Parental lifespan extension improves offspring fitness

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Abstract

Classical theory maintains that ageing evolves via energy trade-offs between reproduction and survival leading to accumulation of unrepaired cellular damage with age. In contrast, the emerging new theory postulates that ageing evolves because of deleterious late-life hyper-function of reproduction-promoting genes leading to excessive biosynthesis in late-life. The hyper-function theory uniquely predicts that optimizing nutrient-sensing molecular signalling in adulthood can simultaneously postpone ageing and increase Darwinian fitness. Here we show that reducing evolutionarily conserved insulin/IGF-1 nutrient-sensing signalling via *daf-2* RNA interference (RNAi) fulfils this prediction in *Caenorhabditis elegans* nematodes. Long-lived *daf-2* RNAi parents showed normal fecundity as self-fertilizing hermaphrodites and improved late-life reproduction when mated to males. Remarkably, the offspring of *daf-2* RNAi parents had higher Darwinian fitness across three different genotypes. Thus, reduced nutrient-sensing signalling in adulthood improves both parental longevity and offspring quality supporting the emerging view that sub-optimal gene expression in late-life lies at the heart of ageing.

Introduction

The long-standing paradigm, the "disposable soma" theory of ageing, postulates that ageing results from competitive energy allocation between somatic maintenance and reproduction leading to slow accumulation of unrepaired cellular damage with age [1-3]. However, this paradigm has suffered several setbacks in recent years, with many empirical studies challenging the importance of energy trade-offs in organismal senescence [reviewed in 4, 5-9]. Instead, several authors proposed that ageing can result from molecular signalling networks being optimized for development, growth and early-life reproduction rather than for late-life reproduction and longevity [6, 10-15]. Specifically, downregulation of evolutionarily conserved nutrient-sensing signalling pathways that govern biosynthesis in response to nutrient availability can achieve increased longevity without a concomitant decrease in reproduction in model organisms [8, 10, 16]. The emerging "hyper-function" theory of ageing maintains that ageing is driven by excessive nutrient-sensing molecular signalling in late-life, which results in cellular hypertrophy leading to age-related pathologies [6, 11-15]. These ideas can be traced back to George Williams, who suggested that the same physiological processes that are beneficial for early-life fitness can become detrimental in late-life because of the reduced strength of natural selection on late-life function [17].

Because the main cost of longevity appears to be associated with reduced early-life function, it seems plausible that age-specific modification of gene expression can potentially circumvent this problem. In their landmark study, Dillin et al. (2002) used age-specific RNA interference (RNAi) approach to knock down *daf-2* gene expression in *Caenorhabditis elegans* nematodes across the life cycle of the worms. While early-life feeding with bacteria expressing *daf-2* double-stranded RNA resulted in reduced early-life reproduction, there was

no detrimental effect of *daf-2* RNAi in adult worms, which enjoyed two-fold lifespan extension without any cost to reproduction [10]. Nevertheless, while this study provided a powerful example for the cost-free lifespan extension, it is possible that key fitness costs were overlooked. One possibility is that fecundity costs become apparent only in mated hermaphrodites. In nature, *C. elegans* live in populations with small (~0.3%) yet appreciable number of males living among self-fertilising hermaphrodites with sometimes high levels of outcrossing [18], and mating, as well as mere presence of male-derived pheromones, has pronounced effects of the life-history of hermaphrodites [19-21]. Perhaps more importantly, it is possible that while fecundity is not affected, the fitness of the offspring and, therefore, Darwinian fitness of the parents, are compromised. The trade-off between offspring number and quality is well known from a number of study systems [22], and is a potential explanation for the apparent lack of fitness costs in the previous studies. To investigate this possibility, we need to understand how late-life reduction in nutrient-sensing signalling affects longevity, offspring number and offspring quality. Here we show that *daf-2* RNAi in adult *C. elegans* results in increased parental longevity, increased parental investment, and offspring fitness across three genetic backgrounds. We discuss these findings in the light of the emerging new theories of ageing and suggest that they support the hypothesis that suboptimal gene expression in late-life shapes the evolution of ageing.

Results

First off, we confirmed that *daf-2* RNAi significantly extended the lifespan of unmated N2 wild-type hermaphrodite worms (censoring matricide: $z = -4.94$, $df = 1$, $p < 0.001$, Fig. 1A; including matricide as dead: $z = -4.97$, $df = 1$, $p < 0.001$), as expected from previous studies [10]. In addition, for mated N2, *daf-2* RNAi extended lifespan when matricide was censored

84 (z = -2.42, df = 1, p = 0.016, Fig. 1B) but not if matricidal worms were included as dead (z =
85 0.16, df = 1, p = 0.87) because of an increase in matricide in the late reproducing mated *daf-2*
86 RNAi N2.

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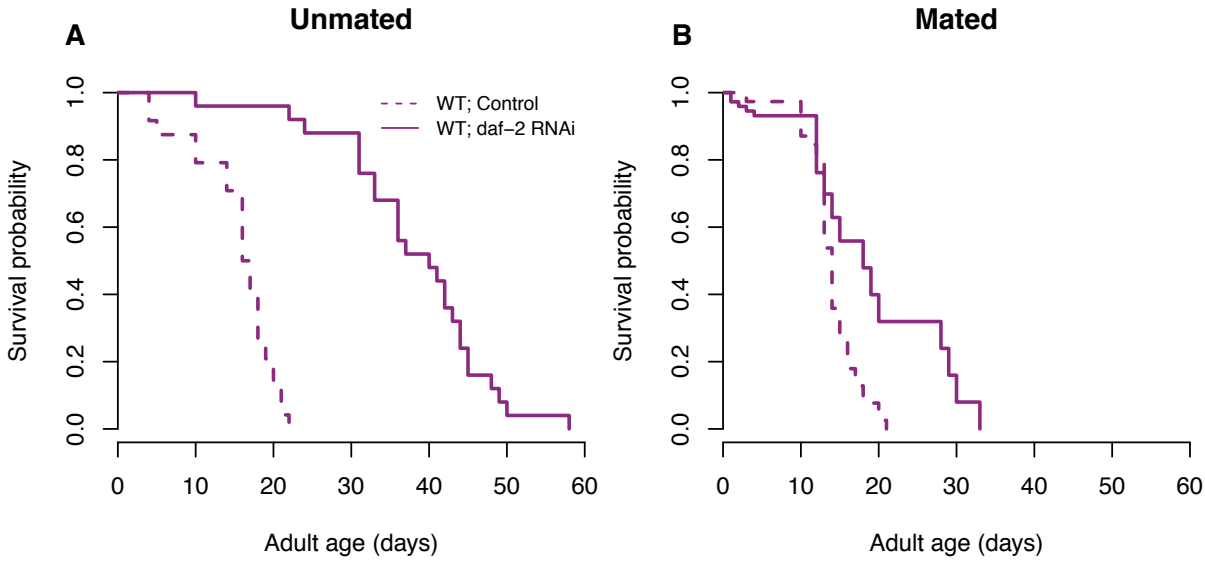

88
89 **Fig. 1. The effect of *daf-2* RNAi on lifespan.** Survival probability for (**A**) unmated or (**B**)
90 mated N2 wild-type worms, treated with either *daf-2* RNAi (solid lines) or control empty
91 vector (broken lines) from adulthood onwards.

92

93 We did not find any effect of *daf-2* RNAi on total reproduction (unmated: F = 0.32, df = 1, p
94 = 0.58; mated: $\chi^2 = 1.11$, df = 1, p = 0.29) or individual fitness λ_{ind} (unmated: F = 0.30, df = 1,
95 p = 0.59; mated: $\chi^2 = 0.43$, df = 1, p = 0.51) for neither unmated nor mated N2 (Table 1, Fig.
96 2). However, *daf-2* RNAi had a positive effect on late (day 5+) reproduction for mated
97 hermaphrodites ($\chi^2 = 24.76$, df = 1, p <0.001, Fig. 2B).

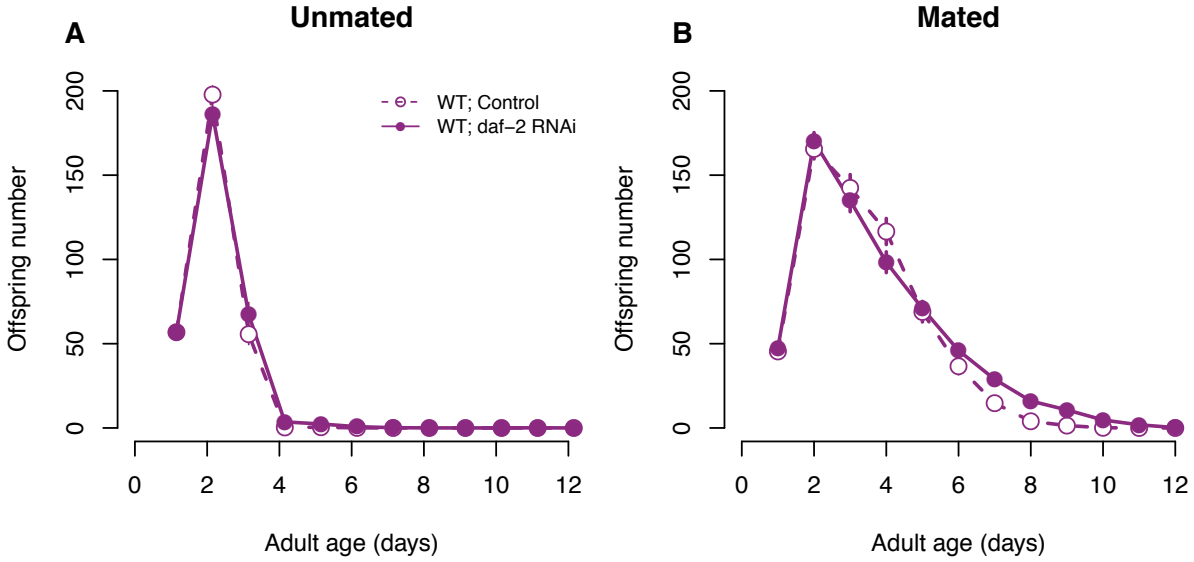

Fig. 2. The effect of *daf-2* RNAi on reproduction. Daily offspring number for (**A**) unmated or (**B**) mated N2 wild-type worms, treated with either *daf-2* RNAi (solid lines, filled symbols) or control empty vector (broken lines, open symbols) from adulthood onwards. Symbols represent mean ± SE.

Table 1. The effect of daf-2 RNAi on reproduction. Total reproduction and individual fitness (λ_{ind}) for unmated and mated *C. elegans* N2 wild-type treated with either empty vector (Control) or *daf-2* RNAi from adulthood onwards. All values expressed as mean ± SE.

	Total reproduction		Fitness (λ_{ind})	
RNAi treatment	unmated	mated	unmated	mated
Control	311.0 ± 7.0	595.7 ± 24.3	4.66 ± 0.03	4.47 ± 0.05
daf-2 RNAi	317.4 ± 8.9	630.5 ± 22.2	4.63 ± 0.05	4.50 ± 0.05

In a second experiment, using unmated hermaphrodites only, we investigated the effect of *daf-2* RNAi on parent lifespan and offspring lifespan and reproduction across three genetic backgrounds (N2 wild-type and the mutants *ppw-1* and *rrf-1*, that are deficient for germline

and somatic RNAi, respectively). Parental treatment with *daf-2* RNAi increased lifespan across all genetic backgrounds, both when matricide was censored (treatment: $\chi^2 = 90.39$, df = 1, p <0.001; strain: $\chi^2 = 21.8$, df = 2, p <0.001; treatment × strain: $\chi^2 = 10.46$, df = 2, p = 0.005, Fig. 3A) and included as dead (treatment: $\chi^2 = 85.25$, df = 1, p <0.001; strain: $\chi^2 = 20.45$, df = 2, p <0.001; treatment × strain: $\chi^2 = 9.43$, df = 2, p = 0.009). In accordance with previously published research [23], parental *daf-2* RNAi increased egg size (treatment: $\chi^2 = 5.11$, df = 1, p =0.024; strain: $\chi^2 = 13.89$, df = 2, p <0.001; treatment × strain: $\chi^2 = 2.68$, df = 2, p = 0.262, Fig. 3B). However, we found that the effect was most pronounced in N2 wildtype worms, and relatively weak in both somatic and germline *daf-2* knockdown (see Fig. 3B), suggesting that *daf-2* knockdown in both somatic and reproductive tissues is required to maximize the effect on egg size.

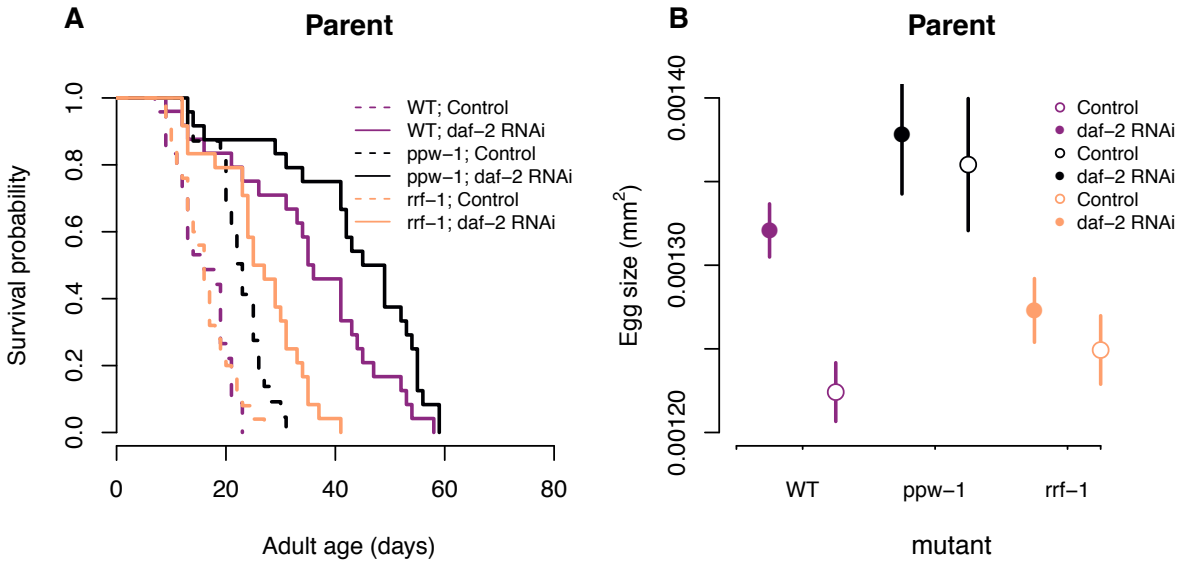

Fig. 3. The effect of *daf-2* RNAi on survival and egg size. Parental worms, unmated, exposed to RNAi treatment. (**A**) Survival probability and (**B**) egg size of N2 wild-type (purple), *ppw-1* (black) and *rrf-1* (orange) mutants, treated with either *daf-2* RNAi (solid lines, filled symbols) or control empty vector (broken lines, open symbols) from adulthood onwards. Symbols represent mean ± SE.

129 Parental *daf-2* RNAi treatment did not, however, influence the lifespan of their offspring,
130 neither when matricidal worms were censored (treatment: $\chi^2 = 0.04$, df = 1, p = 0.85; strain:
131 $\chi^2 = 24.2$, df = 2, p <0.001; treatment × strain: $\chi^2 = 0.61$, df = 2, p = 0.74, Fig. 4A) nor when
132 included as dead (treatment: $\chi^2 = 0.01$, df = 1, p = 0.92; strain: $\chi^2 = 21.8$, df = 2, p <0.001;
133 treatment × strain: $\chi^2 = 0.48$, df = 2, p = 0.79).

134

135 In contrast, parental *daf-2* RNAi treatment significantly increased offspring total reproduction
136 (treatment: F = 15.9, df = 1, p <0.001; strain: F = 33.7, df = 2, p <0.001; treatment × strain: F
137 = 0.09, df = 2, p = 0.91, Fig. 4B-C) and individual fitness λ_{ind} (treatment: F = 11.8, df = 1, p
138 <0.001; strain: F = 13.1, df = 2, p <0.001; treatment × strain: F = 0.18, df = 2, p = 0.84, Fig.
139 4D) across all genetic backgrounds. Importantly, there was no correlation between the effect
140 of parental *daf-2* RNAi on egg size (see above) and offspring total reproduction / individual
141 fitness, suggesting that factors beyond the amount of resources in the egg contribute to
142 increased fitness of offspring of *daf-2* RNAi parents.

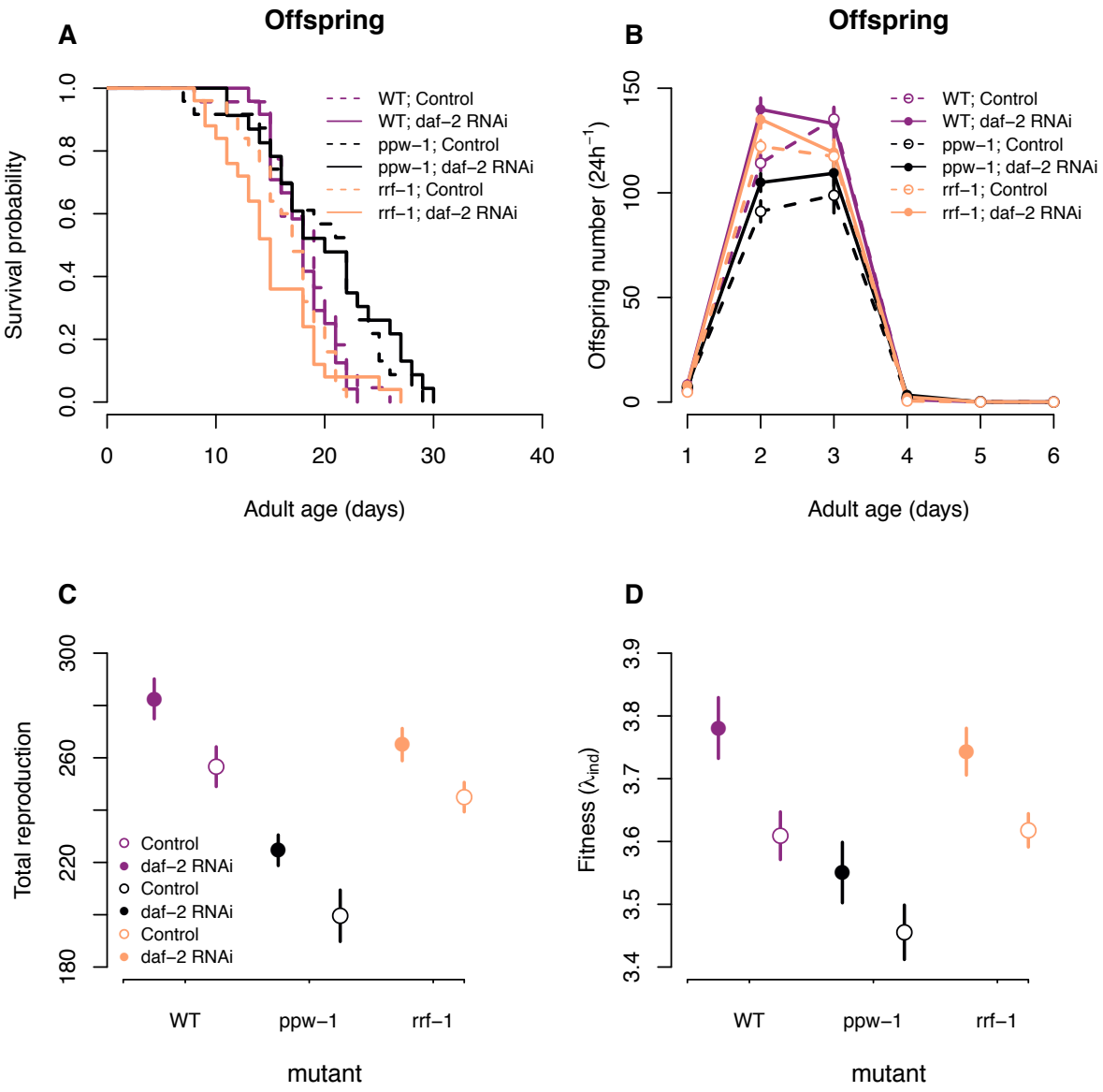

Fig. 4. The effect of parental *daf-2* RNAi on offspring survival and reproduction.

Offspring worms, unmated, on control (empty vector) plates from parents exposed to *daf-2* RNAi or control treatment. (**A**) Survival probability, (**B**) daily offspring number, (**C**) Total reproduction and (**D**) individual fitness (λ_{ind}) of offspring (on control plates) from parents either exposed to *daf-2* RNAi (solid lines, filled symbols) or control empty vector (broken lines, open symbols). The colors reflect N2 wild-type (purple), *ppw-1* (black) and *rrf-1* (orange) mutants. Symbols represent mean ± SE.

Discussion

The "disposable soma" theory of ageing proposes that energy allocation between key life-history traits, such as growth, reproduction and somatic maintenance [1, 24] drive the evolution of ageing. This theory predicts that genetic and environmental manipulations that increase energy allocation to somatic maintenance will result in detrimental effects to growth and reproduction. This is why the findings by Dillin et al. (2002), which suggested that adult-only downregulation of insulin/IGF-1 by *daf-2* RNAi can substantially increase lifespan without any detrimental effect to reproduction, were subsequently scrutinized in an attempt to find the hidden costs of longevity [25, 26]. Nonetheless, both the original findings [10] and our results here, suggest that adult-only *daf-2* RNAi can more than double longevity without any negative effect on reproduction. Moreover, when supplied with sperm from males, *daf-2* RNAi-treated parents have improved fecundity in late-life. It is possible, however, that treatments that improve parental performance have negative effects on their offspring. The trade-off between offspring number and offspring quality is a well known concept in life-history evolution [22] but is rarely considered in biogerontological research [reviewed in 7]. Germline maintenance is costly [7, 27, 28], and increased investment into somatic maintenance can, in theory, result in increased mutation rate and reduced fitness of progeny. Alternatively, it is possible that instead of energy trade-offs, the evolution of senescence is governed by functional trade-offs. Functional trade-offs can occur because the physiological requirements of a young organism can differ substantially from those of a mature one [17]. In his classic 1957 paper, George Williams [17] described a hypothetical example of a mutation that positively affects bone calcification in a developing young organism but increases calcification of the connective tissues of arteries in a mature one with detrimental consequences. More recently, it has been suggested that nutrient sensing IIS/TOR molecular signalling pathways that govern growth and development result in excessive biosynthesis in

late-life leading to different pathologies and increased mortality [6, 11, 13, 15]. These proximate explanations rest on the fundamental assumption that the strength of natural selection declines with age because of environmental mortality from a range of biotic and abiotic hazards (e.g. predation, pathogens, competition, starvation) [17]. Because of such environmental mortality, immediate reproduction is more valuable than future reproduction, and optimizing development, growth and early-life reproduction is more important for organismal fitness that optimizing late-life survival and reproduction [17, 29]. Thus, the weak natural selection in late-life may result in suboptimal levels of IIS/TOR signalling leading to pathology and senescence [13].

Here we found that reduced insulin/IGF-1 signalling in adult worms not only improved longevity and late-life reproduction, but also increased reproduction and Darwinian fitness of the resulting offspring in three different genetic backgrounds. This result contradicts the hypothesis that improved longevity and postponed ageing of *daf-2* RNAi parents comes at the cost of offspring fitness. Instead, our findings are in line with the hypothesis that suboptimal levels of nutrient-sensing signalling in adult life accelerate ageing, curtail lifespan and reduce individual fitness. This result was not caused by direct inheritance of *daf-2* RNAi, since we did not recover the lifespan extension effect of *daf-2* knockdown in these offspring. Because previous research found that both dietary restriction and reduction in insulin-like signalling by *daf-2* RNAi knockdown increased embryo size in *C. elegans* nematodes [23], we replicated these results to test whether increased fitness of adult progeny results from increased resource allocation to eggs by *daf-2* RNAi mothers. While *daf-2* knockdown increased egg size to a different degree in N2, *ppw-1* and *rrf-1* strains, there was no correlation between the effect of parental *daf-2* RNAi on egg size and offspring reproductive performance. We provisionally conclude that increased egg size under reduced maternal

insulin-like signalling can contribute to increased offspring fitness, but it is likely not the sole source of variation in this trait. Future studies should aim to disentangle the relative importance of energy allocation trade-offs versus suboptimal late-life gene expression in the evolution of ageing.

Materials and Methods

Strains

We used the *Caenorhabditis elegans* strains Bristol N2 wild-type (Brenner, Genetics 1974), as well as the mutants *ppw-1(pk2505)* and *rrf-1(pk1417)*, obtained from Caenorhabditis Genetics Center (CGC, Missouri, USA).

Maintenance

Before each assay, worms were recovered from freezing and synchronised by bleaching for two generations to remove any freezing effects. The nematode populations were maintained at 20°C and 60% relative humidity in an environmental test chamber. For regular maintenance, the worms were kept on NGM agar supplemented with the antibiotics streptomycin, kanamycin and nystatin (following Lionaki & Tavernarakis [30]), seeded with the antibiotic-resistant *E. coli* strain OP50-1 (pUC4K).

Outline of the study

The study was run in three separate experiments. In the first experiment, we investigated lifespan and reproduction of mated and unmated N2 hermaphrodites reared from sexual maturity onwards on *daf-2* RNAi or empty vector (EV, control) plates. For logistic reasons, this experiment was conducted in two blocks for mated worms and one block for unmated worms. In the second experiment, we investigated the lifespan and egg size of unmated N2, *rrf-1(pk1417)* and *ppw-1(pk2505)* hermaphrodites on raised from sexual maturity onwards on *daf-2* RNAi or EV plates. In a separate experiment, we collected one egg from each parent at their second day of adulthood (from *daf-2* RNAi and EV treatments) and investigated the lifespan and reproduction of these offspring on control plates. Because different experiments differed in setup time, daily reproduction values (and calculations based upon these, such as λ_{ind}) are only meaningful for comparison between treatments within each experiment.

RNAi

RNase-III deficient, IPTG-inducible HT115 *Escherichia coli* bacteria with empty plasmid vector (L4440) was used as control [31] and the same HT115 bacteria with *daf-2* RNAi construct from the Vidal library was used as RNAi treatment. RNAi treatment started from sexual maturity, and continued until the death of the individual. During the experiments, worms were maintained on 35 mm NGM agar plates (supplemented with 1 mM IPTG and 50 µg/ml ampicillin) seeded with 0.1 ml L4440 empty vector control or *daf-2* bacteria grown in LB supplemented with 50 µg/ml ampicillin for 16-20 hours and seeded (incubated) on the NGM agar plates again for 24 hours (following Hinas et al. [32]).

Lifespan Assays

Lifespan assays were set up for all treatment combinations described above. In the lifespan assays, the individual age-synchronised L4 worms were placed on separate 35 mm plates and the plates were checked daily to record any instances of death. The surviving worms were moved to new plates daily until their death. Fertile worms, which showed odd developmental characteristics and low offspring numbers (<36 offspring), were excluded from the final analysis (3 mated control worms and 7 mated *daf-2* worms).

Reproduction assays

Offspring production was scored in the reproduction assays using the same worms as those scored for lifespan, except for the parental N2, *ppw-1* and *rrf-1* worms in the second experiment, where only lifespan was recorded. Unmated individual hermaphrodites were moved to new plates daily and scored for offspring produced 2.5 days later. In the "mated" treatment, two male *C. elegans* (from the initial sample population of N2 strain) were placed on a plate with a single hermaphrodite for two hours every day to allow time for mating. Offspring production was scored 2.5 days later, as in the "unmated" treatment.

Egg size assays

Egg size was measured in N2, *ppw-1* and *rrf-1* strains (unmated hermpahrodites) growing on either *daf-2* RNAi or empty vector (EV) plates. Two days after maturation, worms were placed individually on new plates and observed continually during five hours for the presence of newly laid eggs, of which the first two eggs were collected. Eggs were picked immediately after laying and placed under a Leica M165C microscope set on 12x magnification; photos

were taken using a Lumenera Infinity 2-6C digital microscope camera. Egg size was analysed from photos using *ImageJ* (https://imagej.nih.gov/ij/). Only eggs laid during gastrulation stage (the normal developmental stage at egg laying) were included in the analyses.

Statistical analyses

Survival was analysed for each experiment in Cox proportional hazard models in *R 3.3.3*. Mated (EV: n=72, *daf-2* n=68) and unmated (n=25 per treatment) individuals were analysed separately, as they were run in different blocks. Unmated individuals were analysed using the *coxph* function in the package *survival*, with *daf-2* RNAi treatment as a fixed factor. For mated individuals, we used the *coxme* package in order to fit block as a random effect, in addition to the fixed effect of RNAi treatment. In the second experiment (n=25 per treatment), in addition to RNAi treatment, we also fitted the fixed factor strain (N2, *ppw-1*, *rrf-1*) and its interaction with treatment using the *coxph* function in the *survival* package.

Reproduction was analysed as total reproduction as well as rate-sensitive individual fitness λ_{ind}, which encompasses the timing and number of offspring [33, 34]. λ_{ind} is estimated by solving the Euler-Lotka equation for each individual using the *lambda* function in the *popbio* package and is analogous to the intrinsic rate of population growth (Stearns 1992). For all unmated worms (n=25 per treatment), we estimated the fixed effect of treatment (*daf-2* RNAi or empty vector). For offspring of the three mutants (n=25 per treatment), we also estimated the fixed effect or strain, using linear models. For the mated worms (EV: n=72, *daf-2* n=68), we also estimated the random effect of block, in addition to RNAi treatment. These models were implemented as mixed effect models using the *lme4* package in *R 3.3.3*, and chi-square tests of fixed effects were performed using the *car* package. Egg size was analysed in a mixed effect model in *lme4*, treating strain and RNAi treatment as crossed fixed effects, and

295 parent ID as well as block as random effects. We obtained the following n: N2 on EV: 56, N2
296 on *daf-2*: 54, *ppw-1* on EV: 44, *ppw-1* on *daf-2*: 42, *rrf-1* on EV: 59, *rrf-1* on *daf-2*: 42.

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Author contributions

MIL and AAM designed the study, with the aid of AH. SR, ZS, MIL and HC collected the data, MIL analysed the data, MIL and AAM drafted the manuscript. All authors contributed to the revision of the manuscript.

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Competing interests

The authors declare no competing interests.

Data archiving

Upon acceptance, the data will be archived at Dryad.