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.

36 **Introduction**

37 The long-standing paradigm, the "disposable soma" theory of ageing, postulates that ageing
38 results from competitive energy allocation between somatic maintenance and reproduction
39 leading to slow accumulation of unrepaired cellular damage with age [1-3]. However, this
40 paradigm has suffered several setbacks in recent years, with many empirical studies
41 challenging the importance of energy trade-offs in organismal senescence [reviewed in 4, 5-
42 9]. Instead, several authors proposed that ageing can result from molecular signalling
43 networks being optimized for development, growth and early-life reproduction rather than for
44 late-life reproduction and longevity [6, 10-15]. Specifically, downregulation of evolutionarily
45 conserved nutrient-sensing signalling pathways that govern biosynthesis in response to
46 nutrient availability can achieve increased longevity without a concomitant decrease in
47 reproduction in model organisms [8, 10, 16]. The emerging "hyper-function" theory of
48 ageing maintains that ageing is driven by excessive nutrient-sensing molecular signalling in
49 late-life, which results in cellular hypertrophy leading to age-related pathologies [6, 11-15].
50 These ideas can be traced back to George Williams, who suggested that the same
51 physiological processes that are beneficial for early-life fitness can become detrimental in
52 late-life because of the reduced strength of natural selection on late-life function [17].

53

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

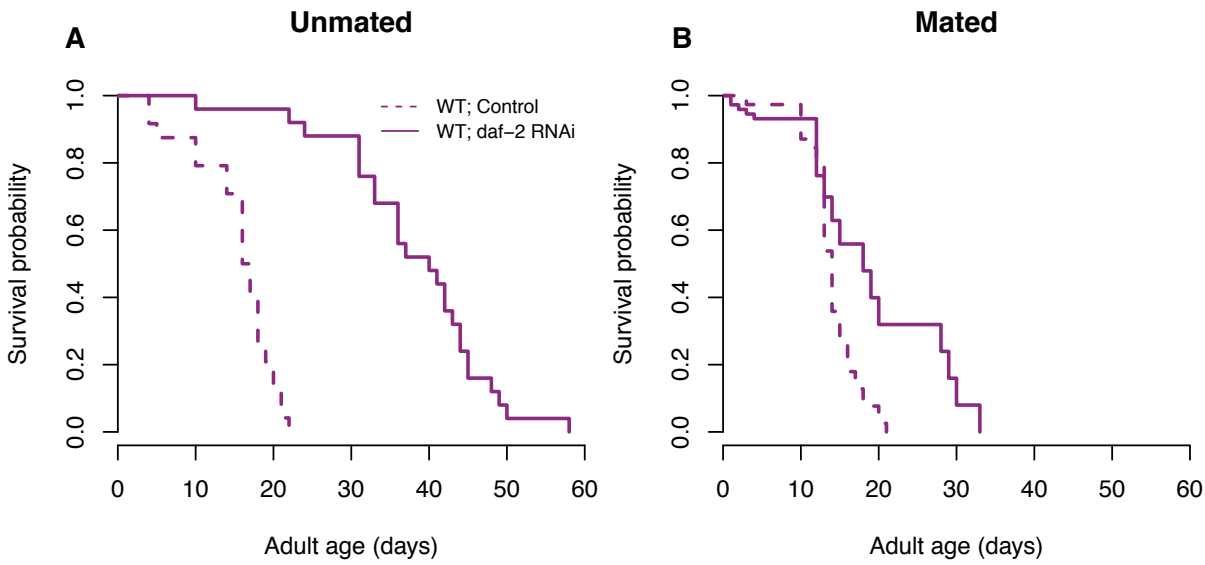
no detrimental effect of *daf-2* RNAi in adult worms, which enjoyed two-fold lifespan extension without any cost to reproduction [10]. Nevertheless, while this study provided a powerful example for the cost-free lifespan extension, it is possible that key fitness costs were overlooked. One possibility 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.

87



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: χ^2 = 1.11, df = 1, p = 0.29) or individual fitness λ_{ind} (unmated: F = 0.30, df = 1,
95 p = 0.59; mated: χ^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 (χ^2 = 24.76, df = 1, p <0.001, Fig. 2B).

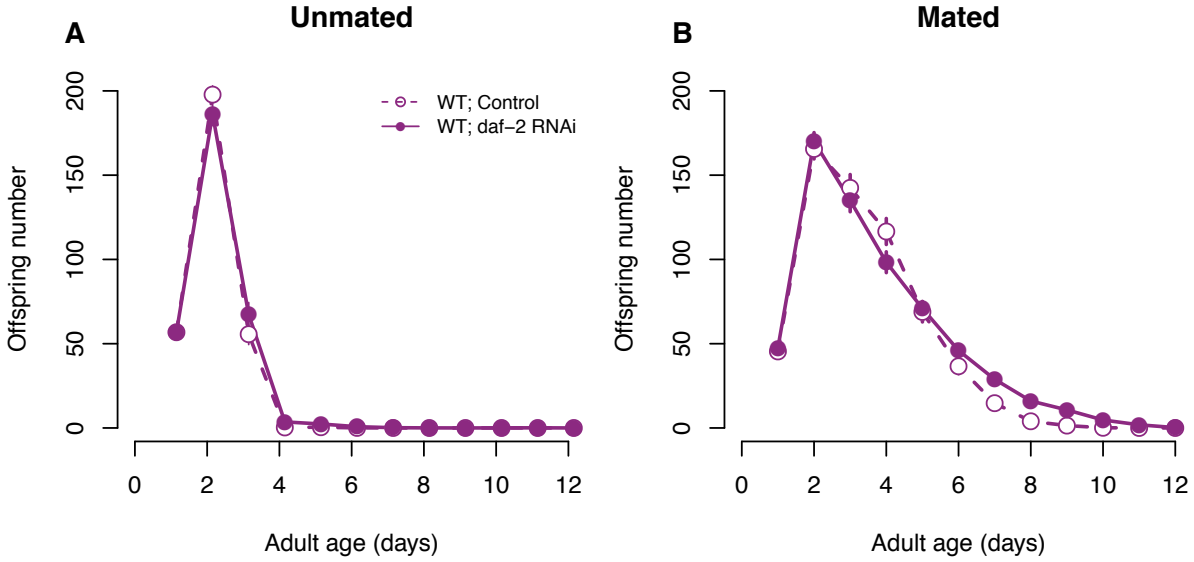


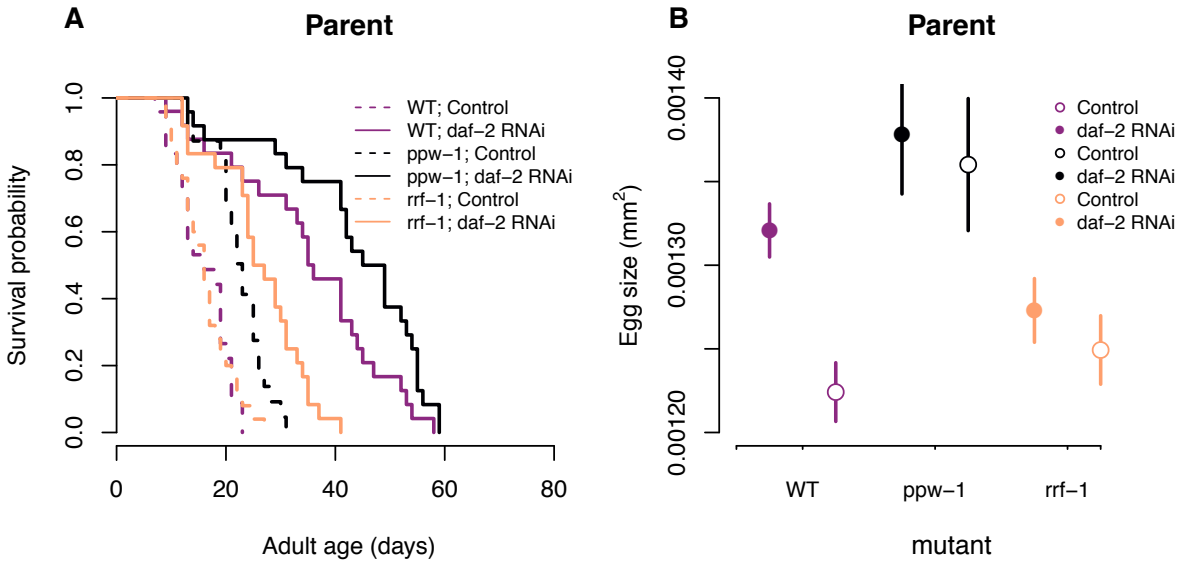
Fig. 2. The effect of *daf-2* RNAi on reproduction. Daily offspring number for (**A**) unmated or (**B**) mated N2 wild-type worms, treated with either *daf-2* RNAi (solid lines, filled symbols) or control empty vector (broken lines, open symbols) from adulthood onwards. Symbols represent mean ± SE.

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

111 and somatic RNAi, respectively). Parental treatment with *daf-2* RNAi increased lifespan
112 across all genetic backgrounds, both when matricide was censored (treatment: $\chi^2 = 90.39$, df
113 = 1, p <0.001; strain: $\chi^2 = 21.8$, df = 2, p <0.001; treatment × strain: $\chi^2 = 10.46$, df = 2, p =
114 0.005, Fig. 3A) and included as dead (treatment: $\chi^2 = 85.25$, df = 1, p <0.001; strain: $\chi^2 =$
115 20.45, df = 2, p <0.001; treatment × strain: $\chi^2 = 9.43$, df = 2, p = 0.009). In accordance with
116 previously published research [23], parental *daf-2* RNAi increased egg size (treatment: $\chi^2 =$
117 5.11, df = 1, p =0.024; strain: $\chi^2 = 13.89$, df = 2, p <0.001; treatment × strain: $\chi^2 = 2.68$, df =
118 2, p = 0.262, Fig. 3B). However, we found that the effect was most pronounced in N2
119 wildtype worms, and relatively weak in both somatic and germline *daf-2* knockdown (see
120 Fig. 3B), suggesting that *daf-2* knockdown in both somatic and reproductive tissues is
121 required to maximize the effect on egg size.



122
123 **Fig. 3. The effect of *daf-2* RNAi on survival and egg size.** Parental worms, unmated,
124 exposed to RNAi treatment. (**A**) Survival probability and (**B**) egg size of N2 wild-type
125 (purple), *ppw-1* (black) and *rrf-1* (orange) mutants, treated with either *daf-2* RNAi (solid
126 lines, filled symbols) or control empty vector (broken lines, open symbols) from adulthood
127 onwards. Symbols represent mean ± SE.

128

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.

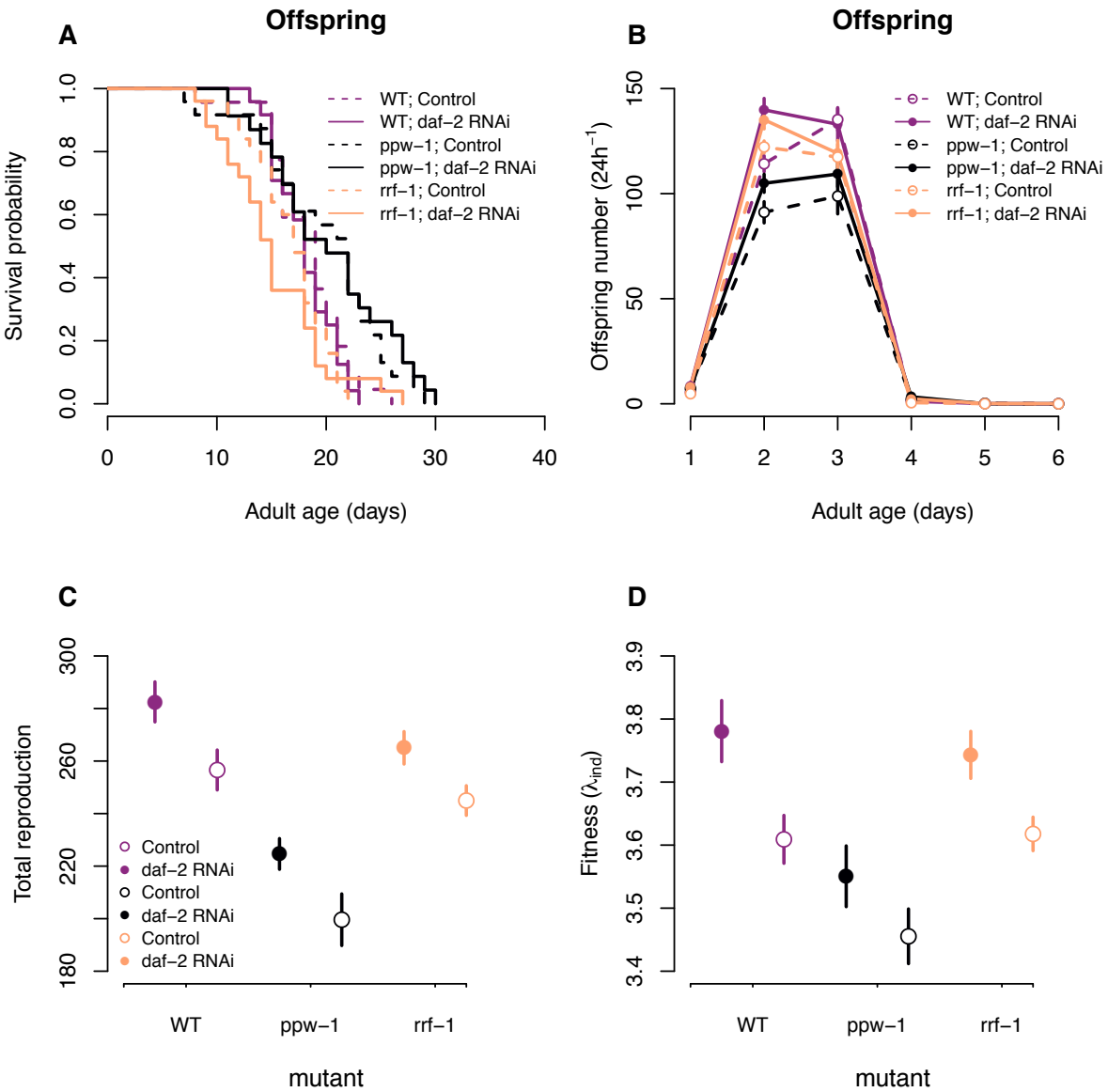


Fig. 4. The effect of parental *daf-2* RNAi on offspring survival and reproduction. Offspring worms, unmated, on control (empty vector) plates from parents exposed to *daf-2* RNAi or control treatment. (**A**) Survival probability, (**B**) daily offspring number, (**C**) Total reproduction and (**D**) 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.

153 **Discussion**

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

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

187

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

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

207

208 **Materials and Methods**

209

210 ***Strains***

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

214

215 ***Maintenance***

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

222

223

224 ***Outline of the study***

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

236

237 ***RNAi***

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

246

247

248 ***Lifespan Assays***

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

255

256 ***Reproduction assays***

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

264

265 ***Egg size assays***

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

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

274

275 ***Statistical analyses***

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

284 Reproduction was analysed as total reproduction as well as rate-sensitive individual fitness
285 λ_{ind}, which encompasses the timing and number of offspring [33, 34]. λ_{ind} is estimated by
286 solving the Euler-Lotka equation for each individual using the *lambda* function in the *popbio*
287 package and is analogous to the intrinsic rate of population growth (Stearns 1992). For all
288 unmated worms (n=25 per treatment), we estimated the fixed effect of treatment (*daf-2* RNAi
289 or empty vector). For offspring of the three mutants (n=25 per treatment), we also estimated
290 the fixed effect or strain, using linear models. For the mated worms (EV: n=72, *daf-2* n=68),
291 we also estimated the random effect of block, in addition to RNAi treatment. These models
292 were implemented as mixed effect models using the *lme4* package in *R 3.3.3*, and chi-square
293 tests of fixed effects were performed using the *car* package. Egg size was analysed in a
294 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.

297

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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.