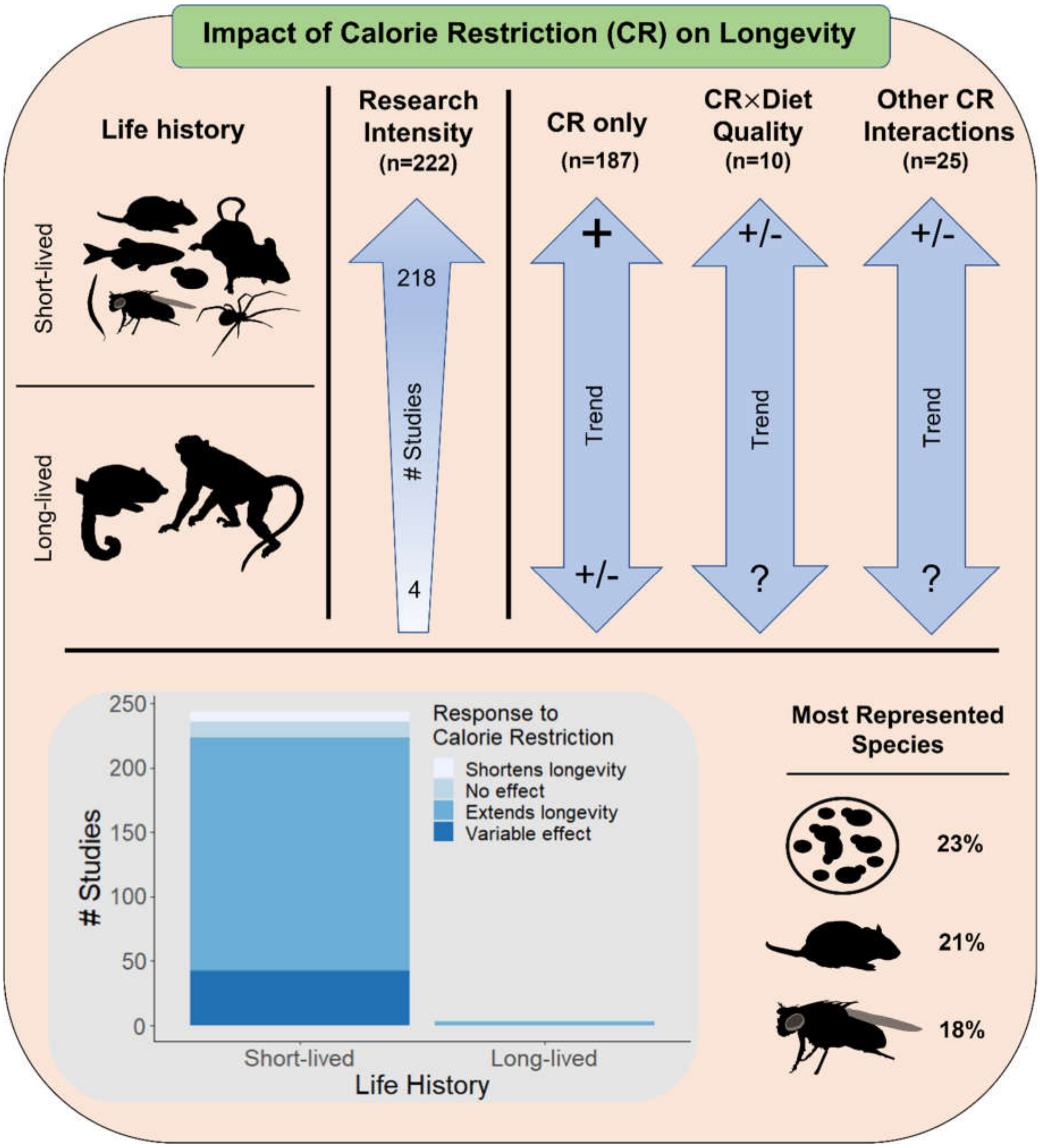

Figure 1. Summary results of a literature search of the impact of calorie restriction (CR) on longevity across 222 peer-reviewed studies between 1935 and 2021. *Top panel*: Life histories of examined species separated into short-lived (<5 years mean life expectancy) and long-lived (>5 years mean life expectancy) to identify differential impacts of CR impact on longevity. *Research intensity* corresponds to the number of studies focusing on short- and long-lived species. *CR only* indicates the reported effect of CR on longevity of studies where no other factor was investigated; *CR×diet quality* indicates the reported effect of studies including CR and diet quality interactions on longevity; *Other CR interactions* shows the reported effect of CR studies that included factors other than diet (*e.g.*, feeding frequency) on longevity. The reported effects are '+' = extends longevity; '-' = shortens longevity; '+/-' = variable between and within studies (reported effect is unclear); '?' = no studies. Silhouettes represent some of the organisms examined in this literature review (top to bottom and left to right): mouse (*Mus musculus*), zebrafish (*Danio rerio*), yeast (*Saccharomyces cerevisiae*), rat (*Rattus norvegicus*), nematode (*Caenorhabditis elegans*), fruit fly (*Drosophila melanogaster*), redback spider (*Latrodectus hasselti*), grey mouse lemur (*Microcebus murinus*) and rhesus macaque (*Macaca mulatta*). *Bottom panel*: Bar graph indicating the total number of studies in the literature review investigating the impact of CR on longevity in short- and long-lived species. Different colours in the bar graph indicate type of impact on longevity. The percentages of the most represented species in the literature review are indicated to the right of the bar graph: yeasts, mice, and fruit flies (top to bottom).

Discussions on CR research, in light of the challenges mentioned, are carried out within the limited context of species that are generally short-lived. Indeed, CR research has historically neglected the rich diversity of life histories (*i.e.,* age specific survival and reproduction rates) across the Tree of Life (2). The importance of life history cannot be underestimated when investigating CR, as the life history strategy of a species dictates how it may respond to changing environmental conditions such as resources. The fast-slow continuum (*i.e.,* species live fast and die young, or live long and develop slowly) is a major role in explaining the variation in animal life history strategies (30–32). As such, variable life history strategies between short- and long-lived species would not necessarily result in similar responses to CR, given that survival and reproduction rates will differ among strategies. We propose that aspects of the life history of a species –specifically whether it is short-lived or long-lived– is a key component in understanding the impact of CR on longevity. Understanding this key component will provide valuable insight into addressing the challenges that exist in CR research.

To examine the current state-of-the-art and generality of CR research, we identified and examined peer-reviewed publications that focused on the impact of CR on longevity across species. Naturally, it is important to also acknowledge the body of research in dietary restriction (DR), which focuses on the effects of dietary manipulations other than calorie intake, such as timing of feeding (*e.g.*, 33) or macro- and micronutrient manipulation (*e.g.*, 34), as opposed to CR, which focuses on reducing calorie intake. Thus, DR refers to an all-encompassing description for multiple forms of dietary interventions, with CR formally considered as a special case of DR (35). Nonetheless, the terms DR and CR are often used interchangeably in the literature (36). In our literature review, we focus on CR research, thus ensuring studies with the aim of specifically manipulating calories. This focus is in line with CR predictions, in which changes in longevity are due to the ultimate effects of *restricted resource intake* (13).

We compiled a literature search of peer-review publications from 1935 until, and including, 2021 via ISI Web of Science with the search terms "calori*" AND "restriction" AND "longevity". All publications captured had the search terms in the title, abstract, keywords and/or the main text (including references). The search terms used also captured publications that discussed the concept of calorie restriction, and the benefits thereof, but where the authors used the term dietary restriction and not calorie/caloric restriction (*e.g.*, 37, excluded after screening; 38, included after screening). As such, where the terms calorie/caloric restriction and dietary restriction have been used interchangeably, the term dietary restriction has been captured in our search terms. Of the 3,058 resulting publications, we screened and kept a subset of publications according to a set of criteria aimed at identifying studies manipulating calorie intake (Supplementary Material, eFigure 1). Initially, we removed publications such as abstracts and meetings from the results followed by reviews and books, as the aim was to identify original research studies. We then excluded studies that did not directly test the impact of restricting calories on longevity (*i.e.*, studies only investigating biomarkers of longevity, *e.g.* (39); studies with genetic mutations or insertions, *e.g.*, 40). We also excluded studies only investigating the impact of calorie restriction mimetics (*e.g.*, 41), as these works investigate compounds that mimic CR effects without actually restricting calorie intake itself. We were left with 222 original research studies, detailed in Supplementary Material eTable 1. We summarise the main findings of these studies, rather than quantitatively analyse their summary statistics, because the latter were not frequently reported to allow for a full meta-analysis (42). For example, in 36% of the 222 studies on experiments comparing calorie restricted diets to non-calorie restricted diets, not enough detail on the study outcomes was provided other than mean values in a table or a figure.

Our first objective was to examine how prevalent short- and long-lived species were in studies focusing on the effects of CR on longevity. Indeed, of the 222 CR studies, the majority (98.2%) focus on short-lived species (mean life expectancy <5 years), while studies on longer-lived species remain scarce (1.8%, Figure 1). The overall reported effect of CR on the longevity of short-lived species is positive; significantly more studies (75.7%)

show a positive effect of CR compared to the number of studies showing negative (4.1%), variable (14.7%), or no effect (5.5%) ($X^2_{1,216} = 58.84$, $p < 0.0001$), with an increase in longevity ranging from 4% in the case of *Mus musculus* to five orders of magnitude in *Saccharomyces cerevisiae* (see Supplementary Material eTable 1). Moreover, when considering the absolute effect size on longevity (positive and negative effects) in short-lived species, there is a significant impact of generation time, whereby species with greater generation time have a more limited effect of CR on longevity ($F_{1,\,209} = 34.685$, $\hat{e} = -0.193$, $R^2 = 0.142$, $p < 0.001$; Figure 2). The finding, that in species with a greater generation time the effect of CR is more limited, is in contrast to the findings of a meta-analysis on the impact of CR on the lifespan of rats and mice (43). In the meta-analysis the author found that in rats, the species with the higher generation time, CR had a greater effect on lifespan than in mice.

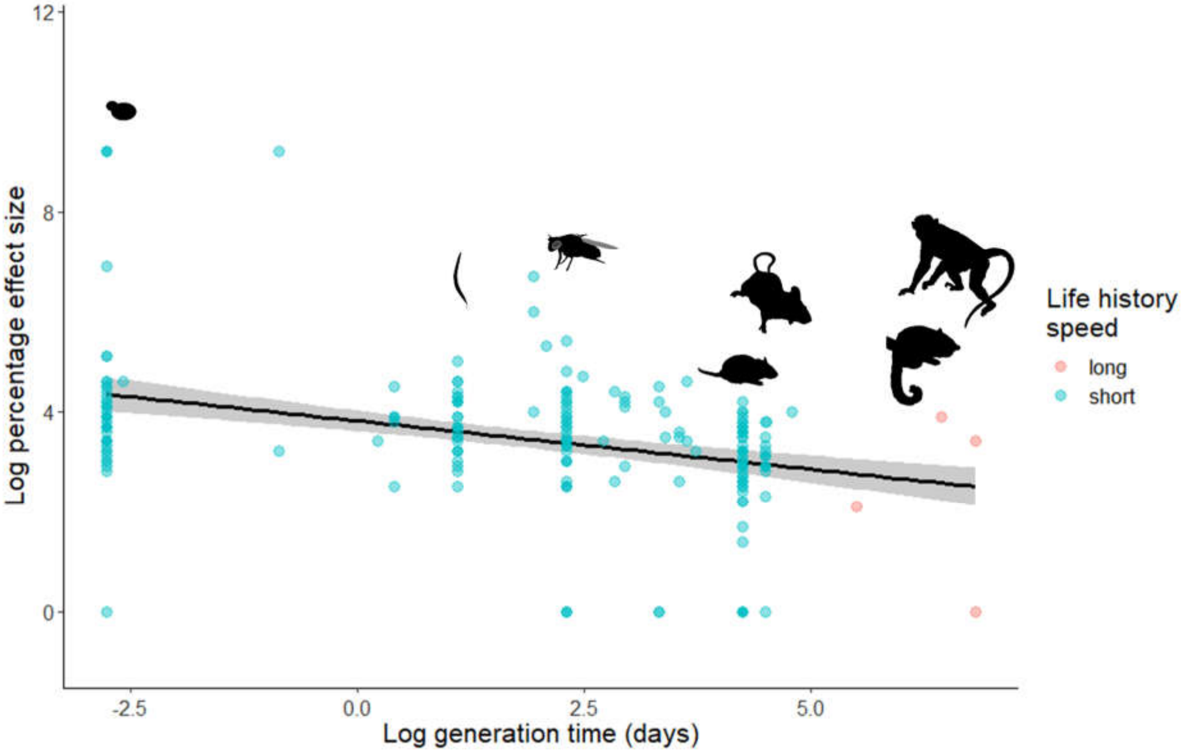

Figure 2. The effect of caloric restriction on longevity decreases with generation time. Percentage effect size relative to generation time (days) on a log scale. Points represent raw data for short-lived (blue) and long-lived species (red), solid black line indicates the model estimate for effect size as a function of generation time ($F_{1,209} = 35.074$, $\hat{e} = -0.193$, $R^2 = 0.144$, $p < 0.001$). Shaded grey area indicates 95% confidence intervals. For calculation of effect sizes, see Supplementary Material. Silhouettes represent some of the organisms examined in this literature review (left to right): yeast (*Saccharomyces cerevisiae*), nematode (*Caenorhabditis elegans*), fruit fly (*Drosophila melanogaster*), mouse (*Mus musculus*), rat (*Rattus norvegicus*), grey mouse lemur (*Microcebus murinus*) and rhesus macaque (*Macaca mulatta*).

The biased focus on short-lived species is unsurprising, as short-lived species are often used as model species due to their ease of rearing and short generation time. This finding is in agreement with a comparative meta-analysis study of dietary restriction and its impact on life extension (44). In it, Nakagawa and colleagues assess the life-extending effects of CR across 36 species, from filamentous fungus (*Podospora anserina*) to the rhesus macaque (*Macaca mulatta*), and find the life-extending effect is twice as effective in model species (*e.g.*, yeast, *Saccharomyces cerevisiae*; common fruit fly, *Drosophila melanogaster*) than non-model species (*e.g.*, three-spined stickleback, *Gasterosteus aculeatus*; rhesus macaque). Our findings, and that of Nakagawa and colleagues, highlight the importance of understanding CR across diverse taxa as key life history traits (*i.e.*, organismal features of the life cycle that impact fitness; *e.g.*, generation time (45)) may play a role in determining the effectiveness of CR on longevity. Furthermore, while three of the four studies on long-lived species in our literature review align with CR's predictions on expanded lifespan (rhesus macaque, *Macaca mulatta* (46); grey mouse lemur, *Microcebus murinus* (47); domestic dog, *Canis lupus familiaris* (48)), the fourth study does not show a detectable extension in lifespan. The findings of the latter study are in direct odds with the results from the other CR study on the same species, the rhesus macaque (49) (Figure 1). Likely reasons for this discrepancy include the lack of standardised protocols of nutritional demands (27), or controls receiving an inadequate diet (50).

The importance of standardised protocols in CR studies has been raised in the past (*e.g.*, (51)) and reiterated in a recent review on experimental design limitations (52). In the latter, contradictory findings of the impact of CR on longevity is attributable to methodological differences in feeding regimes, diet composition, age of onset, genetics, and sex. The impact of diet composition and sex is also highlighted in the comparative analysis of Nakagawa and colleagues (44). Their analysis is conducted on a combination of calorie and protein restriction while accounting for sex differences. In it, the life extending effect of dietary restriction is 20% smaller in males than females, however when considering the combination of calorie restriction and protein restriction the effect of protein restriction is larger than calorie restriction. The role of diet composition is also raised in a perspective piece (29), where the authors highlight that contradictory findings of the impact of CR on longevity are driven by poor diets in the experimental design. Specifically, over feeding and protein:carbohydrate ratios contribute to exaggerated survival costs in animals not fed on CR diet (*e.g.*, *ad libitum* diets). Indeed, the frequent –and still largely unattended– call for standardised protocols in CR suggests a need to formalise a framework for CR research, subsequent standardised protocols would then allow for comprehensive between- and within-species comparison of the impact of CR on longevity.

Our review of the CR literature highlights the lack of biological realism. Indeed, species do not live in isolation, and the selection pressures they are exerted to are neither single, nor non-interacting (53). Yet, most of the studies in our literature review lacked interaction effects in their treatments. Only 15.8% (n=35) of the 222 CR studies examine the interaction of CR with other variables such as diet quality (54) or a stressor (e.g. oxidative stress (55)). Interestingly, the overall reported number of studies that show only a positive effect of CR and other factors (n=15) on longevity is not significantly different to the number of studies that do not report a positive effect or report both positive and negative effects (n=20) ($X^2_{1,35} = 1.706$, $p = 0.304$). Indeed, in the instance where studies do not report a positive effect or report both positive and negative effects, the studies showing both positive and negative impacts are in the majority (n=18) (CR response = 'variable', Supplementary Material eTable 1). Of the total number of studies that focus on the interaction of CR and other variables (n=35), 28.6% (n=10) focus on the interaction of diet quality with CR (see Supplementary Material eTable 1) and only two of these report positive impacts on longevity. Beyond the lack of studies investigating interaction effects in CR, our literature review shows no support for universally positive effects of CR on longevity in studies *with* interaction effects, and a skewed focus on the interaction of diet quality and CR over other important factors such as feeding frequency or temperature. Recent reviews (28,29) provide several suggestions to incorporate interaction effects, for example holding wild animals under restricted food intake or exposing food restricted animals to injuries and/or pathogens to identify impacts on longevity. These suggestions would indeed move CR research in the right direction. However, there are several overlooked, yet significant, effects that could interact with CR. In the following, we argue that (1) examining actuarial (*i.e.,* survival) and reproductive senescence separately (56), (2) the role of stochastic environments (57), and (3) the influence of temperature (*i.e.* independent impacts of temperature on lifespan) will provide key insights on the effects of CR in more realistic scenarios and under meaningful evolutionary pressures.

1.1. Actuarial and reproductive senescence

The focus of the majority of the ageing literature has been primarily on actuarial senescence (*i.e.*, mortality risk changes with age after maturity, *e.g.* (58,59)) and not on reproductive senescence (but see (60,61)). This is a significant knowledge gap, as classical senescence theories predict reproduction to decline as mortality risk increases with age (56,62). However, recent work has shown that actuarial and reproductive senescence are often decoupled (63), even though they are often assumed not to be (58). A recent study (63) suggests that key life history traits (*e.g.*, adult body size (64)) and ecology of the organism –including resource availability– may be crucial in shaping senescence outcomes. Thus, we argue that the impact of CR on senescence can only be satisfactorily identified in the context of both actuarial and reproductive senescence due to well-known trade-offs between survival and reproduction (64). Of importance here too is the fact that different moments in the distribution of reproduction (*e.g.*, frequency, intensity, duration) have recently been shown to be independent of investments in longevity in both animals (30,65) and plants (66), and so the mechanisms forcing an increase in mortality risk might be independent from those shaping age-specific reproduction in some species. The independence regarding age-based performance of survival and reproduction under calorie restriction has been highlighted recently (29), though based on an alternative view. In their review, Adler & Bonduriansky (29) assert that the key target of selection in the evolution of physiological responses to CR is immediate reproductive output and not survival to reproduce later. The view that the key target of selection is immediate reproductive output is because autophagy and apoptosis are up-regulated under CR (29,67), which frees up stored nutrients allowing the animal to function more efficiently, and thus allowing for immediate reproduction. Extended survival is considered a secondary consequence because high rates of autophagy and apoptosis reduce the intrinsic aging rate. These authors argue that there is no trade-off between survival and reproduction. We, however, disagree and believe that a trade-off between survival and reproduction plays a pivotal role as it is a fundamental component in life history evolution and the variation in life history strategies (64).

The inclusion of life history theory in the study of CR has recently been raised by Regan et al. (28), which we echo here. Explicitly incorporating life history theory into CR is required disentangle direct and indirect effects of resource availability. Indeed, CR reduces energy intake of individuals which, in long-lived species, life history theory predicts to result in a reduction or halting of reproduction (64). Reduced reproduction, in turn, may free up resources for maintenance that then can increase longevity (68). Additionally, the role of life history in understanding the effect of CR on longevity is explicitly considered by Directionality Theory in conjunction with the metabolic stability hypothesis (19,69). In this case, the effect of CR on lifespan is predicted to be constrained by life history; in short-lived species, in contrast, the effect of calorie restriction on lifespan will be large, although this effect could potentially be highly variable (Figure 2), while in long-lived species the effect will be negligible (19,69). However, to disentangle direct and indirect effects of resource availability requires a greater understanding of the interaction of CR with other variables.

1.2. Stochastic environments

The last decades has witnessed significant progress in our understanding of how individuals perform and age in stochastic environments (70–72). This body of research has shown that optimal age-based strategies under constant environments can differ from those under stochastic environments (72). In the latter, the effect of serial correlation on fitness (*i.e.* increase or decrease in fitness through time) can be predicted by the life history of the organism (*i.e.* age specific survival and reproduction rates) (72). Thus, the field of CR needs to move beyond constant conditions in experimental approaches, since variation in environmental quality causes variation in individuals' life history traits, such as age at maturity and longevity (64). For example, some organisms mature earlier as environmental conditions become more favourable (64) while others mature earlier when conditions are less favourable (73). The documented vast range of life history responses to changes in environmental quality (57,74–76) highlights the importance of interacting factors for determining longevity, and that the reported findings of CR in constant environments may not be consistent with those in fluctuating environments.

Variable environments, in turn, play a crucial role in population dynamics by influencing survival and reproduction (77). Furthermore, an increase in the variation in environmental quality has profound impacts on species through changes in habitat and structure of ecosystems (78,79). Examples include the change in synchrony with a species' food and habitat resources due to warm and/or dry years, as in Ediths' checkerspot butterfly (*Euphydryas editha*) and its host plant, the Torrey's blue eyed Mary (*Collinsia torreyi*), which results in population crashes and extinctions (78,80). In our literature search, stochastic environments are much less represented and only investigated in short-lived species. Only two of the 222 studies, one study on *Drosophila* (81) and another on medfly (23), explicitly investigate CR impacts on senescence in stochastic environments. In these species, longevity is extended under a stochastic feeding regime when compared to constant environments, supporting CR predictions under real-world conditions. However, several environmental factors with interacting effects such as temperature and resource quality are likely to influence how CR impacts organismal vitality in stochastic environments and may therefore be more accurate when examining CR impacts.

1.3. Temperature

A key –yet often overlooked– environmental factor to consider in the context of CR is temperature. For instance, mammals under CR show reduced body temperature as a mediator of CR on longevity (82), and low body temperature can independently increase lifespan (82). Likewise, in invertebrates, temperature can play a key role, particularly in expanding lifespan under cold conditions (83). Furthermore, temperature can affect nutrient assimilation efficiency. Plasman et al. (84) show that temperature differentially affects nutrient use in a lizard, with higher temperatures increasing protein but decreasing lipid assimilation. So too can temperature impact the macronutrient requirement of organisms, with increasing temperatures resulting in the decline in the N and P content of whole organisms (85). Consequently, understanding how resource × temperature interactions shape organismal vitality is key for projections of an organism's environmental niche space (86,87), as climatic models predict both factors to change (88). Ultimately, how these interactions are impacted with a changing climate will dictate the quality of the full environmental niche space that the specific study species may experience.

2. Moving forward

We agree with previous reviews (see 28,29) that CR should be investigated in more ecologically realistic scenarios than in pristine, constant environments, as commonly done to date. We argue, however, that moving forward there are several key factors that should be the focus of CR research. Indeed, CR may become an increasing challenge in natural systems due to global climate change, given the uncertainty in environmental regimes. From a human perspective, the impacts of climate change will not only influence food production (quantity) (89,90) but also its quality (90). As such, understanding CR in combination with factors such as diet composition, feeding regimes (*i.e.* feeding frequency or temporal autocorrelation of resource availability, *e.g.*, 91,92), and temperature in short- and long-lived species will be key when considering how CR impacts human health and well-being.

Addressing the consequences of CR in more realistic environments and across short- and long-lived species is a challenging but necessary prospect to advance ageing research. This challenge is especially apparent in species where the experimental logistics of determining relevant interactions are not feasible. For example, in species such as non-human primates and mice the required numbers for replicated designs would not be feasible. However, a viable alternative is using study systems that can experimentally accommodate multiple effects to identify key CR interactions that impact senescence. Such systems would need to be easily maintained, allow for the necessary replication to ensure robust experimental designs, and preferably encompass short- and long-lived species.

Much CR research has focused on short-lived invertebrates like *Drosophila* (81,93), including in the best of cases interaction effects (81). Other promising short-lived systems that would allow for experiments investigating multiple interacting effects in high replication are yeast (*Saccharomyces cerevisiae*) and *Caenorhhabditis elegans*; these systems can be relatively easily and quickly reared in the lab. In addition, we suggest two candidate systems to investigate key interactions that play a role in how CR impact senescence in long-lived species: Planarians and Hydra. Both systems are long-lived invertebrates (up to decades (94–96) and projections of centuries in Hydra (97)) and can be lab-reared in high numbers while occupying little space (98,99). Interestingly, these long-lived systems have been studied to understand their regenerative properties and the apparent absence of ageing in certain species (100,101). However, fewer studies have turned to Hydra as a system to explore the impact of CR and its interactions on longevity (*e.g.*, 102), with planarians yet to be utilised.

Long-lived invertebrate systems provide the opportunity to utilise predictions from life history theory to understand the impact of CR and its interaction effects on longevity. For example, selection pressures that increase lifespan result in a low mean and variance in adult mortality (103). If factors that interact with CR increase variation in adult mortality, the increased variation could negate the expected prolonged longevity under CR. Outcomes from such studies will then provide much needed insight into the role of CR on long-lived species and how life-history traits and whole populations respond to rapidly changing environmental conditions and resources driven by climate change.

Crucially, these insights from more realistic CR designs and on a broader range of taxa will contribute to the fundamental and translational understanding of human senescence. We also do not expect the mechanistic outcomes from the invertebrate studies to perfectly map to higher taxa. However, from a demographic and life history perspective, identifying the impacts of CR interaction effects on longevity encompassing short- and long-lived species will help us understand why some species senesce, but others do not (2). In particular, comparing long-lived and short-lived species within the same taxonomic group and of similar adult body mass (*e.g.*, rats live up to 5 years, while the naked mole-rat (*Heterocephalus glaber*) live for 30 years (104)) will provide a greater understanding of the confounding factors, due to varying evolutionary trajectories, that shape the relationships between CR and longevity. CR has gained prime relevance in ageing research (93,105), now more than ever in the light of climate change and its effects on securing resources (79). However, only through standardised protocols applied to a wider variety of study systems that are not logistically constrained, can we address the heavily debated challenges currently facing CR research and finally test whether volunteering as a tribute in the Hunger Games does indeed postpone the onset of senescence and extends longevity.

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