Dietary restriction and ageing: recent evolutionary perspectives

Abstract

Dietary restriction (DR) represents one of the most robust interventions for extending lifespan. It is not known how DR increases lifespan. The prevailing evolutionary hypothesis suggests the DR response redirects metabolic resources towards somatic maintenance at the expense of investment in reproduction. Consequently, DR acts as a proximate mechanism which promotes a pro-longevity phenotype. This idea is known as resource reallocation. However, growing findings suggest this paradigm could be incomplete. It has been argued that during DR it is not always possible to identify a trade-off between reproduction and lifespan. It is also suggested the relationship between reproduction and somatic maintenance can be uncoupled by the removal or inclusion of specific nutrients. These findings have created an imperative to re-explore the nexus between DR and evolutionary theory. In this review I will address this evolutionary conundrum. My overarching objectives are fourfold: (1) to outline some of the evidence for and against resource reallocation; (2) to examine recent findings which have necessitated a theoretical re-evaluation of the link between life history theory and DR; (3) to present alternatives to the resource reallocation model; (4) to present emerging variables which potentially influence how DR effects evolutionary trade-offs.

Keywords: Evolution, Caloric Restriction, Dietary Restriction, Disposable Soma Theory, Resource Reallocation, Longevity

1. Introduction

Many ideas have been proposed to explain the evolution of ageing (Flatt and Partridge, 2018; Gems, 2022; Giaimo and Traulsen, 2022; Johnson et al., 2019; Kirkwood, 2005; Wensink and Cohen, 2022). However, three classical theories dominate the literature. All three ideas are united by a common thread. Namely, ageing is the result of a decline in the force of natural selection with age (Figure 1). Based on this premise the mutation accumulation theory suggests ageing results from a passive build up in pernicious alleles which are only functionally expressed later in life (Medawar, 1952). The antagonistic pleiotropy (AP) theory extends this notion by proposing that natural selection acts on alleles that have differing effects during the life history of an organism (Williams, 1957). If an allele confers a beneficial effect on fitness early in life, it is selected for, regardless of its detrimental impact in later life, as the negative effect is offset by the positive effect. The disposable soma theory (DST) suggests ageing occurs because natural selection would not favour investing high levels of metabolic resources into long-term maintenance of somatic tissues (Kirkwood, 1977). What distinguishes the DST from MA and AP is its emphasis on a specific class of mechanisms, rather than on the underlying architecture of a gene/genes (Kirkwood, 2005). Rather, the DST is a physiological theory which posits that resources need to be strategically partitioned between investment in somatic maintenance versus other activities such as growth and reproduction. The optimal strategy for resource allocation is determined by the life history of the organism. Accordingly, organisms evolve so that sufficient resources are invested in somatic maintenance so that the soma retains viability during the period when expected survivorship remains significant, against a background of environmental and other mortality risks, but not longer than this. Thus, the resources invested in somatic maintenance are insufficient for indefinite survival. In other words, ecological context determines resource allocation, which in turn shapes life history. There is empirical evidence that increased investment in somatic maintenance and repair are synonymous with a pro-longevity phenotype. The bow headed whale invests heavily in DNA repair processes, which possibly contribute to its impressive longevity (Keane et al., 2015). In other cases, such as Pacific Ocean rockfish repeated signatures of Darwinian selection in DNA repair (DNAR) pathways have been identified (Kolora et al., 2021). It can be argued however, that such an extreme rate of DNAR is metabolically demanding. This reduces the energy available for overall somatic maintenance. Thus, enhanced somatic maintenance may not be responsible for increased longevity. Despite this caveat other observations suggest enhanced somatic maintenance is involved in longevity. For instance, dominant male/female meerkats who monopolize reproduction endure a higher rate of telomere attrition than reproductively inhibited subordinates (Cram et al., 2018). Although, it is important to note that it is equally possible to identify studies which are inconsistent with the DST.

Given the persistence of the main evolutionary theories it is unsurprising the DST remains the prevailing framework used to explain the effects of food restriction (Sziráki et al., 2018). The logic underpinning this idea is that during food restriction natural selection favours resource reallocation towards somatic maintenance at the expensive of reproduction (Harrison and Archer, 1989; Holliday, 1989; Kirkwood and Shanley, 2005; Masoro and Austad, 1996; Shanley and Kirkwood, 2000). The resource reallocation hypothesis (RRH) is conceptualized in figure 2 where a hypothetical population undergoes a period of food restriction. In figure 2 the DST provides a framework for optimising resource allocation, such that a temporary redirection of resources from reproduction to somatic maintenance during food restriction might be adaptive. While there is still support for this idea, growing recent studies appear inconsistent with the RRH (Dasgupta et al., 2022; Moger-Reischer et al., 2020; Piper et al., 2022; Zajitschek et al., 2016). Based on these observations it has been argued it is not always possible to identify a trade-off between reproduction and lifespan in food restriction studies. It is also suggested the relationship between reproduction and somatic maintenance can be uncoupled by the removal/inclusion of specific dietary nutrients (Moatt et al., 2020; Piper et al., 2022; Regan et al., 2020). This review explores these findings. Before doing this however, recent evidence for and against the RRH will be outlined. Next, alternative evolutionary explanations to the RRH are presented. I conclude by considering important factors for future investigations. Where possible, the discussion is confined to recent examples which examine food restriction and evolution. In fact, it is beyond the scope of this work to examine every dietary modality. Such protocols have been reviewed recently (Green et al., 2022a; Lee et al., 2021). Here, I begin by introducing food restriction. This is followed by a more intricate evolutionary informed exploration of this field.

2.Dietary restriction

Dietary restriction (DR) encompasses a range of food manipulation regimes. Non-exhaustively, this includes, intermitting fasting (IF), protein restriction (PR), amino acid restriction and time restricted feeding (chrononutrition) (de Cabo and Mattson, 2019; Dong et al., 2018; Manoogian and Panda, 2017; Trautman et al., 2022). However, caloric restriction (CR) is the most well-known means of dietary manipulation (Erbaba et al., 2021; McCay et al., 1935; McDonald and Ramsey, 2010; Speakman and Mitchell, 2011; Weindruch et al., 1986). In model organisms CR typically involves decreasing the intake of calories by between 30-40% without eliciting malnutrition or nutrient deficiency (Anderson et al., 2009; Hofer et al., 2022; Masoro, 2005). It is parsimoniously logical to infer that CR is a phylogenetically ancient adaptation. This is evidenced by CR extending lifespan across evolutionary boundaries in a broad range of taxa, including yeast, fruit flies, worms, mice and certain primates (Fontana et al., 2010; Ingram and de Cabo, 2017; Lakowski and Hekimi, 1998; Mattison et al., 2017; Piper and Partridge, 2018; Sinclair, 2005). Findings in humans are also promising. The Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy (CALERIE) is a long-term CR study focusing on healthy, non-obese humans. CALERIE has revealed that CR retards age-associated pathophysiology and enhances cardiometabolic health in this cohort (Kraus et al., 2019). Most recently, CALERIE findings suggest the timing of eating is key to optimising the CR response in humans (Fleischer et al., 2022). In addition, findings from an ancillary trial bolted to phase 2 of CALERIE observed that CR was associated with dampened thyroid axis activity and reactive oxygen species (ROS) production (Redman et al., 2018). It was posited such observations align CR with the free radical theory of ageing (FRTA), and the rate of living theory. This is intriguing given the criticism of both theories (Pomatto and Davies, 2018; Stark et al., 2020). However, studies in the wild do suggest food restriction defines the life-history of many animals (Houser et al., 2012; Ortiz et al., 2010; Rigano et al., 2017). And in certain animals this period coincides with increased resistance to oxidative stress (Ensminger et al., 2021). This helps reconcile FRTA with CR. Clearly, however ideas based on human CR studies which support the FRTA/the rate of living theory need to be fully reconciled with the literature which argues they have a negligible role in ageing.

Despite the positive findings outlined above the impact of CR remains controversial. It is suggested laboratories are nutritionally poor environments and CR inevitably will reduce morbidity/mortality (Le Bourg, 2018; Wolf, 2021). Closely tied to this is the idea that reduced lifespan in control groups, particularly in rodent studies is due to poor diet/overfeeding (Wolf, 2021). More troubling for CR are observations which imply it is harmful. In the gray mouse lemur (*Microcebus murinus*) it has been observed that CR is associated with an accelerated loss in cerebrum grey matter (Pifferi et al., 2018). This occurred despite a 50% extension in lifespan. An evolutionary perspective could help understand this. It is plausible primate evolution was influenced by an increased ability for neurologically processing (Falk, 2007; Hofman, 2014). Such processes are energetically demanding (Laughlin, 2001). If CR is too severe it could detrimentally impact brain function. A study in rats suggests this is the case (Padamsey et al., 2021). During periods of CR their neocortex saved energy by reducing coding precision (Padamsey et al., 2021). This proved harmful the longer this regime was administered. Thus, long term severe CR may unsuitable in humans due to the energy demands of the brain. This does not mean CR per se is detrimental to brain function. Evidence suggests otherwise (Smith, 2020). In fact, there is an evolutionary rationale which suggests excessive food consumption is detrimental to the human brain. It is posited that our human ancestors routinely went for substantial periods without food (Mattson, 2019; Seidler and Barrow, 2022). Within this context natural selection favoured individuals that had the cognitive capacity to outperform their competitors. Based on this idea overfeeding is regarded as detrimental to human cognition. As such a modest dose of CR is beneficial. Interestingly, a recent study in humans reported that a ~14% reduction in calories over 2 years had significant health benefits (Spadaro et al., 2022). A ~14% drop in calories contrasts sharply with the 30% reduction used in the gray mouse lemur study. This emphasizes that milder CR is more effective in humans.

3. Resource reallocation and dietary restriction

How food restriction extends lifespan remains an open question for biogerontology. As alluded to the dominant evolutionary idea centres on the RRH. According to the RRH during periods of food restriction resources are redirected from reproduction towards somatic maintenance (Kirkwood and

Shanley, 2005; Shanley and Kirkwood, 2000). More precisely, from a Darwinian perspective an organism optimizes its fitness by investing in somatic maintenance/survival while concurrently postponing reproduction until resources are plentiful. According to the RRH it is the reproduction-longevity trade off that is exploited by DR studies which observe an increase in lifespan. There is evidence for the DR response being underpinned by a reproduction-longevity trade off. Support derives from a meta-analysis which examined DR across different animals (Moatt et al., 2016). On average DR resulted in a significant reduction in reproduction. However, important caveats were identified. It was found the DR response was greater in model organisms including *Caenorhabditis elegans* (*C. elegans* and *Drosophila melanogaster (D. melanogaster)*. Not all reproductive traits were affected equally. The effect of DR on reproduction was stronger in females than males, however this reduced to near zero when co-factors such as the cost of the reproductive trait were accounted for. Low cost reproductive factors included ejaculate production, while high cost factors included lifetime courtship investment. Since this investigation there have been other studies which are consistent/inconsistent with RRH (Tables 1). Some studies in table 1 did not identify a trade-off between reproduction and survival. Accordingly, it has been proposed that the RRH does not determine the effects of DR. Rather, it has been suggested full feeding is biologically costly. And lifespan extension can be achieved without increased somatic maintenance, when a nutrient rich environment is escaped (McCracken et al., 2020). These inferences are based on the absence of a trade-off between reproduction and survival; however it is not always possible to determine evolutionary trade-offs (Bolund, 2020). Moreover, the DST predicts that species have different fitness curves depending on their environment, this allows significant variation in somatic maintenance (Drenos and Kirkwood, 2005). Other work in table 1 suggests a tri-directional relationship exists between the RRH, CR and epigenetic plasticity. This is intriguing because there is a general consensus that epigenetic processes mediate resource allocation and shape life history schedules in a range of taxa (Ashe et al., 2021; Lamka et al., 2022). However, it is not fully understood how evolutionary theory fits with epigenetic ageing (Mc Auley, 2021; Morgan et al., 2020; Zagkos et al., 2021). Moreover, other observations in table 1 do not support the epigenetic coupling of DR and the RRH. In fact, the study by Xu et al. (2018) suggests DR could elicit its effects by modulating the activity of AP genes.

4. Dietary composition and resource reallocation

4.1 Protein restriction

Altering the ratio of nutrients in a diet can recapitulate the pro-longevity/pro-health effects of CR in model organisms without necessitating a reduction in calories (Bárcena et al., 2018; Brandhorst and Longo, 2019; Richardson et al., 2021). This suggests severe CR is unnecessary for eliciting the beneficial effects of energy restriction because other modalities can stimulate the same biological pathways as CR (Green et al., 2022a). In fruit flies high protein, low carbohydrate dietary regimes correlate with increased reproduction and shorter lifespan (Bruce et al., 2013). Conversely, low-protein, high-carbohydrate diets correlate with increased lifespan and diminished reproduction (Lee, 2015). Recent PR studies which are consistent/inconsistent with RRH are outlined in table 2. There is an evolutionary explanation which aligns RRH with PR. Although carbohydrate is needed for reproduction in fruit flies, it is preferentially used for somatic maintenance, while protein is favoured for reproductive processes (Le Couteur et al., 2016). For example, when Queensland fruit flies were provided with various ratios of P:C diets, egg production rate was mainly modulated by protein (Fanson and Taylor, 2012). These studies illustrate that the relationship between protein intake and lifespan in flies are equivocal. In fact, a high protein diet can confer a survival advantage. For example, on a high protein diet the toxic effect of visible light on survival was rescued (Shen et al., 2019). Moreover, flies injected with *Serratia marcescens* pivot to a carbohydrate-biased diet, which increased their survival (Dinh et al., 2019). Sexual dimorphism also affects dietary response (Carey et al., 2022; Wu et al., 2020). Females are more effective at storing/allocating nutrients for reproduction. For example flies which were given the same protein to carbohydrate (P:C) ratio (constant feeding), or a diet with a different P:C ratio each day (Davies et al., 2019). Male reproductive output was affected by unpredictable feeding, while females were unaffected. Moreover, in a study which examined how development diet affects dietary choice in *Drosophila melanogaster*, adult females selected the same P:C diet regardless of development diet (Davies et al., 2018). In contrast, males selected a diet which compensated for

developmental PR. Other organisms also demonstrate how sex influences the PR response. In mice sex and genetics interact with PR to modulate metabolic behaviour (Green et al., 2022b). Collectively these studies imply that optimum protein intake is context, organism, and sex specific.

4.2 Dietary cholesterol

Cholesterol (Chol) is an essential macronutrient that in mammals participates in a variety of processes, including bile acid, vitamin D and steroid hormone synthesis (Hu et al., 2010; Straniero et al., 2020; Warren et al., 2021). In the cell Chol reinforces cell membranes, and acts a signalling molecule (Luo et al., 2020). Despite its key roles, dysregulated Chol metabolism is associated with age-related pathology (Mc Auley and Morgan, 2022; Morgan et al., 2016a). Furthermore, disrupted Chol metabolism could contribute to ageing (de Medina et al., 2022; Gille et al., 2021; Mc Auley, 2018; Mc Auley and Mooney, 2017; Morgan and Mc Auley, 2020). The canonical organism *C. elegans* has been used to explore how dietary Chol influences lifespan. Unlike mammals *C. elegans* cannot synthesize Chol and depend on a source of dietary sterols (Kurzchalia and Ward, 2003; Otarigho and Aballay, 2020; Rauthan and Pilon, 2011; Shanmugam et al., 2017). The importance of Chol to *C. elegans* is emphasised by a recent study which found that Chol restriction (CholR) negated the life-extending effects of IF (Ihara et al., 2017). Other work suggests that Chol could modulate lifespan in *C. elegans* by optimising its immune response (Otarigho and Aballay, 2020).

D. melanogaster have also been used to investigate how dietary Chol modulates lifespan. Crucially, dietary Chol is essential to the health of *D. melanogaster* (Niwa and Niwa, 2011). If Chol is missing from their diet death occurs at the larval stage (Niwa and Niwa, 2011). The biological value of Chol is further emphasized by CholR studies. Chronic CholR significantly reduces female lifespan (Wu et al., 2020). Dietary Chol also impacts the lifespan of other organisms. In *D. magna* somatic growth progresses asymptotically as dietary Chol increases (Lukas et al., 2011). *D. magna* also respond to dietary lipids in a sexually dimorphic manner. For instance, lipid supplementation significantly benefits female reproduction, however it is accompanied by a depletion in somata nutrients (Martin-Creuzburg et al., 2018). In contrast when males are supplemented with lipids they do not invest in reproduction to the same extent, and unlike females they increase their somata nutrients (Martin-Creuzburg et al., 2018). Clearly, the response of female *D. magna* to dietary lipids is consistent with the RRH. It also offers one explanation as to why male *D. magna* have been observed to live longer than females (Pietrzak et al., 2010). However, other observations involving dietary Chol and survival are inconsistent with the RRH (see table 2). This emphasises the challenge of reconciling macronutrient studies with life history theory.

4.3 Methionine restriction

The essential amino acid (AA) methionine (Met) is key to methylation reactions (Sanderson et al., 2019). Met is also needed for protein synthesis/regulation (Finkelstein, 1990). Paradoxically, dietary Met restriction (MetR) has been observed to extend lifespan in yeast, worms, flies, mice and rats (Lee et al., 2014; Miller et al., 2005; Ogawa et al., 2022; Plummer and Johnson, 2019; Richie Jr et al., 1994). Findings from some of these studies are inconsistent with the RRH. Table 2 details an influential DR study in *D. melanogaster* which were provided with essential AAs (EAAs) (Grandison et al., 2009). The AAs recapitulated the effects of full feeding. Having Met as the only AA source was associated with increased reproductive output. Increased fecundity failed to correlate with a decrease in lifespan. A finding inconsistent with the RRH. However, a more recent investigation which is also outlined in table 2 suggests MetR requires further untangling. This work questions the role of Met and the other essential AAs (EAAs) to the DR response (Gautrey and Simons, 2022). It was observed in *D. melanogaster* that AA availability was not essential for lifespan extension by DR (Gautrey and Simons, 2022). In contrast the effect on lifespan of EAA depended on the genetic line of the fly, and its diet. Under the most severe DR fecundity was constrained by nutrients other than the EAAs.

There are also broader questions about the role dietary Met plays in shaping life-history traits. For instance, queen honey bees consume a diet of royal jelly which is rich in Met (Fallah et al., 2022). Queens live longer than workers (Maleszka, 2018). This is inconsistent with excessive Met consumption reducing lifespan. In fact, Met could be advantageous to queen lifespan. Such a view is

supported by observations from other work. In a recent *D. melanogaster* study it was found that a royal jelly and collagen diet extended lifespan (Qiu et al., 2020). It must be noted however that applying senescence focused evolutionary ides to social insects is challenging. Firstly, caste differences exist between infertile workers and a fecund queen. Secondly, some social insects are subject to seasonal fluctuations in worker extrinsic mortality (Lemanski et al., 2020). An idea conceptually close to the DST views social insects as a superorganism where infertile workers are 'disposable', due their reduced lifespan compared to queens (Rascón et al., 2012). This means worker lifespan is evolutionary constrained. Although, a recent study in *Temnothorax rugatulus* suggests this is an oversimplification, because workers who become fertile express longevity and fecundity genes (Negroni et al., 2021b). Interestingly, the findings of another study by Negroni and colleagues which is outlined in table 1 implies that the RRH accounts for the DR response in *Temnothorax rugatulus* queens (Negroni et al., 2021a). According to the findings of this work it would appear that under DR queens maximize fitness by delaying reproduction and investing in somatic maintenance.

5. Alternatives evolutionary ideas to resources reallocation

5.1 The nutrient recycling hypothesis

Alternative ideas have been proposed to explain the relationship between DR and evolutionary theory. The nutrient recycling hypothesis (NRH) is a compelling example (Adler and Bonduriansky, 2014). The kernel of the NRH is that DR associated lifespan extension is a laboratory "artefact". The NRH postulates that most animals living in the wild would fail to benefit from lifespan extension if exposed to DR. The main reason is wild animals encounter persistent challenges, such as pathogen exposure. Recently the NRH was tested using *D. melanogaster* (Savola et al., 2021). Ten different P:C diets and flies were either infected with *Pseudomonas entomophila*, injured with a sterile pinprick, or unstressed. The rationale was to help determine if lifespan extension is a by-product of an ostensibly innocuous laboratory environment. By including infections, it was predicted DR flies would be weaker and struggle with this burden at the same time as being food restricted. However, it was found that lifespan extension persisted. Interestingly, infected flies on a low protein diet had a higher rate of mortality. This suggests protein confers a benefit for fighting infection in *D. melanogaster*. In other organisms such as *Spodoptera littoralis* caterpillars dietary protein level is vital to the infection response (Cotter et al., 2019). Therefore, the finding of Savola and colleagues is perhaps unsurprising.

5.2 The clean cupboards evolutionary hypothesis

A new interpretation of CR known as the as the clean cupboards hypothesis (CCH) has been introduced recently (Speakman, 2020). The CCH suggests the CR response is the result of an energy balance to survive the immediate physiological challenge of CR. It is posited that when animals encounter CR they face an energy budgeting challenge. They overcome this by firstly using fat reserves and deriving metabolic energy by removing "cell junk". Examples of junk elimination include autophagy upregulation and senescent cell removal. This is not a long-term evolutionary strategy. Rather, the goal is to achieve "an immediate energy balance". Based on the CCH a beneficial side effect of the 'clearing out' process is life extension. According to Speakman the CCH contrasts with the RRH because autophagy and senescent cell removal are a "deliberate strategy" to increase lifespan by protecting the soma. This theoretical distinction separates the CCH and the RRH. Interestingly, the CCH was recently tested against the RRH (García-Flores et al., 2021). Measurements in mice identified shared biological signatures across different tissue types in response to graded CR. Thirty-eight shared metabolic characteristics responded to CR in a similar manner across tissue types, in many pathways associated with energy and lipid metabolism. It was suggested no activated pathway corresponded to an upregulation of somatic maintenance. Accordingly, it was concluded that the metabolic response to CR was more consistent with the CCH that RRH. However, this conclusion had several caveats. The CR protocol was short and may have failed to capture the CR response associated with lifespan extension. A longer protocol might have captured RRH. A single strain of inbred mice was used which positively responds to CR. It is commendable these limitations were discussed in such detail by the authors.

5.3The hyperfunction evolutionary theory of ageing

The hyperfunction theory was outlined several years ago (Blagosklonny, 2006). Over the years it has gained a degree of momentum (Blagosklonny, 2013; Gems, 2022; Gems and Partridge, 2013). However, it is not without its detractors (De Grey, 2015; de Grey, 2021; Zimniak, 2012). Its theoretical premise is that ageing is driven by growth which extends into adult life. The growth occurs in the main due to hyperfunctioning signalling pathways. A classic example being the mechanistic target of rapamycin (mTOR) pathway (Blagosklonny, 2006, 2022). Arguably there is a degree of ideological alignment with the DST because the hyperfunction theory is based around a physiological interpretation of ageing. However, it posits that suboptimal physiology later in life is the key driver of ageing not damage accumulation due to limitations in somatic maintenance. The hyperfunction explanation for the DR response suggests that a drop-in food intake is associated with a reduction in growth pathway signalling, which in turn diminishes hyperfunction (Blagosklonny, 2007, 2010, 2022; Gems, 2022). Support linking this idea with the DR response derives from studies which have observed that DR supresses the activity of mTOR signalling (Ham et al., 2022; Ma et al., 2015; Tucci, 2012).

6. Considerations for future work and emerging variables

6.1 Descriptive models require a mathematical framework

The evolutionary models discussed above are thought provoking. However for a descriptive/verbal model to be paradigm shifting it needs to embrace mathematics (Motta and Pappalardo, 2013). Mathematics enables the behaviour of a biological process to be predicted from basic assumptions (Alon, 2006; Mc Auley et al., 2017; Thieme, 2018). This premise has enabled meaningful predictions about ageing, and its intersection with diet to be made (Mc Auley et al., 2012; Morgan et al., 2016b; Van Leeuwen et al., 2002). Moreover, empirically informed models have shaped our conceptual understanding of how animals interact with food in the wild and in the laboratory (Raubenheimer et al., 2022; Raubenheimer and Simpson, 2018). Dynamic energy budget (DEB) models are a worthwhile example of this (Nisbet et al., 2000; Nisbet et al., 2010; van Leeuwen et al., 2010). It is biologically plausible that DEBs could examine the NRH and the CCH. DEBs use simple constraints to account for resource allocation towards growth, reproduction and somatic maintenance, throughout the life of an animal (Kearney et al., 2010). This approach has been used to model the physiology of animals in the wild (Ballesta-Artero et al., 2019; Talbot et al., 2019). Other approaches that can be used to identify MA/AP include population genetic models. Population genetic models use mathematical inference to identify genes which are undergoing selection (Day and Gandon, 2007) For instance, this technique has been used to identify AP as a ubiquitous mechanism for the maintenance of polymorphic disease alleles (Carter and Nguyen, 2011) Such approaches are a necessity in order to disentangle the kaleidoscopic effects of food restriction both in the wild and in the laboratory.

6.2 Bacteria and the microbiome

Other variables are becoming increasingly recognised as modulators of life history trade-offs (Figure 3). For example, microbes potentially make a much broader contribution to the fitness of insects (Anderson et al., 2018; Ludington and Ja, 2020). An inventive recent study investigated how natural food sources impact *Drosophila* fitness (Davies et al., 2021). Food was collected from an orchard compost heap; the natural habitat for certain *Drosophila* species. Collections were made over 9-months to reflect seasonal changes in nutrient composition. It was anticipated the P:C ratio of the 'organic' diet would mirror the effects of a similar laboratory-based protocol. However, apart from the critical thermal maximum and developmental time no traits correlated significantly with the P:C ratio of the 'organic' diet. It was concluded that laboratory diets possess limited microbial diversity. Other work underscores how microbes can influence diet studies. Female *Bactrocera dorsalis* (Diptera: Tephritidae) fed a diet supplemented with *Pantoea dispersa* and *Enterobacter cloacae* laid more eggs but a had shorter lifespan (Akami et al., 2019). Flies fed *Enterococcus faecalis* and *Klebsiella oxytoca* enriched diets lived longer but had lower fecundity.

There is also a growing acknowledgement that the gut microbiome has a part to play in life history studies. For instance, certain gut microbes in *D. melanogaster* can use sterols as a source of energy (Li and Jing, 2020). This has implications for studies which investigate how Chol influences evolutionary trade-offs. The reason is certain strains of endosymbiontic bacteria in *D. melanogaster* compete for host

sterols (Paredes et al., 2016). It is possible the evolutionary 'goals' of the microbiome are not aligned with its host. More specifically, a subtle balancing act exists between cooperation and conflict between the microbiome and its host (Alcock et al., 2014). When the balance tips in favour of conflict this could constrain host fitness and influence lifespan. This idea is not unorthodox. It is consistent with the idea of an extended phenotype (Dawkins, 1982; Henry et al., 2021). In other words, the effects of a gene(s) transcend their host. Empirical support for the extended phenotype of the microbiome is found in *C. elegans* studies. DR correlated longevity has been associated with decreased microbiome folate production (Choi et al., 2019). The extended phenotype of the microbiome is evident in other species. Mice subjected to a five-month period of MetR underwent change in *Bacteroidaceae Verrucoccaceae,* and *Rumminococcaceae* species (Wallis et al., 2020). It was uncertain if these bacterial changes impacted lifespan; however, findings in other organisms suggest this could be the case. For example, in *D. melanogaster* the microbiota is a significant contributor to physiological Met levels (Parkhitko et al., 2021). Moreover, certain long lived *D. melanogaster* possess high physiological levels of Met (Parkhitko et al., 2016). What this suggests is that studies which alter gut Met metabolism have the potential to modulate the survival of *D. melanogaster* via the extended phenotypical effects of the microbiome.

6.3 Early life nutrition and lifespan

Early-life nutrition impacts lifespan (Hayward et al., 2013; Langley-Evans, 2015; Vaiserman, 2014). Based on observations across taxa it is broadly accepted that early life nutrition can in certain situations affect a variety of life history traits (Buchanan et al., 2022; Gluckman et al., 2007; Hammers et al., 2013). Some studies indicate that early life nutrition has a lasting impact on lifespan. For example, *D. melanogaster* subjected to a very low protein diet from larval to adult stage had an increased development period and an extended lifespan (Krittika et al., 2019). Other work also suggests early life nutrition could impact senescence in certain species. A meta-analysis which examined 14 bird/mammal species found that an improved developmental environment correlated with reduced reproductive senescence (Cooper and Kruuk, 2018). This was described as "ageing with a silver-spoon" because a better development period was associated with reproductive decline in later life. Other work implies early-life food restriction has a broad impact. For instance, early life starvation in the turnip sawfly, *Athalia rosae* (Hymenoptera: Tenthredinidae) had a strong intra-generational impact on several life-history parameters (Paul et al., 2019). However, not all studies suggest early-life nutrition impacts lifespan. A comprehensive meta-analysis was unable to identify an overall impact of early-life diet on lifespan (English and Uller, 2016). This work examined studies that manipulated pre-or post-natal diet and measured its effect on lifespan.

6.4 Examining evolutionary strategies in the wild

Most studies discussed in this review were conducted in a laboratory. However, the importance of the wild to future DR studies cannot be understated. Life-history strategies are the result of evolutionary adaptations which are ecologically specific (Stearns, 2000). In the wild animals optimise survival/reproductive success by altering their behaviour/scheduling activities in response to food availability, climate and predation (Flatt and Heyland, 2011; Harvey, 2005). Such factors underpin a necessity to allocate limited dietary resources between a variety of processes (Stearns, 1992). An effective survival response is needed when confronted with extrinsic perturbations. Diet flexibility fuels a capacity to survive in the absence of preferred food sources. For instance, Japanese macaques (*Macaca fuscata*) have a preferred diet of fruit, flowers, fungi and insects, which becomes restricted in winter (Hill, 1997). *Macaca fuscata* respond by pivoting their diet to freshwater biota (Milner et al., 2021). Such dietary shifts can confer fitness benefits. For example, thin toed frogs (*Leptodactylus savage)* who modify their diet to a greater extent have higher fitness (Costa-Pereira et al., 2019). Such observations underscore the fact that being able to feed on different foods is a key trait of animal behaviour. In the wild food sources are heterogenous and food consumption behaviour can be stochastic.

It is imperative future DR studies make greater use of the natural environment of the organism under investigation. Previous efforts to investigate senescence and DR in wild animals generated some interesting insights and conflicting data (Harper et al., 2006). In this study wild mice were captured and given a CR protocol which failed to extend their lifespan. A finding consistent with the idea that CR

negates the toxic effects of a laboratory diet. It also underscored the notion that laboratory mice are strikingly different from their wild counterparts. Another study used the captive antler fly, *Protopiophila litigate*, to measure age-specific male survival and mating success in laboratory cages versus a natural field environment while supplementing with protein or sugar (Mautz et al., 2019). Significant increases in both survival and mating rates in the laboratory compared to the field were found. There was no difference between environments in reproductive ageing. Protein had a detrimental impact on survival in both environments. These studies are commendable for their creativity and more studies need to investigate DR in the wild. Emerging insect models could make studying DR in the wild easier. Crickets, damselflies, dragonflies and butterflies are all suitable models for examining senescence in the wild (Zajitschek et al., 2020). Moreover, it is possible *D. melanogaster* could be studied in the wild. For instance, a recent investigation combined field experimentation with a laboratory garden experiment to do this (Rudman et al., 2022). This methodology could be used to examine DR using *D. melanogaster.*

7. Discussion

It is almost 100 years since the pioneering work of McCay and colleagues (McCay et al., 1935). The observation that food restriction extends the lifespan of rats was a milestone event for biogerontology. It provided the impetus for DR to be investigated across a range of taxa. Findings from these studies have revealed the malleability of ageing. There is now a growing possibility DR could be employed to promote human healthspan. To fully exploit DR there is an imperative to further understand it. This review highlights how life-history theory can be used to gain a deeper insight into the effects of DR. By viewing DR with an evolutionary lens, it can be concluded its effects are an adaptation to variations in food availability. What is less certain however, is how these effects are mediated. One way to interpret the DR response is to view it as a strategic physiological change which results in metabolic resources being directed from reproduction to somatic preservation. However, as this review explicitly outlined this is not a universally accepted idea. The findings from several studies are inconsistent with the RRH. Investigations mainly in *D. melanogaster* have observed that the reproduction-somatic maintenance trade-off can be uncoupled by using diets with varying amounts of protein, methionine and cholesterol. Although, these findings have caveats. Trade-offs are not always detectable. Moreover, despite their advantages, canonical organisms are imperfect analogues. For example, in female *D. melanogaster* fecundity is routinely estimated via a proxy measurement, which entails counting egg production (Ng'oma et al., 2018). Another limitation is the food used in DR studies does not always associate with increased lifespan (Krittika and Yadav, 2021). Although efforts to standardise the diets used in *D. melanogaster* studies have been made (Piper et al., 2014).

It is worth reaffirming another point revealed in this review. Most DR studies have been conducted in a laboratory. This is a clear limitation. In the wild animals inhabit environments where their nutritional needs are subject to continual change. To survive it is likely animals invoke ancient evolutionary conserved biological mechanisms. This invariably enables organisms to adapt to nutrient-specific dietary fluctuations. Moreover, within an ecological niche a mosaic of interconnected variables contributes to the fitness of organisms such as *D. melanogaster* (Dasgupta et al., 2016; Nandy et al., 2013; Nandy and Prasad, 2011). These factors are also capable of altering the direction of life-history trade-offs. For example, it was recently observed that nymphs exposed to cardenolide develop faster and live longer (Pokharel et al., 2021). It is possible this response is mediated by insulin/insulin-like signalling pathway (IIS). IIS is suggested to underpin a widespread phenotypic plastic response to environmental perturbations (Moatt et al., 2020; Regan et al., 2020). Given that factors other than diet influence life-history trade-offs it is perhaps unsurprising some observations are inconsistent with the RRH. However, this does not mean the RRH is a weak idea. Perhaps a more nuanced way of viewing both the RRH and alternative explanations for the DR response is to regard them pluralistically. This thoughtful approach has been applied to other complex areas of evolution (Gangestad and Simpson, 2000). By adopting this framework, the DR response can be viewed in more than one way without either interpretation being incorrect. This removes the need for a single evolutionary idea to predict a universal response among species.

The ultimate goal of biogerontology is to identify actionable treatments which promote longevity. Obstacles exist to achieving this. Humans are complex organisms whose dietary behaviour is influenced by factors such as the society they live in. The importance of society to animal dietary behaviour is underscored by some findings in other organisms. In the clonal raider ant *Ooceraea biroi* foraging behaviour is regulated by social and personal hunger (Chandra and Kronauer, 2021). This is the case in other species. During periods of DR *C. elegans* elevate foraging activities (Skora et al., 2018). Moreover, during DR adult female cabbage white butterflies (*Pieris rapae*) increase investment in flight related activities (Jaumann and Snell-Rood, 2019). In *D. melanogaster* DR correlates with increased locomotion (Yu et al., 2016). Of course, model organisms are not humans. However, what is extrapolable to humans is that physical activity (PA) superimposed on the DR response adds a further layer of complexity. Moreover, it can be argued foraging is a form of 'exercise' analogous to PA in humans. To further complicate matters the relationship between PA and human evolution remains to be fully elucidated. Although, evolutionary parallels could exist between DR and PA. The "active grandparent" hypothesis (AGH) underscores the parallels (Lee et al., 2021). According to this idea selection for PA in humans promotes adaptations which favour resource allocation pathways which retard age-related pathology/senescence. This resonates with DST as it implies PA repartitions resources towards somatic maintenance. As Lee and colleagues outline, high intensity PA transiently diminish mitochondrial function in skeletal muscle, it then quickly ensures muscles cells stimulate mitochondrial function (Kim et al., 2017). Thus, PA counteracts the oxidative stress it generates by eliciting mechanisms which dampen oxidative stress.

The AGH is also a compelling evolutionary idea given that PA and optimal diet have been identified as key to advanced life. For instance, in the European Union NU-Age project, a Mediterranean diet (MedDiet) comprised of small meals, combined with daily PA was a characteristic theme in the life of centenarians (Martucci et al., 2017). In fact, it has been suggested centenarians are physiologically similar to individuals on a CR diet (Franceschi et al., 2018). Although, exactly how the MedDiet confers its benefits remains debateable as a recent meta-analysis identified that it had a negligible effect on low density lipoprotein cholesterol, high density lipoprotein cholesterol and triglycerides. Despite this it is clear that diet and PA are significant contributors to human health/life-span in humans (Rees et al., 2019). However, the active grandparent hypothesis and centenarian studies suggest PA is equally as crucial as diet to healthspan. The potential equal standing of PA and diet to human survival could have an evolutionary explanation. It has been suggested food intake behaviour evolved under selection for the optimization of foraging (Lalwani et al., 2019). This has pathophysiological implications for modern society as human feeding is now uncoupled from foraging. There are other human factors which mean that DR cannot be immediately interpreted as a universal panacea for preventing age-associated disease. In humans there is a well described correlation between acute and chronic stress exposure and elevated food seeking and food intake (Masih et al., 2017). 'The threat' of DR in humans, or transient DR has the potential to provoke increased food consumption, which in an obesogenic environment could have pathophysiological implications for health. In summary, there are many factors to be considered before DR is widely used to advance human healthspan.

8. Conclusion

This review leads to the general conclusion that the relationship between diet and longevity depends on the organism and the ecological context it evolved in. There is little doubt that additional experimental work is required to reconcile some of the seemingly contradictory results outlined this review with evolutionary theory. There is also a need to conduct future DR studies in the wild. Finally, it is crucial to recognise that human behaviour is influenced by a multitude of factors which are underpinned by human evolution. This will likely influence how humans interact with DR protocols in the future. Understanding human behaviour and the evolutionary factors which influence it could ultimately determine the success of DR as a therapeutic strategy for prompting human healthspan.

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Table 1. Evidence for and against the resource relocation hypothesis

Evidence for the RRH		
Organism	**Study summary**	**Observations**
C. elegans	Toxic cyclic peptides were introduced to the environment of *C. elegans*, leaving them to feed on low quality bacteria (Liu et al., 2021).	Resources redirected to DNA repair processes at the expense of a significant drop in reproduction which was accompanied by an increase in life-span.
D. magna	*Daphnia* were used to perform a food restriction study (Pérez-Fuentetaja and Goodberry, 2016).	During periods of low food *D. magna* invested in somatic maintenance and produced fewer neonates.
The ant *Temnothorax rugatulus*	Nexus between DR and queen fecundity examined (Negroni et al., 2021a).	Reduced egg production. Increased expression of cellular repair genes.
D. magna	DR applied to a DR mutant (Nguyen et al., 2021).	A DNA methyltransferase 3 (DNMT3) ortholog regulated energy allocation between growth and reproduction. The DNMT3 ortholog modulated life-span.
Mus musculus	Examined the blood DNA methylome of 141 mice during ageing and CR (Sziráki et al., 2018).	Initially DR altered the trajectory of the DNA methylome towards ageing, then shifted it to a younger state. DNA methylation changes to maintenance /repair genes central to the transition.
Evidence against the RRH		
Two-spotted spider mite *Tetranychus urticae* Koch (Acari: Tetranychidae)	Organism exposed to a dietary protocol of two days fasting in every four days (Li and Zhang, 2021).	No trade-off between reproduction and female longevity observed. Altered female reproductive schedule. Increased male mortality.
Neriid fly, *Telostylinus angusticollis*.	Examined DR in different environmental contexts (Macartney et al., 2018).	Trade-offs between survival and reproduction not always identifiable. Coupling of life-span and reproduction context and sex dependent. Males and females benefited from an increase in life-span. DR rendered females infertile. Association between DR and male fecundity apparent in certain environments.
D. melanogaster	Examined somatic maintenance across 11 different genotypes (McCracken et al., 2020).	Significant mortality after defaulting to rich diet post DR.
European starlings (*Sturnus vulgaris*)	Birds exposed to food insecurity (temporally variable access to food) (Andrews et al., 2021).	Increased fat storage and a gain in body mass. Reduction in somatic maintenance.
C. elegans	Centred on Wnt signalling (Xu et al., 2019). Wnt signalling- crucial for developmental programs Its hyperactivation is associated with ageing (Palomer et al., 2019; Steinhart and Angers, 2018).	Wnt signalling needed for DR-induced longevity. DR associated with increased expression of microRNA (mir-235). mir-235 inhibited cwn-1/WNT4 expression at the beginning of adulthood. This did not interfere with development.

		DR regulated adult lifespan by utilising this microRNA switch to modulate Wnt signalling.

Table 2. Dietary composition and resource reallocation

Evidence for the RRH		
Organism		**Observations**
D. melanogaster	Protein restriction study: Fecundity (eggs laid) and survival determined in females evolved for fifty generations on three different diets. Diets had either a low, standard, or high protein content (Zajitschek et al., 2019).	Flies on a high protein diet evolved increased fecundity with reduced survival on low/standard protein diets. Flies on low protein evolved reduced survival without a commensurate rise in reproductive output.
C. elegans	Cholesterol restriction study: Worms cultured without cholesterol (Shanmugam et al., 2017).	Displayed late egg production, diminished lipid levels, and a reduced lifespan.
D. melanogaster	Cholesterol restriction study: Egg-laying flies administered a high P:C diet (Zanco et al., 2021).	On the high P:C diet flies had a reduced lifespan. Flies rescued from lifespan reduction when cholesterol was added to the diet. Reproduction uncoupled from lifespan.
D. melanogaster	Methionine restriction study: Flies provided with essential AAs (EAAs) (Grandison et al., 2009).	The amino acids (AAs) recapitulated the effects of full feeding. Met without the other AAs was associated with increased reproductive output. Effects consistent with full feeding. Increased fecundity failed to correlate with a decrease in lifespan. Reproduction uncoupled from lifespan.
	Evidence against the RRH	
D. melanogaster	Protein restriction study (Krittika and Yadav, 2020).	No relationship between protein intake and longevity. PR did have an age-specific impact on fecundity.
D. melanogaster	Compared life span, egg production rate, pre-adult survival, and the development time of six fly strains which were allocated to one of four diets differing in protein to carbohydrate (P:C) ratio (Kim et al., 2020). .	Adults had a shortened lifespan and improved egg production on a diet with the highest P:C ratio of 4:1. In all strains, larvae fed the lowest P:C ratio, had a high rate of mortality, delayed development time, and reduced body mass. The effects of P:C balance on life history traits were comparable across each strain.
D. melanogaster	AA restriction study (Gautrey and Simons, 2022). Used the exact concentration and	The effect on lifespan of EAA depended on the genetic line of the fly examined, and its particular diet.

	composition of EAA as administered by Grandison et al., 2009.	Under the most restricted diet fecundity was constrained by nutrients other than EAA.
Mus musculus	Methionine restriction study in mice (Duan et al., 2022).	MetR correlated with hydrogen sulphide production which is thought to combat oxidative damage (Kitada et al., 2021) Finding provides tentative evidence that methionine restriction mediates a resource reallocation shift towards somatic maintenance

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Figure 1. Graphical representation of the decline in the force of natural selection with age and a summary of the main evolutionary theories of ageing.

Figure 2. Conceptual framework outlining the DR response according to the resource reallocation model in a hypothetical animal population. a) under a 'normal' diet reproductive levels are maximized

and morbidity and mortality are defined by ecological context. b) the DR response results in a reallocation of resources towards somatic maintenance at the expense of reproduction. This results in a decrease in morbidity and mortality. This model does not hold for all studies, as several investigations have been unable to identify a trade-off between reproduction and longevity. This has led to a number of alternative evolutionary ideas which are discussed in the main body of the manuscript.

Figure 3. Factors which impact the dietary restriction response. Some variables such as sex and genetic background are well known modulators of the dietary restriction response. Others such as the gut microbiome are beginning to emerge as important modulators which require careful consideration in future studies.