Sex-specific lifespan and its evolution in nematodes

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Abstract

Differences between sexes of the same species in lifespan and aging rate are widespread. While the proximal and evolutionary causes of aging are well researched, the factors that contribute to sex differences in these traits have been less studied. The striking diversity of nematodes provides ample opportunity to study variation in sex-specific lifespan patterns associated with shifts in life history and mating strategy. Although the plasticity of these sex differences will make it challenging to generalize from invertebrate to vertebrate systems, studies in nematodes have enabled empirical evaluation of predictions regarding the evolution of lifespan. These studies have highlighted how natural and sexual selection can generate divergent patterns of lifespan if the sexes are subject to different rates or sources of mortality, or if trade-offs between complex traits and longevity are resolved differently in each sex. Here, we integrate evidence derived mainly from nematodes that addresses the molecular and evolutionary basis of sex-specific aging and lifespan. Ultimately, we hope to generate a clearer picture of current knowledge in this area, and also highlight the limitations of our understanding.

Keywords: Nematode**,** evolution, lifespan**,** aging, sex-specific lifespan

Highlights:

- Nematode diversity offers great potential for understanding sex-specific aging
- Sexual dimorphism of lifespan is plastic and context-dependent
- Nematode studies highlight the importance of sex-specific selection Costs related to natural conditions must be incorporated into experimental design

1. Introduction

Improvements in healthcare and nutrition have led to a rapidly widening section of the population entering into old age. This is coupled with an increase in the burden of chronic diseases, including neuro-degeneration, cancer and heart disease. Cumulative physiological decline – or aging – is the predominant risk factor for death [1]. Aging therefore has clear biomedical implications [2], but also presents a fascinating evolutionary challenge [3]. In a variety of taxa, lifespan – a frequently measured proxy for aging defined as time from birth until death – varies according to sex [4-6]. In humans and other mammals, lifespan and aging also show sex-specific patterns, with a bias towards longer female lifespan [4]. Suggested explanations for sex-biased patterns range from male mal-adaptation driven by innate asymmetries in the transmission of genetic material, to differential selection arising from divergence of reproductive strategy [7]. Understanding the basis of sex differences in aging and longevity could reveal novel mechanisms underlying intraspecific variability in aging rate [4].

Nematode worms have been a fruitful system for uncovering the mechanistic and evolutionary causes of aging. Their popularity arises largely from lab tractability, manageable lifespans and – particularly for the androdioecious (hermaphrodite and male) species *Caenorhabditis elegans* – a fully sequenced and annotated genome with an abundance of genetic resources [8]. Crucially, aging in *C. elegans* recapitulates many aspects of mammalian senescence, including accumulation of macromolecular and cellular damage, progressive deterioration of physiological function, and increased mortality and morbidity [9]. Substantial modulation of aging has been achieved in *C. elegans* through mutation or down-regulation of widely conserved aging-associated pathways, such as insulin/insulin-like growth factor (IGF)-1 signalling and mitochondrial response networks, as well as restriction of food intake without starvation (dietary restriction) and the application of pharmacological agents [10]. The expression of over 800 genes have been shown to change in expression with age in the standard N2 (Bristol) strain [11], while many genes regulating *C. elegans* aging are deregulated in human age-associated diseases [9]. Although *C. elegans* primarily comprises self-fertilizing hermaphrodites with rare males, several studies have examined dioecious species in which lifespan is sexually

dimorphic [12, 13]. Broader insights have been gained from a range of free-living and parasitic nematodes, in which enormous diversity in lifespan – from a few days to decades – has been documented [14]. However, aging patterns are to date poorly characterised in nematodes, except for *Caenorhabditis* and, more recently, *Pristionchus* [13-16].

Investigation in nematode systems has been limited by factors including a poor understanding of nematode ecology, as well as the difficulty of characterizing aging itself. Physiological decline over time can be assessed in nematodes using parameters including motility and stress resistance [17], which are informative for understanding organismal health span (the period of unimpaired activity and function preceding age-related decline [18]). However, as studies focusing on sexual dimorphism in such traits are limited, comparisons of intrinsic lifespan comprise the majority of this review.

2. Sexual dimorphism of intrinsic lifespan and aging in the laboratory

The culture of nematodes in laboratory conditions facilitates the monitoring and control of food, interactions with other individuals, and extrinsic mortality [19]. Phenotypes associated with somatic aging in *C. elegans* hermaphrodites include deterioration of muscle integrity, leakage of yolk from the intestine into the body cavities, immunosenescence [18], and degradation of intestinal microvilli and nuclei [20]. The pathobiology of aging in *C. elegans* males is currently unknown. The majority of studies in *C. elegans* focus on hermaphrodites, which is largely attributable to the difficulties associated with studying males. This includes their rarity (0.1% of hermaphrodite self-progeny), their mate-searching behavior leading to desiccation on the plate walls, as well as their attempts to mate with themselves via the excretory pore, leading to mortality [21, 22]. In this section, we review sex differences in nematode lifespan and reproductive aging, and consider how the physiological factors behind intrinsic senescence are heavily contingent on genetic and environmental interactions.

2.1 Sex differences in lifespan

How robust and generalizable are the sex-specific lifespan and aging patterns in nematodes? In *Caenorhabditis* nematodes, comprising both androdioecious (males and hermaphrodites) and dioecious (males and females) species, male longevity

biases have been broadly observed, with the exception of the androdioecious nematode *C. briggsae* [12]. However, the pattern is complex. Male-biased longevity was found in nine out of twelve wild *C. elegans* isolates, but hermaphrodite lifespan bias (possibly owing to sickly males) was also identified, and certain isolates showed no clear bias [12]. Alongside genetic background, culture conditions and intra/intersexual interactions can greatly influence the sexually dimorphic patterns observed. It is particularly important to determine whether mortality arises as a consequence of aging itself, as opposed to non-optimal culture conditions or other sources of age-independent mortality. Nematode populations are generally maintained on lawns of *Escherichia coli* at 15-25 °C. When populations are cultured in isolation at 20 °C, N2 *C. elegans* males have a similar pattern of age-specific mortality but reduced aging rate compared to hermaphrodites [22]. Males live ~20% longer than hermaphrodites under solitary conditions, as a result of reduced mortality rate acceleration. In single-sex groups, however, median hermaphrodite lifespan exceeds that of males by ~60% because homosexual male-male interactions shorten their lifespan [22]. Harmful male interactions within grouped populations might explain why *C. remanei* females outlive males when nematodes are housed in same-sex groups of 20 individuals [23], whereas males of *C. remanei* spp. *vulgaris* live longer than females when housed under solitary conditions [12]. A further factor known to dramatically alter nematode longevity is mating, which reduces the lifespan of *C. elegans* hermaphrodites by around 40% [24]. The lifespan of *C. remanei* males exceeds that of females in grouped mated populations, reversing the pattern seen in grouped virgin populations [25], which highlights the substantial cost of intersexual encounters.

Clearly, a variety of known and unknown variables modify the relationship between sex, aging and fitness in nematodes, which must be carefully considered when drawing conclusions about the evolution of sexually dimorphic aging. Equally, however, this plasticity and variability among different nematode groups presents great opportunity for comparative approaches. For example, the putative pattern of male-biased longevity in certain rhabditid nematodes is reversed in *Pristionchus,* with females generally outliving males [13], opening avenues for research into the influence of reproductive biology on sexual selection and sex-specific aging.

2.2. Sex differences in reproductive aging

There has been growing interest in understanding the underlying molecular causes of

reproductive senescence in nematodes, which could shed light on female reproductive decline and degeneration of oocyte quality in humans [26-28]. Unsurprisingly, studies in *C. elegans* have focused almost exclusively on hermaphrodites, which produce progeny by self-fertilization for 7 days at 20°C, after which point they can be crossed with males for up to 15 days [29]. The decline in hermaphrodite fertility with age has been attributed to TGF-β and Insulin/IGF-1 signaling-dependent deterioration of oocyte quality [27]. A recent analysis of genes influencing reproductive span has indicated that contact with males influences reproductive as well as somatic aging [28] (also see section 3.3.). Males of *C. elegans* lose the ability to cross-fertilize by day 7 of adulthood, around 1/3 of their average lifespan, and this seems to reflect a declining ability to execute mating behavior that can be modulated by insulin signaling, rather than deterioration of gamete function [29]. However, *C. elegans* males are dispensable for reproductive success, whereas in dioecious species the maintenance of male vigour has more bearing on fitness. Indeed, males of the dioecious nematode *C. remanei* maintain progeny production for longer and reach peak reproductive performance at a later age than females [25]. A study in another dioecious species, *P. exspectatus,* found that changes in crawling speed, a proxy for somatic senescence, contributed to male but not female reproductive decline. This demonstrates some sex-specificity of the age-related mechanisms behind reproductive senescence and their interaction with somatic deterioration [15]. Specifically, reproductive senescence in *P. exspectatus* males might, as in *C. elegans,* depend on diminished efficacy of mating behavior, or on some other male-specific activity such as mate search. Whether shared molecular mechanisms underlie sex-specific features of reproductive senescence largely remains to be determined.

2.3. Sex-specific effects of genetic and pharmacological interventions on intrinsic senescence

Within a laboratory setting, genetic and pharmacological interventions conferring long life and/or healthier aging have been used extensively to unpick the mechanisms of senescence. The *daf-2* gene encodes an insulin-like receptor, which signals through a conserved pathway to negatively regulate the FOXO transcription factor *daf-16* in response to environmental signals. If the longevity of wild-type *C. elegans* males and *daf-2* mutants share a common mechanism, the lifespan of *daf-2* males should be the same as or similar to that of wild-type males. In fact, the lifespan of *daf-2*(*m577)* males is increased relative to wild-type males to the same extent as that of

hermaphrodites [22], suggesting that reduced insulin/IGF-1 signaling is not responsible for male longevity. There is some complexity, however, as males with a mutation in a different allele (*e1391*) of the same gene live around 6 times as long as their wild type counterparts, whilst lifespan is merely doubled in hermaphrodites [30]. Interestingly, *daf-16* mutation largely suppresses male longevity [22], indicating that a *daf-2*-independent signal modulates *daf-16* levels in a sex-specific manner. Higher activity of DAF-16 therefore plays a significant part in the longevity of solitary *C. elegans* males.

In *C. elegans,* interactions between insulin signalling and steroid pathways control lifespan and aging in a sex-specific way. The nuclear receptor DAF-12 responds to a bile acid-like steroid ligand to regulate lifespan. In a wild-type background mutation of this gene weakly reduces the lifespan of males but promotes longevity in hermaphrodites [31]. Furthermore, whereas the *daf-12* mutation in hermaphrodites extends lifespan in a manner that is dependent on the strength of *daf-2* mutation, in males the effect of *daf-12* is marginal regardless of *daf-2* background [31]. The secretion of sex hormones is a key component of vertebrate reproductive strategy, and male-specific testosterone production has received attention as a factor in male-biased mortality rates [32].

Although in many *Caenorhabditis* nematodes males are the longer-lived sex, the sexually dimorphic effects of DAF-12 on lifespan might similarly derive from sex differences in steroid-derived hormone production, a possibility that demands further inquiry. Alternatively, there may be sex differences in DAF-12 tissue localisation or protein levels, or sex-specific availability of co-repressors and co-activators [31]. Aside from insulin and steroid signalling mutants, a number of uncoordinated (*unc)* mutants have sex-specific effects on lifespan in *C. elegans*, increasing male but not hermaphrodite lifespan even beyond the lifespan of solitary wild-type males [22]. This indicates that some behaviour that depends on normal motility, and is distinct from deleterious interactions with other nematodes, reduces male lifespan.

Pharmacological agents that alter the activity of nutrient-sensing pathways can also induce sexually dimorphic responses. The target of rapamycin (mTOR) pathway responds to nutrients to control cell growth in multicellular organisms, and interacts with insulin signaling to control development and lifespan in *C. elegans* [33]. The antibiotic rapamycin specifically inhibits mTOR, and feeding mice rapamycin extends lifespan more prominently in females than in males [34]. In *C. remanei*, however,

lifelong exposure to rapamycin extends the lifespan of males and does not alter their fitness [23], whereas high concentrations of rapamycin increase female lifespan only slightly and reduce reproductive output. The authors also showed that adult exposure to rapamycin reduces body size in both males and females of *C. remanei.* This suggests that the sex-specific relationship between size and fitness is responsible for sexually dimorphic lifespan changes in response to rapamycin exposure. In this view, the smaller sex (males in *C. remanei*), whose fitness depends less on body size, benefits more from reduced mTOR signaling. This is reflected in a more prominent lifespan increase in males [23]. Rapamycin treatment is also potentially informative for understanding the genetic variation underlying natural lifespan variability. If differences in baseline levels of TOR signalling drive variation in lifespan and aging, then long-lived individuals would be expected to respond less to rapamycin treatment. However, when short- and long-lived lines of *C. remanei* generated by experimental evolution [35] were exposed to rapamycin, female lifespan was additively extended across all lines. This suggests that lifespan variability in the lines cannot be largely attributed to variation in TOR signalling [36], and supports the idea that lifespan variation in natural populations is a quantitative trait influenced by many loci rather than major genetic variants [36].

2.4. Sex-specific effects of diet on intrinsic senescence

The intrinsic processes that affect senescence interact with environmental variables, sometimes in a sex-specific way [37, 38]. For instance, wild male flies age much more rapidly than captive male flies, but no such pattern occurs in females [39]. Clearly, environmental factors that are independent of background mortality (e.g. temperature, nutrient availability) alter the relationship between sex and aging. One key variable that may depend on the environment is dietary intake. Glucose, considered toxic under many conditions to *C. elegans* [40, 41], exerts a sexually dimorphic effect on lifespan and motility. In hermaphrodites exposed to 250 mM glucose, lifespan was reduced by 30-40% and mid-life paralysis increased, whereas in males, glucose increased the mean lifespan by 10% and reduced paralysis [42]. Potential explanations for the sex-dependent effect of glucose on lifespan and healthspan are wide-ranging given the central role of glucose in metabolism, warranting further study [42]. More generally, different nutrient schedules are likely to maximize fitness and influence lifespan in each sex, ultimately owing to differences in life history strategy. Dietary restriction (DR), the reduction of nutrient intake without malnutrition, improves lifespan and health in many taxa, and generally has a more

pronounced effect in females than in males [43]. DR reduced *C. elegans* body size and protein content to a greater extent in hermaphrodites, and had sex-specific effects on the expression of genes related to reproduction [44]. In *Drosophila*, DR decreased the baseline mortality rate to a greater extent in females compared to males [45], whereas the sex-specific effects of DR on lifespan and aging remain undetermined in nematodes.

3. Evolutionary explanations for sex-specific aging in nematodes

3. 1. Sex-specific extrinsic mortality

Evolutionary theory argues that organisms senesce as a result of the declining force of natural selection with age [46]. Over time, late-acting deleterious alleles will accumulate in the germline (mutation accumulation, [46]) as will those that enhance fitness during early life whilst reducing fitness at later ages (antagonistic pleiotropy, [47]). This occurs because mortality caused by extrinsic causes (e.g. predation, harsh abiotic conditions and disease) is likely to take place before such mutations can exert their detrimental effect [46, 48]. These variants will therefore not be subject to natural selection. Another conceptual framework for understanding senescence is provided by the disposable soma (DS) theory [49], which views aging as a consequence of the partitioning of limited resources into somatic maintenance versus current reproduction, leading to a trade-off [50]. The driving force behind these ideas is the level of extrinsic mortality, which defines the strength of the 'selection shadow' in late life [46, 47] and also shapes resource investment into reproduction versus maintenance and repair. As for somatic aging, the declining strength of selection over time and resource trade-offs between soma and germline are predicted to shape declines in reproductive output [46, 47, 49]. Initial predictions regarding sex-specific aging focused on strong sexual selection in males leading to high mortality and therefore higher male senescence [47], with the more general prediction that high rates of extrinsic mortality should accelerate senescence in the focal sex. However, this prediction has since been elaborated by considering mortality source, with an increasing understanding that high mortality rate can lead to different outcomes depending on whether mortality is random or related to individual condition (for example, susceptibility to predation or disease) [51, 52]. Empirical studies in nematodes have demonstrated that selection on condition can lead to positive pleiotropic effects on lifespan [35, 53]. Notably, in one experimental evolution study, lines of the dioecious nematode *C. remanei* were submitted to heat-shock to induce

high (80%) condition-dependent mortality [35]. After 12 generations of selection, both sexes evolved longer lifespan and improved heat-stress resistance with no reduction in female reproductive performance. However, in line with the classic prediction, high random mortality reduced lifespan in the evolved lines.

A similar study in *C. remanei* has addressed the influence of sexual selection on sexually dimorphic lifespan patterns [53]. In these experiments, condition-specific mortality was applied only to males of *C. remanei* over the course of 20 generations. Only the 20% of males best at finding females were selected, which led to longer-lived males in the evolved lines. The females, however, retained their ancestral lifespan [53], indicating that genetic variation for lifespan can be sex-specific. This demonstrates that extrinsic mortality can target both individual and shared aspects of lifespan in males and females. Sexual selection can also act on late-life performance to delay physiological senescence in male field crickets, providing a further caveat to the classic prediction regarding the effect of extrinsic mortality on aging [54-56]. Such mechanisms offer some explanation for the general lack of evidence for male-biased aging rates despite high rates of male mortality across taxa [32].

Nematodes inhabit diverse ecological niches associated with both free-living and parasitic lifestyles [57]. *C. elegans,* for example, persists in nature on rotting vegetable matter that supports rich microbial communities [58]. Under these conditions, various sources of extrinsic mortality, including predation by mites, flatworms, tardigrades, springtails and predatory nematodes will be encountered. Susceptibility to pathogenic organisms like viruses, bacteria, fungi and microsporida [59-61] depends partly on sex-specific variation in immune defense [62]. Males of *C. elegans* were less resistant than hermaphrodites to infection by the soil-residing nematode microparasite, *Bacillus thuringiensis* [63], although males also displayed much higher pathogen escape behavior, which is likely to limit pathogen exposure. In contrast, *C. elegans* males showed higher resistance to the mammalian fungal pathogen *Cryptococcus neoformans*, which is largely (although not wholly) dependent on DAF-16 [64]. Interestingly, the pattern of longevity across *Caenorhabditis* nematodes, and between sexes of the same species, seems to be recapitulated in their resistance to *C. neoformans;* this indicates some interplay between pathways for sex-specific lifespan and immunity at the molecular level [64].

Stress-resistant and dispersive dauer larvae are induced in many nematodes by harsh environmental conditions including food shortage and overcrowding. Sex differences in dauer induction could potentially entail sex-specific mortality. Males of *C. elegans* become dauers more readily [12, 65], whereas a hermaphrodite dauer bias has been observed in other species including *Oscheius myriophila* (in which males outlive hermaphrodites) and *C. briggsae* [12]. However, there is no apparent correlation between the propensity of males to become dauers in response to crowding or starvation and male longevity across species [12]. The rate of emergence from dauer into reproductive adults is also potentially relevant. One study reported that males of a natural *C. elegans* isolate were able to survive the dauer stage at higher rates than hermaphrodites [66]. Another factor that imposes sex-specific mortality, and which is thought to contribute to male longevity bias in *Caenorhabditis* nematodes, is internal hatching of larvae inside mothers ("matricide") [12, 15]. In summary, when assessing the impact of sex-dependent extrinsic mortality on sexually dimorphic aging and lifespan, it is important to consider both the rate of mortality and whether it is random or selects for certain phenotypes.

3.2. Mating system and sex-specific lifespan

Intense male-male competition for females and risk-taking reproductive strategies may lead to high rates of male injury and mortality [32], which should in turn influence sex-specific lifespan and aging. In vertebrates, male mortality is associated with high intra-specific competition among males [67]. *Caenorhabditis species* have provided insight into the importance of the frequency and intensity of male-male competition in driving sexual conflict [68]. One prediction applicable to nematode populations is that male-biased longevity should be associated with androdioecy, given the lower frequency of males and reduced competition in androdioecious mating systems. However, hermaphrodites of *C. briggsae* live substantially longer than males, and gonochoristic nematodes exhibit even greater male longevity bias than androdioecious species [12]. A potential resolution is that the rarity of males in androdioecious species reduces the effect of selection, enabling male-specific deleterious mutations to accumulate [12]. In general, though, evaluation of the influence of mating system on lifespan may be complex in *Caenorhabditis* nematodes, owing to the potentially confounding influence of high ecological diversity in this group [13, 69].

Unlike the ambiguous connection between mating system and longevity in *Caenorhabditis,* the lifespan of *Pristionchus* nematodes appears to have been driven by shifts from dioecy to androdioecy that have occurred independently throughout the genus on multiple occasions [13]. In a study of 6 dioecious and 5 androdioecious species of *Pristionchus*, hermaphrodite lifespan was found to be consistently shorter than that of females, and this was not a simple cost of reproduction of the type predicted by DS theory [13]. Since hermaphrodites commence self-progeny production immediately upon reaching adulthood, their reproductive period will peak earlier in life than that of females, which need to locate a mate to reproduce. Under the assumption that late-life out-crossing is not a significant component of hermaphrodite fitness, this would be expected to weaken selection for late-life somatic maintenance in hermaphrodites, providing a convincing explanation for the observed pattern that is consistent with classic theory [13].

3.3. The role of sexual conflict

In many species a prominent source of extrinsic mortality is the existence of the opposite sex. Owing to their different modes of reproduction arising ultimately from dissimilar gametes (anisogamy), males and females often have divergent interests from a genetic perspective. Since males invest less in each offspring, it may pay to invest a larger share of resources into a single reproductive opportunity even if longevity is sacrificed [70]. This can also entail the evolution of strategies that manipulate potential mates to optimize reproduction and reduce successful female re-mating [68]. These strategies may in turn be countered by females, leading to adaptations benefiting one sex to the detriment of the other [32]. This sexual conflict can be considered ‘interlocus” since it involves distinct genetic loci, and is clearly reflected in the costliness of mating encounters [71]. Although the physical act of mating alone is insufficient for lifespan reduction [24], signals in the sperm and seminal fluid that induce *daf-12*-dependent shrinking and susceptibility to osmotic stress [24], as well as secreted male pheromones [72], are detrimental for hermaphrodite lifespan. In females of *C. remanei*, mating also induces shrinking and premature death [24]. Importantly, it seems that at least some of the detrimental effects of male mating attempts are unintended and may not reflect true sexual conflict. Male secreted cues were initially interpreted as a sexually antagonistic interaction maximizing male reproductive success at the expense of females [72]. However, ascaroside and non-ascaroside signals secreted by *C. elegans* males

accelerate sexual maturation and increase mated progeny production of sperm-depleted or *fog-2* hermaphrodites by delaying the loss of germline precursor cells [73]. Interestingly, these signals operate in a range of androdioecious and gonochoristic nematodes. Male ascaroside pheromones also stimulate the hermaphrodite reproductive system, improving recovery from heat stress [74]. Male signals therefore modulate and even delay hermaphrodite reproductive senescence, raising the possibility that female fitness is not necessarily compromised by seemingly antagonistic interactions [73, 75], particularly under complex natural conditions. However, either by reducing survival or by diverting resources from maintenance of the female soma, antagonistic intersexual interactions should in many cases affect lifespan and/or aging rate in one or both sexes [5]. This could be in a positive direction, if there is selection for individual condition [32]. Although yet to be empirically tested, such a mechanism might explain the observation that median lifespan of individually housed *Pristionchus exspectatus* females exceeds that of males by roughly 60% [13], despite premature reproductive senescence relative to that of males [15]. Exposure of *P. exspectatus* females to males compromises survival, most probably as a direct result of male harassment. If female survival is condition-dependent, this could lead to the evolution of improved robustness and extended lifespan after the reproductive period [15].

Life history theory provides a useful framework for understanding sexual conflicts involving shared genetic loci. As males and females of the same species share much of their genetic architecture, optimization of trade-offs in either sex between current and future reproduction is likely to be constrained by antagonistic interactions – dubbed ‘intralocus’ sexual conflicts (intralocus SC) (reviewed in [76]). These interactions may prevent one or both sexes from attaining a phenotypic optimum for a particular trait, thereby shaping the life-history traits that are observed in each sex [32]. Empirical studies involving a variety of taxa including seed beetles ([77-79]), Indian meal moths [80] and crickets [81] have provided evidence for and against the relevance of intralocus SC in shaping sex-specific life histories. Despite the comparatively limited investigation of this phenomenon in nematode systems, experimental evolution experiments in *C. remanei* have provided some insight into intralocus SC. Whilst condition-dependent mortality under heat stress increases lifespan in both sexes and fecundity in females [35, 82], male fitness was found to be detrimentally affected when the cryopreserved evolved lines were revisited [83]. This

supports the notion that sex-specific covariances between lifespan, reproduction and heat-shock resistance maintain polymorphism for lifespan and aging at antagonistic loci. In certain undescribed trioecious nematode species, sex-specific gene expression (phenotypic plasticity) enables females and hermaphrodites to have different lifespans despite being genetically identical (A. P. da Silva, unpublished observation). Intralocus SC might play a pervasive role in shaping lifespan and aging in these cases, if the same allele expressed in either sex gives rise to conflicting outcomes owing to sex-specific optima in lifespan and reproductive strategy. Ultimately, to determine whether intralocus SC is occurring, both the presence of sex-specific selection on a trait, and an indication that independent evolution of the trait is constrained by intersexual genetic correlations are required [70].

3.4. Learning performance and sex-specific lifespan

Learning and memory are costly traits. Several studies have reported genetic correlations between these and other life-history traits, including lifespan. Moreover, memory and cognition are themselves significant parameters of aging with particular relevance to human populations. In *Drosophila,* populations selected for higher ability to learn became shorter lived and less fecund late in life, whilst selecting populations for extended lifespan reduced early-life learning ability relative to controls [84], suggesting an evolutionary trade-off. Studies in nematodes also indicate that learning ability and lifespan may co-vary, sometimes in a sex-specific way. *Caenorhabditis* nematodes are capable of forming short and long-term memories in both associative and non-associative paradigms [85]. Females of *C. remanei,* the shorter-lived sex, were found to be better able to form associative memories than males early in life [85], but by day 5 of adulthood their learning performance had deteriorated more dramatically than that of males. However, in a subsequent study, males outperformed both young and old females in olfactory learning [25], likely due to differences in culture conditions between the studies. In a different associative learning paradigm, hermaphrodites of *C. elegans* displayed a higher ability to associate salt with starvation in early life than longer-lived males. Long-lived *daf-2* and *age-1* mutants with decreased insulin/IGF-1 showed impaired learning ability compared with that of wild-type, whereas hyperactivation of this pathway enhanced learning ability [86]. However, selection of *C. remanei* females for poor learning performance in an experimental evolution study led to reduced virgin female lifespan compared to upward-selected lines [25], demonstrating that the relationship between these parameters is not a simple trade-off. Interestingly, the lifespan of virgin males

in these lines was increased, reversing the usual pattern of sexual dimorphism in this species. These studies demonstrate that selection on a complex trait can entail rapid evolution of sex-specific life histories. The identification of intersexual genetic correlations further raises the possibility that intralocus SC related to learning performance may act to shape the evolution of correlated traits.

4. Asymmetric inheritance of genetic material

Alongside theories centered on sex-specific selection, more mechanistic explanations propose that mal-adaptation arising from asymmetric inheritance of the X chromosome and mitochondria explains putative male-biased aging. In most species the mitochondria are inherited solely from the mother. Therefore, mutations in mitochondrial genomes will only be subject to selection acting on females [87], allowing male-detrimental mutations to accumulate if the cost to females is low or nonexistent [7]. Males might therefore be expected to inherit a mitochondrial genome that interacts sub-optimally with their nuclear genome, leading to accelerated aging compared to females [88], known as the 'mother's curse' hypothesis. However, maternal inheritance of mitochondria has been confirmed in *C. elegans*, in which males outlive hermaphrodites [89]. In other taxa, a limited number of studies have sought to define the generality of mother's curse in lifespan evolution. It is notable that female-biased longevity is seen in some taxa with maternal inheritance of mitochondria (such as birds). Similarly, as males are usually the heterogametic sex, they carry the burden of deleterious recessive mutations on the X chromosome, which are not 'guarded' by the second chromosome [7]. The 'unguarded X' hypothesis postulates that such detrimental mutations may contribute to accelerated aging in males. Sex determination in nematodes is usually chromosomal. Typically, XX animals become females/hermaphrodites, while those with a Y chromosome or a single X (XO) develop as males. The molecular basis of sex determination can vary greatly between phyla, but in *C. elegans* the process is signaled by the ratio of X chromosomes to the autosome set [90]. Consistent with optimization of the X chromosome for hermaphrodites, the *C. elegans* X chromosome is depleted of sperm-enriched genes [91, 92]. Additionally, a trend of enrichment for genes with high female-biased expression and depletion of those with male-biased expression is apparent on nematode X chromosomes [93]. However, empirical support for a role of unguarded X mechanisms in sex-specific aging patterns is lacking in nematodes, and limited in other taxa [94]. Whilst maladaptation to X likely contributes to aging patterns in nematodes, its general importance is contentious; XO males live shorter

than females in *C. briggsae*, while in *Oscheius*, *C. elegans* and *C. remanei* the XO males live longer [12]. Most studies have been performed in XX/XO species, and no ZZ/ZW nematodes are currently known to further test this hypothesis. Interestingly, it may be possible to find examples in nematodes where the X chromosome or mitochondria have become adapted for the male sex. Male cross-progeny of the trioecious nematode *Rhabditis* sp. SB347 inherit the X chromosome from their father [95], raising the question of what proportion of genes on the X are expressed in males. Whether the mitochondria in SB347 males are inherited maternally or paternally is not currently known, but paternal mitochondrial inheritance can occur in *C. briggsae* [96]. *C. briggsae* is a genetically tractable species that could aid in clarifying the relevance of asymmetric inheritance for patterns of senescence. Overall, it seems that nematode systems have been underexploited for addressing the role of both mother's curse and unguarded X in sex-specific aging patterns.

5. Natural variation and aging

Although genetic, pharmacological and dietary interventions have provided insight into the pathways involved in age-related degeneration, their relevance in natural populations is less apparent. In order to understand how long-lived hermaphrodite mutants of *C. elegans* (as well as mutants of *D. melanogaster* and mice) fare when conditions more closely approximate the natural environment, their lifespan in challenging environments (e.g. exposure to pathogens, food competition) and standard laboratory environments has been compared to that of wild-type controls. A review of these studies found that most reported reduced lifespan of long-lived mutants in challenging environments, with the wild type outliving the mutant in a number of cases [19]. Similarly, in these environments the frequency of long-lived mutants either decreased or did not change compared to that of wild type controls [19]. For example, *C. elegans age-1(hx546)* and *daf-2*(*e1368*) mutants subjected to laboratory natural selection dramatically declined in frequency in environments with cyclical starvation [97, 98]. It should be noted that in one study in which populations were exposed to periodic temperature stress, *age-1(hx546)* mutants were at a selective disadvantage to N2 only when food was limited, but had higher fitness when food was freely available [99]. Although there is clearly complexity, these studies broadly reveal fitness costs of extended lifespan under stressful conditions. This is consistent with the idea that their extended lifespan in the laboratory depends on resources being diverted to the soma that would normally be invested into processes that improve fitness in natural environments [19]. In this case, the

mechanisms that extend lifespan in these mutants, and which contribute to the sex-specific aging effects of certain mutations, might have limited relevance for understanding aging differences in natural populations. These studies also highlight how sex-dependent resource investment is likely to shift with environmental fluctuations, altering observed patterns of sexual dimorphism in lifespan and aging. An alternative to the use of mutant screens for understanding the genetic variants controlling aging is experimental laboratory evolution, although these studies can only provide proof of concept [100].

Such limitations may be difficult to address using nematode systems, largely owing to the impracticality of ecological studies in nematodes. However, subjecting experimental populations to more ecologically-relevant interventions will greatly aid understanding of sexual dimorphism in aging, and therefore the mechanisms that operate in natural populations [19, 70]. In combination with this approach, our understanding of the natural genetic variants controlling lifespan and health must be improved by studying genetically heterogeneous nematode populations that differ in these traits. Unlike *C. elegans, C. remanei* is a promising system for this approach because it has significant levels of natural genetic variation and low linkage disequilibrium [101]. Research in *Pristionchus* has unveiled substantial lifespan variability within the *P. pacificus* species complex [13], and hybrid crosses between these species have begun to uncover the genetic variants underlying interspecific lifespan variation in natural populations [16]. Pronounced lifespan heterosis was observed in F1 hybrids, implicating recessive loci that are masked in hybrid genomes in the relatively short lifespan of *P. pacificus* hermaphrodites and *P. arcanus* females. These studies also demonstrate that the magnitude of sexually dimorphic lifespan is highly evolvable – *P. arcanus,* a close relative of *P. exspectatus* in which females substantially outlive males, has no sex difference in lifespan [13]. The complexity and natural replication within *Pristionchus* make this an exciting system for comparative studies of sex-specific lifespan and aging.

6. Conclusion and outlook

Studies in nematodes have demonstrated that sexually dimorphic lifespan patterns can be rapidly altered or even reversed by selection on complex traits including learning ability, heat-shock resistance and mate-searching proficiency under laboratory conditions. Analysis of natural variation similarly indicates that sex-specific lifespan patterns can evolve rapidly. One implication of this research is that

evolutionary explanations for sexual dimorphism in lifespan and aging that are based on differential selection might ultimately prove more informative than those that focus on asymmetric inheritance of genetic material. The molecular and genetic factors that are important for sex-specific aging patterns are only beginning to be uncovered. Future work must focus on senescence as opposed to lifespan alone, with a greater appreciation of differences in demographic aging between the sexes. Additionally, more complex genotype-by-environment interactions in challenging environments must be considered before genetic, pharmacological and dietary manipulations can be said to be of relevance in a natural setting. For example, *C. elegans* hermaphrodites are receptive to male pheromones secreted by other nematode species, which can delay reproductive senescence [73]. Therefore, although males of *C. elegans* are rare, it seems plausible that males of other species can influence hermaphrodite aging. Such approaches will help to test the generality of evolutionary and mechanistic hypotheses for sex-specific lifespan and aging [95].

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Table 1
Summary of key insights into sex differences in lifespan gained from nematode species

Genus/ key species	Mating system	Longer-lived sex (Unmated solitary nematodes)	Key insights
Caenorhabditis			• Intra/intersexual interactions (e.g. mating) can alter sex biases in longevity [1, 2]. • Longer lifespan can evolve under high rates of extrinsic mortality if survival is condition-dependent [3]. • Sexually dimorphic lifespan can evolve rapidly through sex-limited mortality [4] or sex-specific trade-offs with learning ability [5] (insight from laboratory evolution). • Genetic variation for lifespan can be maintained by sexually antagonistic selection on shared loci [6].
C. elegans	Androdioecy	M [7]	
C. remanei	Dioecy	M [7]	
Pristionchus			• Sexually dimorphic lifespans can evolve rapidly (insight from comparative approaches) [8]. • Transitions to androdioecious mating systems have driven sex differences in lifespan [8].
P. pacificus	Androdioecy	NA [8]	
P. exspectatus	Dioecy	F [8]	
P. arcanus	Dioecy	No difference [8]	

F = female; M = male.

[1] D. Gems, D.L. Riddle, Genetic, behavioral and environmental determinants of male longevity in *Caenorhabditis elegans*, Genetics 154(4) (2000) 1597-610.
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