

Research



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Evolutionary biology

Dietary restriction increases variability in longevity

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Nutritional environments, particularly those experienced during early life, are hypothesized to affect longevity. A recent cross-taxa meta-analysis found that, depending upon circumstance, average longevity may be increased or decreased by early-life dietary restriction. Unstudied are the effects of diet during development on among-individual variance in longevity. Here, we address this issue using emerging methods for meta-analysis of variance. We found that, in general, standard deviation (s.d.) in longevity is around 8% higher under early-life dietary restriction than a standard diet. The effects became especially profound when dietary insults were experienced prenatally (s.d. increased by 29%) and/or extended into adulthood (s.d. increased by 36.6%). Early-life dietary restriction may generate variance in longevity as a result of increased variance in resource acquisition or allocation, but the mechanisms underlying these largely overlooked patterns clearly warrant elucidation.

1. Introduction

The nutritional environment directly affects the resources that are available for an individual to invest in growth, reproduction and somatic maintenance [1]. As such, dietary constraint, through either the restriction of total food or an imbalance of specific nutrients (i.e. deficits and associated relative excesses of specific nutrients), is expected to impact life-history traits, and ultimately fitness (e.g. [2,3]). A number of studies have attempted to quantify the relationship between dietary constraints and longevity, with both positive and negative effects being observed.

Moderate dietary restriction of both protein and energy can extend lifespan under laboratory conditions [4]. When viewed through the lens of life-history theory, dietary restriction is predicted to alter adaptive trade-offs between longevity and other traits (e.g. fecundity or growth), such that somatic damage is reduced, allocation to somatic maintenance is increased, or both [5]. Other studies, however, point to restriction reducing longevity, possibly through pathological effects on key developmental processes [6].

A recent cross-taxa meta-analysis of studies on early-life (qualitative and quantitative) dietary restriction concluded that restrictions experienced at a prenatal stage can decrease average longevity, but restriction can also extend average lifespan under other circumstances, e.g. the absence of 'catch-up growth' (rapid growth that follows a period of impeded development; see [7]), and in vertebrates [8]. Here, we have built upon this study by addressing the impacts of dietary restriction on among-individual variation in lifespan. Understanding how dietary restriction impacts variation in longevity is important, because it is through such variation that selection can act to cause life-history evolution and alter mean lifespan. Furthermore, establishing circumstances under which

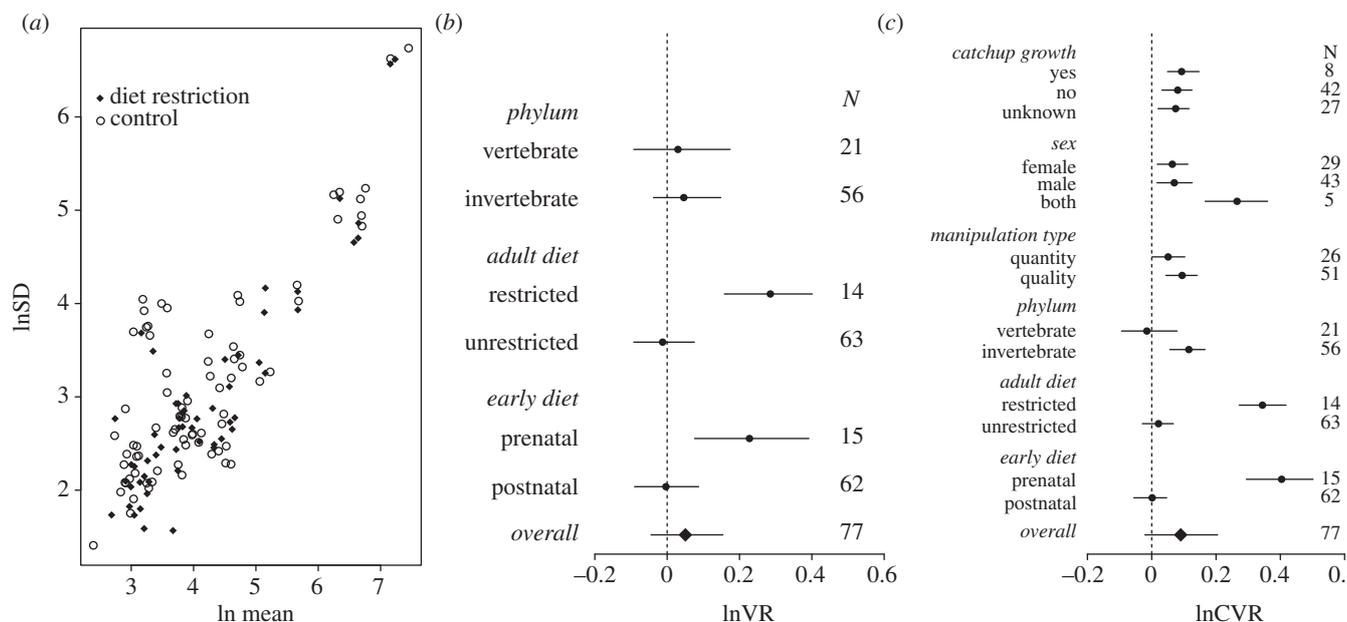


Figure 1. (a) Log mean against log standard deviation of each group from which data were extracted (diet restricted, diamond; control, circle). Overall effects ($\pm 95\%$ credible intervals), and group-specific effects based on model averaging, for: (b) $\ln VR$ and (c) $\ln CVR$. Only moderators appearing in the top model set are shown. Estimates for each category are overall unconditional estimates from model averaged posterior distributions. Estimates of contrasts between groups are given in table 1. N corresponds to the number of effect sizes in each category.

variation in longevity is extreme may help identify phenotypes that can be used to explore the mechanistic underpinnings of the diet–ageing relationship.

An emerging body of literature suggests that, in general, stressors increase phenotypic variation by exposing cryptic-genetic and/or epigenetic variation (reviewed in [9]). Considering diet, confinement to a nutrient-deficient food across life increases among-individual variance in life-history traits [10–12], and the effects of caloric restriction on longevity vary substantially among mouse strains [13]. These outcomes are probably driven by individuals varying in their optimal nutritional intake and/or condition, which in turn exposes variation in the response of individuals to the nutritional deficiencies of dietary restriction [10]. Dietary restriction experienced early in development, in particular, might be predicted to exacerbate variation in longevity by affecting long-term resource allocation and impacting rates of cellular attrition during critical developmental periods [14]. Here, we test the prediction that early-life dietary restriction increases variation in longevity using recently developed meta-analytic methods for variance [15].

2. Methods

Data were obtained from English & Uller [8]. For each comparison between longevity on ‘restricted’ and ‘control’ diets within a study we calculated two effect sizes for differences in variance in longevity between treatments: (i) the log variance ratio ($\ln VR$) and (ii) the log coefficient of variance ratio ($\ln CVR$), along with associated sampling errors [16]. $\ln VR$ and $\ln CVR$ correspond to the logarithm of the ratio of the of standard deviation (s.d.), and coefficient of variance (CV), in longevity in the two treatment groups, respectively. $\ln VR$ is an estimate of the relative absolute variance of the two groups, whereas $\ln CVR$ assesses differences in variation corrected for the effects of treatment on the mean; any effects of diet on mean longevity may cause concomitant changes in variance if a mean–variance relationship exists, as was observed here (figure 1a) [16]. Correcting for

changes in the mean using $\ln CVR$ makes a number of assumptions about the nature of the mean–variance relationship (discussed in [15,16]). We tested the sensitivity of our results to these assumptions using an alternative analysis, finding our conclusions were broadly robust (see the electronic supplementary material, table S1). Effect sizes were calculated such that positive values indicate higher variance (s.d. or CV) under dietary restriction.

Data were analysed using multi-level meta-analytic (MLMA) and meta-regression (MLMR) models, which controlled for sampling error, study and the covariance among effects that are contrasted with the same control-group data [16]. From MLMA, we report overall effects along with back-transformed estimates to aid interpretation. In the main text, we report total statistical heterogeneity as I^2_{total} , and the percentage of variance explained by study-effects as I^2_{study} [17]. MLMR models explored the same moderator variables as English & Uller [8]. Rather than using a global model, where MLMRs contain all predictors of interest simultaneously, we used model averaging based on deviance information criterion (DIC); variables in the models within 3 DIC of the top model were averaged (see [10]). We tested the sensitivity of English & Uller [8]’s conclusions about mean longevity to their choice of analytical approach, as well as their implicit assumptions about the effects of diet on among-individual variance in longevity, and found their results robust. All models were implemented in the package *MCMCglmm* [18]. We present 95% credible intervals (CIs), and interpret estimates with CIs excluding zero as significant. See electronic supplementary material for technical details of analyses and additional results.

3. Results

As predicted, overall $\ln VR$ and $\ln CVR$ were positive, although not statistically significant ($\ln VR = 0.050$, $CI = -0.045$ to 0.154 ; $\ln CVR = 0.090$, $CI = -0.021$ to 0.205 ; figure 1b,c). These effects correspond to the s.d. and CV in longevity being around 8% and 15% higher under dietary restriction relative to the control, respectively. Although overall effects were not significant, heterogeneity was high ($\ln VR I^2_{total} = 76.2\%$; $\ln CVR I^2_{total} = 88.4\%$), with small to moderate heterogeneity being explained by among-study

Table 1. Model averaged coefficients and 95% credible intervals for lnVR and lnCVR. Italicized estimates indicate that the 95% credible interval does not include zero. LCI, lower credible interval; UCI, upper credible interval.

parameter	lnVR			lnCVR		
	mode	LCI	UCI	mode	LCI	UCI
(intercept)	-0.074	-0.152	0.042	0.177	0.073	0.279
ExptLifeStage _{Prenatal}	0.231	0.050	0.402	0.420	0.290	0.509
ManipType _{Quantity}	—	—	—	-0.048	-0.079	-0.003
CatchUp _{No}	—	—	—	0.004	-0.014	0.029
CatchUp _{Yes}	—	—	—	0.020	-0.013	0.045
Sex _F	—	—	—	-0.201	-0.299	-0.100
Sex _M	—	—	—	-0.202	-0.300	-0.095
AdultDiet _{Restricted}	0.277	0.193	0.423	0.307	0.250	0.396
Phylum _{Vertebrate}	-0.023	-0.156	0.142	-0.122	-0.233	-0.033

effects ($\ln VR I_{\text{study}}^2 = 37.1\%$; $\ln CVR I_{\text{study}}^2 = 17.4\%$), suggesting inconsistency among studies in the reported effects of early diet on variation in longevity.

MLMRs detected significant and high lnVR and lnCVR by studies using prenatal dietary restriction (figure 1*b,c* and table 1; electronic supplementary material, table S2), with a 29% and 57.5% increase in s.d. and CV in longevity, respectively, under restricted relative to control diets. lnVR and lnCVR were negligible when dietary restriction was solely experienced in the juvenile period, but high and significant when dietary restriction continued post-maturity (figure 1*b,c* and table 1; electronic supplementary material, table S2); s.d. and CV were increased by 36.6% and 48.4%, respectively by lifelong dietary restriction. lnCVR was also higher for invertebrates than vertebrates, for restriction of food quality than quantity, and for mixed-sex groups, although most of these moderators did not appear in the top model set for lnVR (figure 1*c* and table 1; electronic supplementary material, table S2 through S4).

4. Discussion

Early-life dietary restriction that is initiated prenatally and/or is extended into adulthood can substantially increase among-individual variability in lifespan. The effect of dietary restriction on variance (i.e. lnVR) in longevity did not differ between invertebrates and vertebrates. While we did detect differences between these groups for the effect of dietary stress on lnCVR, this difference was driven by inter-taxon differences in the effect of diet on mean longevity as discussed in English & Uller [8], rather than the absolute variance *per se*.

Prenatal dietary restriction may have particularly potent effects on variation in longevity through effects on important developmental processes, in turn causing permanent organizational changes. At a molecular level, the patterns we describe are most probably caused by variation in ability to cope with cellular stress (e.g. dealing with free radicals, mitochondrial dysfunction or telomere shortening). For example, dietary restriction may generate variation in rates of mitochondrial DNA replication and associated replication errors, which are known to contribute to somatic decline [19].

At the level of the whole organism dietary restriction during critical developmental periods may result in

permanent changes in either energy utilization or allocation that lead to individuals adopting different life-history strategies, generating variance in longevity [20]. There will also likely be differences in digestive/post-ingestive physiology, which translate into variation in the efficiency with which individuals acquire resources from a given diet, and in the net intake of nutrients required to optimize lifespan [10]. Such variation may be relatively cryptic under optimal conditions, but become more prominent as nutrients become scarce under dietary restriction.

Lifelong exposure to nutritional imbalance has been shown to generate variation in multiple life-history traits [10,12]. Quantifying the within-population covariance between longevity and other life-history traits (e.g. reproduction or growth) on a range of diets may discern between the relative magnitudes of variation in the aforementioned acquisition- and allocation-type processes. Positive correlations may indicate greater variance in resource acquisition than net allocation, and negative correlations the opposite [21,22].

By altering phenotypic variation in longevity, diet may affect the strength with which selection can act on longevity. A more holistic understanding of the consequences of dietary constraints for life-history evolution, however, requires studies of the genetic variance in, as well as the genetic covariance among, traits as a function of the nutritional environment. Many of the studies included here imparted restriction by reducing dietary protein. Going forwards, nutritional geometry is an approach that can be used both to define dietary constraints in terms of nutritional imbalances and caloric deficits, and to disentangle their effects on life-history traits and their correlations [1,3].

Data accessibility. Data can be accessed at: <https://github.com/sineadenglish/early-diet-longevity>.

Authors' contributions. A.M.S. conceived the study. A.M.S. and D.W.A.N. conducted analyses. All authors contributed to interpretation of the data and preparation of the manuscript, approved the final version of the manuscript and agree to be held accountable for the content therein.

Competing interests. We declare no competing interests.

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