

1 **Does early-life diet affect longevity? A meta-analysis across experimental**
2 **studies**

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13 **Abstract**

14 Life-history theory predicts that nutrition influences lifespan due to trade-offs between
15 allocating resources to reproduction, growth and repair. In spite of occasional reports that
16 early diet has strong effects on lifespan, it is unclear whether this prediction is generally
17 supported by empirical studies. We conducted a meta-analysis across experimental studies
18 manipulating pre- or post-natal diet and measuring longevity. We found no overall effect of
19 early diet on lifespan. We used meta-regression, considering moderator variables based on
20 experimental and life-history traits, to test predictions regarding the strength and direction of
21 effects that could lead to positive or negative effects. Prenatal dietary manipulations reduced
22 lifespan, but there were no effects of later diet, manipulation type, development mode or sex.
23 The results are consistent with the prediction that early dietary restriction disrupts growth and
24 results in increased somatic damage, which incurs lifespan costs. Our findings raise a
25 cautionary note, however, for placing too strong an emphasis on early dietary effects on
26 lifespan, and highlight limitations of measuring these effects under laboratory conditions.

27

28 **Keywords**

29 early development, nutrition, caloric restriction, lifespan, meta-analysis

30 **Introduction**

31 Conditions in early development can influence a suite of life history traits later in life,
32 including the pace of ageing and total lifespan [1–3]. King penguin chicks which experience
33 rapid catch-up growth have shorter telomeres [4], for example, and red deer born under harsh
34 environmental conditions show faster senescence [5]. An important feature of early
35 development is the amount and type of food received, which has immediate effects on growth
36 and can influence later traits. Several studies have manipulated nutrition in early life –
37 providing diets to pregnant mothers or to young before maturity – and measured offspring
38 survival. These studies have traditionally been conducted on laboratory rodents [6], although
39 there are an increasing number of manipulations on a range of species [7,8]. Despite
40 occasional reports of strong effects [9,10], which have raised concerns in the health sciences
41 [11], it is not yet known how general these effects are across biological systems.

42 Life-history theory provides a framework for understanding how and when early-life
43 diet should influence lifespan. Individuals face trade-offs when allocating resources among
44 traits that enhance growth and reproduction, versus those, such as somatic repair, that increase
45 longevity [12]. Individuals who experience resource limitation in early life may invest in
46 earlier reproduction, incur higher levels of damage, and pay a cost of reduced lifespan [13].
47 Alternatively, those individuals with low resources during development may experience
48 slower growth, delayed reproduction and live a longer life [14].

49 Whether restricted diet in early life *per se*, rather than nutritional limitation across
50 development, extends or reduces lifespan depends on several factors. Reducing total energy
51 content might extend lifespan through increasing allocation towards somatic repair [15];
52 whereas limiting key nutrients for healthy development, such as protein, might impose
53 damage during development and reduce lifespan [16]. The diet experienced beyond early
54 development is likely important. A switch from low to high nutrition can result in catch-up

55 growth, which accrues costs later in life [17]. In contrast, being maintained on a low-nutrition
56 diet could enhance lifespan-extending effects if individuals allocate more to repair [9]. There
57 may also be sex differences in how individuals respond to dietary challenges [7,10]. Increased
58 allocation to growth and reproduction may reduce lifespan to a greater extent for the sex
59 experiencing stronger selection for condition-dependent traits or incurring higher energetic
60 costs to reproduction. Continuous developers might have higher plasticity when conditions
61 improve, compared to organisms with metamorphosis, where adult size is established by
62 larval diet.

63 Here, we conduct a meta-analysis, selecting studies in which diet was manipulated in
64 early development – at any period from early embryonic stages until age of first reproduction
65 – and later longevity was recorded. We used meta-regression [18] to test hypotheses regarding
66 the causes of heterogeneity across studies (Table 1).

67

68 **Methods**

69 We conducted a comprehensive literature search on Google Scholar and SCOPUS for studies
70 linking early-life diet with longevity, based on keywords (ageing, "compensatory growth",
71 "catch-up growth", damage, development, "developmental programming", "early life",
72 growth, lifespan, longevity, maternal, "maternal diet", oxidative, senescence, stress, survival,
73 telomere), and surveying papers cited by or in several key reviews. We only included studies
74 that conducted a dietary manipulation on pregnant females or offspring before the age of
75 sexual maturity. For studies which provided survival curves, we extracted the log hazards
76 ratio, $\ln(\text{HR})$, based on differences in percentage of experimental and control individuals alive
77 at 75%, 50% and 25% of control group survival. However, not all studies report survival
78 curves and we therefore repeated our analysis using mean longevity. Where data were
79 provided separately for groups of individuals, for example by sex, we calculated multiple

80 effect sizes. In total, our search yielded 50 effect sizes of $\ln(\text{HR})$ from 18 studies, and 77
81 effect sizes of mean longevity from 21 studies across 14 species (Table S1).

82 We used meta-regression to investigate whether the effect of early diet on longevity
83 was mediated by manipulation type, post-treatment diet, sex, stage of manipulation, vertebrate
84 versus invertebrate and whether catch-up growth was observed (Table 1). We conducted
85 Bayesian mixed-effects meta-analysis (BMM) using the library MCMCglmm [19] in the
86 statistical environment R (version 2.15 [20]). We first fit an intercept-only model to examine
87 an overall effect of early diet on longevity. As $\ln(\text{HR})$ provides a measure of risk of death, a
88 negative effect indicates that diet manipulation extends lifespan. We then fit a model
89 including all moderators and examined their 95% higher posterior densities (HPD, or credible
90 interval). Any moderators whose HPD did not overlap zero were considered statistically
91 significant. We tested for publication bias by inspecting funnel plots and conducting Egger's
92 regression [21]. We calculated marginal and conditional R^2 to establish the total variance
93 explained by fixed effects or both fixed and random terms in each model, respectively [22].
94 We included study as a random term. Further details are provided in the electronic
95 supplementary material (ESM).

96

97 **Results**

98 We found no overall effect of early diet on subsequent risk of death (HPD: -0.150, 0.125, Fig.
99 1a). The lack of effect may be due to heterogeneity among studies, for example by combining
100 studies where reducing calories increased lifespan and others where reducing specific
101 nutrients reduced lifespan. Heterogeneity in the data was moderate ($I^2 = 57.7\%$, Table S2 in
102 ESM). In our meta-regression to examine differences between studies, we found no
103 significant effects of moderators on risk of death (Fig. 1b). The marginal R^2 was only 0.04
104 (Table S2 in ESM).

105 We did not find an overall effect of early diet on mean longevity (HPD: -0.200, 0.101,
106 Fig. 1c), and these data had low heterogeneity ($I^2 = 32.5\%$, Table S2 in ESM). Several
107 moderators had significant effects (Fig. 1d), although the marginal R^2 was only 0.08 (Table
108 S2 in ESM). Early dietary restriction extended longevity to a greater extent in vertebrates than
109 in invertebrates (HPD: 0.219, 0.944), and when there was no catch-up growth (HPD: 0.039,
110 0.624). Longevity was reduced when dietary restriction occurred before birth (HPD: -1.343, -
111 0.471), and in studies combining both sexes (HPD: -1.086, -0.152).

112 To understand contrasting results in models analysing $\ln(\text{HR})$ and longevity, we
113 repeated our analysis on those studies measuring both. Only the effect of pre- versus post-
114 natal stage on longevity remained significant (HPD: -1.069, -0.024). Publication bias was
115 weak or absent.

116

117 **Discussion**

118 The impact of early-life nutrition has recently come to the forefront of concerns regarding
119 healthy ageing [23]. Life history theory provides explanations for why early diet restriction
120 should influence lifespan [13,15]. However, we find that experimental studies generally fail to
121 demonstrate these effects. A plausible explanation for the lack of an overall effect is that
122 positive and negative effects cancel out. Indeed, there are evolutionary rationales for
123 expecting opposite patterns across studies. We found little evidence, however, that these
124 factors explain the overall lack of an effect of early diet on mortality risk and longevity. The
125 general conclusion of narrative reviews, that early nutrition affects later-life mortality [6],
126 thus appears to be driven by a small number of key studies (e.g. [8,9], Fig S2).

127 While it is tempting to draw conclusions about the evolutionary basis for early diet
128 effects on lifespan, studies testing these effects are almost always conducted under laboratory
129 conditions. In the laboratory, causes of mortality typical of natural conditions are absent, and

130 individuals experience predictable food, no predation and a different reproductive regime to
131 that in the wild. Thus, evidence for weak or absent effects in laboratory studies may simply be
132 due to the fact that intrinsic damage may not be sufficiently strong to cause increased
133 mortality risk [24].

134 Nevertheless, our analysis identified predictors of the effect of early-life diet on mean
135 longevity. We found prenatal diet manipulations had stronger negative effects compared to
136 postnatal manipulations. Thus, at least in live-bearing species, mothers do not fully buffer
137 their offspring from nutritional stress. This is also consistent with observations that variation
138 in biomarkers of ageing, such as telomere length, primarily accrue early in life [4]. Early diet
139 extends lifespan in vertebrate but not invertebrate species, potentially because juvenile and
140 adult function are decoupled through metamorphosis. Our results may thus be more easily
141 interpreted in light of mechanistic theory concerning the link between diet, damage reduction
142 and lifespan [25] than broader life history explanations.

143 Our analyses suggest weak general evidence that reduced nutrients early in life
144 influences lifespan. Whatever effects exist, and we have theoretical reasons to believe that
145 they should, may be specific to the study system. This conclusion is similar to a recent
146 extensive meta-analysis on lifespan-enhancing effects of diet restriction [26]. This study
147 found that protein restriction had stronger life-extending effects than caloric restriction, yet
148 replication in our study was not sufficient to make this comparison. Indeed, animals show
149 plasticity in growth and development across their life, such that single effects of diet
150 restriction may be weak and context-dependent. Insofar as laboratory conditions are
151 informative, the overall evidence as it stands does not provide strong support that food
152 restriction during development causes major effects on adult intrinsic mortality or lifespan.

153

154 **Data accessibility:** Data and code are available on GitHub [27]:

155 <https://github.com/sineadenglish/early-diet-longevity>

156 **Author contributions:** SE and TU designed the study. SE extracted the data and conducted
157 the analysis. SE and TU wrote the paper. Both authors approve the final version of the
158 manuscript and agree to be held accountable for the content therein.

159 **Competing interests:** None.

160 **Funding:** This research was funded by the EU FP7 programme (agreement 259679, IDEAL).
161 SE and TU were supported by the Royal Society of London. TU received support from the
162 Knut and Alice Wallenberg Foundations.

163 **Acknowledgements:** We are grateful to all authors who contributed data (listed in ESM) and
164 to Shinichi Nakagawa for statistical advice.

165

166 **References**

- 167 1. Ricklefs, R. E. 2010 Embryo growth rates in birds and mammals. *Funct. Ecol.* **24**, 588–
168 596. (doi:10.1111/j.1365-2435.2009.01684.x)
- 169 2. Barnes, S. K. & Ozanne, S. E. 2011 Pathways linking the early environment to long-
170 term health and lifespan. *Prog. Biophys. Mol. Biol.* **106**, 323–36.
171 (doi:10.1016/j.pbiomolbio.2010.12.005)
- 172 3. Metcalfe, N. & Monaghan, P. 2003 Growth versus lifespan: perspectives from
173 evolutionary ecology. *Exp. Gerontol.* **38**, 935–940. (doi:10.1016/S0531-
174 5565(03)00159-1)
- 175 4. Geiger, S., LE Vaillant, M., Lebard, T., Reichert, S., Stier, A., LE Maho, Y. &
176 Criscuolo, F. 2012 Catching-up but telomere loss: half-opening the black box of
177 growth and ageing trade-off in wild king penguin chicks. *Mol. Ecol.* **21**, 1500–1510.
178 (doi:10.1111/j.1365-294X.2011.05331.x)

- 179 5. Nussey, D. H., Kruuk, L. E. B., Morris, A. & Clutton-Brock, T. H. 2007
180 Environmental conditions in early life influence ageing rates in a wild population of
181 red deer. *Curr. Biol.* **17**, R1000–1. (doi:10.1016/j.cub.2007.10.005)
- 182 6. Sayer, A. A. & Cooper, C. 2002 Early diet and growth: impact on ageing. *Proc. Nutr.*
183 *Soc.* **61**, 79–85. (doi:10.1079/PNS2001138)
- 184 7. Houslay, T. M., Hunt, J., Tinsley, M. C. & Bussière, L. F. 2015 Sex differences in the
185 effects of juvenile and adult diet on age-dependent reproductive effort. *J. Evol. Biol.*
186 **28**, 1067–1079. (doi:10.1111/jeb.12630)
- 187 8. Saastamoinen, M., Hirai, N. & van Nouhuys, S. 2013 Direct and trans-generational
188 responses to food deprivation during development in the Glanville fritillary butterfly.
189 *Oecologia* **171**, 93–104. (doi:10.1007/s00442-012-2412-y)
- 190 9. Ozanne, S. E. & Hales, C. N. 2004 Lifespan: catch-up growth and obesity in male
191 mice. *Nature* **427**, 411–412.
- 192 10. Boggs, C. L. & Freeman, K. D. 2005 Larval food limitation in butterflies: Effects on
193 adult resource allocation and fitness. *Oecologia* **144**, 353–361. (doi:10.1007/s00442-
194 005-0076-6)
- 195 11. Mentis, A.-F. A. & Kararizou, E. 2010 Does ageing originate in utero? *Biogerontology*
196 **11**, 725–9. (doi:10.1007/s10522-010-9293-4)
- 197 12. Roff, D. A. 2002 *Life history evolution*. Sunderland, MA: Sinauer Associates Inc.
- 198 13. Kirkwood, T. 1977 Evolution of ageing. *Nature* **270**, 301–305.
- 199 14. Kirkwood, T. B. L. 2005 Understanding the odd science of aging. *Cell* **120**, 437–47.
200 (doi:10.1016/j.cell.2005.01.027)
- 201 15. Kirkwood, T. B. L. & Shanley, D. P. 2005 Food restriction, evolution and ageing.
202 *Mech. Ageing Dev.* **126**, 1011–6. (doi:10.1016/j.mad.2005.03.021)
- 203 16. Lee, K. P., Simpson, S. J., Clissold, F. J., Brooks, R., Ballard, J. W. O., Taylor, P. W.,

- 204 Soran, N. & Raubenheimer, D. 2008 Lifespan and reproduction in *Drosophila*: New
205 insights from nutritional geometry. *Proc. Natl. Acad. Sci. U. S. A.* **105**, 2498–503.
206 (doi:10.1073/pnas.0710787105)
- 207 17. Metcalfe, N. B. & Monaghan, P. 2001 Compensation for a bad start: grow now, pay
208 later? *Trends Ecol. Evol.* **16**, 254–260.
- 209 18. Nakagawa, S. & Santos, E. S. A. 2012 Methodological issues and advances in
210 biological meta-analysis. *Evol. Ecol.* **26**, 1253–1274. (doi:10.1007/s10682-012-9555-5)
- 211 19. Hadfield, J. D. 2010 MCMC Methods for Multi-Response Generalized Linear Mixed
212 Models: The MCMCglmm R Package. *J. Stat. Softw.* **33**, 1–22.
- 213 20. R Development Core Team 2012 R: A Language and Environment for Statistical
214 Computing.
- 215 21. Egger, M., Davey Smith, G., Schneider, M. & Minder, C. 1997 Bias in meta-analysis
216 detected by a simple, graphical test. *BMJ* **315**, 629–34.
217 (doi:10.1136/bmj.316.7129.469)
- 218 22. Nakagawa, S. & Schielzeth, H. 2013 A general and simple method for obtaining R²
219 from generalized linear mixed-effects models. *Methods Ecol. Evol.* **4**, 133–142.
220 (doi:10.1111/j.2041-210x.2012.00261.x)
- 221 23. Gluckman, P. D., Hanson, M. A., Cooper, C. & Thornburg, K. L. 2008 Effect of in
222 utero and early-life conditions on adult health and disease. *N. Engl. J. Med.* **359**, 61–
223 73. (doi:10.1056/NEJMra0708473)
- 224 24. Speakman, J. R. et al. 2015 Oxidative stress and life histories: Unresolved issues and
225 current needs. *Ecol. Evol.* , 5745–5757. (doi:10.1002/ece3.1790)
- 226 25. Gavrilov, L. A. & Gavrilova, N. 2003 Early-life factors modulating lifespan. In
227 *Modulating Aging and Longevity* (ed S. I. S. Rattan), pp. 27–50. Dordrecht: Kluwer
228 Academic Publishers.

- 229 26. Nakagawa, S., Lagisz, M., Hector, K. L. & Spencer, H. G. 2012 Comparative and
230 meta-analytic insights into life extension via dietary restriction. *Aging Cell* **11**, 401–9.
231 (doi:10.1111/j.1474-9726.2012.00798.x)
- 232 27. English, S. 2016 Code and data from: "Does early-life diet affect longevity? A meta-
233 analysis across experimental studies" (accepted in *Biology Letters*, July 2016). Zenodo.
234 doi:10.5281/zenodo.59865

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237 **Table and figure legends**

238

239 **Table 1.** Rationale for predictor variables in meta-regression.

240

241 **Figure 1.** Funnel plot (a,c) of effect sizes against power, with counter-shaded confidence
242 intervals (90%, 95% and 99% CI); and forest plot (b,d) of HPD intervals (posterior mean and
243 95% CI) in the meta-analysis on ln(HR) and mean longevity.

244

245 **Table 1**

Predictor	Rationale
Manipulation type (diet quality or quantity)	If dietary restriction extends lifespan, expect positive effect for reduced quantity but not quality of food. In contrast, if certain nutrients have carry-over effects for individual quality, expect quality effect to be stronger.
Post-treatment diet (control or restricted)	If dietary restriction extends lifespan, expect stronger positive effect if adults are on restricted diet too. If there is a cost of dietary mismatch, expect stronger negative effects when juveniles are on a restricted diet then adults are on a high-food diet.
Sex	If restriction reduces lifespan due to allocation trade-offs between growth and reproduction, predict stronger effect in males due to condition-dependent sexual selection; or in females if they experience high costs of reproduction.
Manipulation stage (pre- or post-natal)	Predict stronger effect of pre-natal diet due to disruption of sensitive stages in development; alternatively predict weaker effect if mothers buffer offspring from nutritional stress.
Vertebrate vs Invertebrate	Expect positive or negative effect sizes to be stronger in invertebrates because of indeterminate growth, hence less plasticity in response to early diet.
Evidence for catch-up growth (yes or no)	Expect weaker effect if individuals compensate for effect of manipulation through catch-up growth. Alternatively, if catch-up growth incurs costs, expect stronger effect under catch-up growth.

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