Understanding Patterns of Life History Trait Covariation in an Untapped Resource, the Lab Mouse

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Accepted 4/3/2023; Electronically Published 7/7/2023

Online enhancement: appendix.

ABSTRACT

Through artificial selection and inbreeding, strains of laboratory mice have been developed that vary in the expression of a single or suite of desired traits valuable to biomedical research. In addition to the selected trait(s), these strains also display variation in pelage color, body size, physiology, and life history. This article exploits the broad phenotypic variation across lab mouse strains to evaluate the relationships between life history and metabolism. Life history variation tends to exist along a fast-slow continuum. There has been considerable interest in understanding the ecological and evolutionary factors underlying life history variation and the physiological and metabolic processes that support them. Yet it remains unclear how these key traits scale across hierarchical levels, as ambiguous empirical support has been garnered at the intraspecific level. Within-species investigations have been thwarted by methodological constraints and environmental factors that obscure the genetic architecture underlying the hypothesized functional integration of life history and metabolic traits. In this analysis, we used the publicly available Mouse Phenome Database by the Jackson Laboratory to investigate the relationships among life history traits (e.g., body size, reproduction, and life span) and metabolic traits (e.g., daily energy expenditure and insulin-like growth factor 1 concentration). Our findings revealed significant variation in reproductive characteristics across strains of mice as well as relationships among life history and metabolic traits. We found evidence of variation along the fast-slow life history continuum, though the direction of some relationships among these traits deviated from interspecific predictions laid out in previous literature. Furthermore, our results suggest that the strength of these relationships are strongest earlier in life.

Keywords: artificial selection, insulin-like growth factor 1 (IGF-1), fast-slow continuum.

Introduction

Variation in traits that effect growth, size, reproduction, and survival (i.e., life history traits) is a hallmark of biodiversity. These traits tend to cluster along a fast-slow continuum correlated with variation in energetic expenditure (Harvey et al. 1989; Promislow and Harvey 1990; Stearns 1992; Ricklefs and Wikelski 2002; Roff 2002). Promislow and Harvey (1990) found support for this pattern within Mammalia, such that larger mammals tend to lead slower lives characterized by longer life spans, lower mass-specific metabolic rates, and less frequent production of small litters. In contrast, smaller mammals tend to live faster lives with shorter life spans, higher mass-specific metabolic rates, and more frequent production of large litters. Size, reproductive traits, and longevity also vary among individuals within species (Careau et al. 2010; Jimenez 2016, 2021), though it remains unclear whether the life history patterns observed between species continue to govern performance within species, as patterns found at the interspecific level tend to break down as comparisons are made between organisms at lower levels of taxonomic organization (e.g., from order level to population level; Clutton-Brock and Harvey 1979; Harvey 1982; Clutton-Brock 1984; Earle and Lavigne 1990). Previous work on intraspecific patterns of life history trait covariation in rodents either shows no conclusive pattern of covariation among traits (Derting and McClure 1989; Earle and Lavigne 1990; Derting 1997) or shows a pattern of life history trait covariation that is the opposite of what would be expected based on interspecific observations (Jimenez 2016).

Identifying patterns of life history trait covariation, as well as the proximate and ultimate factors that contribute to their variation, is fundamental to evolutionary biology, particularly in relation to the fast-slow life history continuum and the hypothesized metabolic traits that underlie the predicted patterns (Ricklefs and Wikelski 2002). Several experimental paradigms (e.g., artificial selection experiments, sibling analysis, offspring-parent regression) have been used to evaluate genetic variation and

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  https://doi.org/10.1086/725435

covariation among life history traits (Conner 2003; Garland and Rose 2009; Swallow et al. 2009). Studies using organisms that have been selected for desirable phenotypic characteristics, such as strains of laboratory mice, can answer whether traits covary and can inform us of the architecture and strength of the genetic constraints that underlie life history evolution (Conner 2003). We used life history data collected from multiple strains of inbred laboratory mice (*Mus musculus*) to explore intraspecific relationships among life history and metabolic traits. Domestication of the house mouse (*Mus musculus*) was a by-product of the commensal relationship that this species has with humans, leading to breeding fancy lines of mice based on coat color and other phenotypic characteristics; this intentional phenotype-driven selection gained attention from scientists, and the laboratory mouse was created in the early twentieth century (Boursot et al. 1993; Beck et al. 2000; Didion and de Villena 2013; Phifer-Rixey and Nachman 2015). In the century that followed, the laboratory mouse became a popular model organism (with over 450 strains available) because it is small, can be maintained cost effectively, and has short gestation periods. Laboratory strains of mice therefore arose through a long history of artificial selection to increase and maintain the expression of phenotypic and functional traits (Beck et al. 2000; Swallow et al. 2009). All classic inbred strains of lab mice, including those used in the present study, have been inbred for at least 60 generations, at which point their genome is considered to be homozygous across individuals, excluding spontaneous mutations (Silver 1995). This high homozygosity means that phenotypic variation among individuals within strains can be attributed to environmental factors, such as maternal effects, differences in handling and husbandry practices, and an individual's social environment (Careau et al. 2012). In contrast, phenotypic variation across strains can be attributed not only to these effects but also to genetics and genes caused by environmental effects (Careau et al. 2012). Phenotypic variation across strains or breeds that have been artificially selected is typically greater than the variation found in populations subject to natural selection (Grafen 1988; Conner 2003), though inbreeding can increase the expression of disease phenotypes and introduce the expression of rare and deleterious alleles. This increase in variation should be particularly true for traits that play a large role in determining fitness, as natural selection should remove phenotypes that decrease fitness in the wild. Therefore, comparing traits across strains of laboratory mice will capture a greater breadth of covarying traits than is expected in a natural population.

Both extrinsic and intrinsic constraints impose an upper limit on an individual's ability to maximize reproductive performance. Previous research has identified metabolic rate as a key determinant of reproductive performance, with metabolic rate impacting the amount of energy available for allocation toward reproduction (Johnson et al. 2001). Lab mice are a valuable model for evaluating trade-offs associated with reproduction, as females display a remarkably high energetic demand during breeding. Lactating female house mice have one of the highest sustained metabolic scopes identified in a vertebrate (Hammond and Diamond 1997), and when given continuous access to a mate, they will spend most of their lives allocating resources to the pre- and postnatal care of offspring (Latham and Mason 2004). Given this exceptionally large demand, reproductive trade-offs are expected to be particularly pronounced in this species.

Here, we propose that data from lab mice can be used to identify the pleiotropic traits that contribute to intraspecific life history variation. To achieve this goal, we used the publicly available Mouse Phenome Database by the Jackson Laboratory (http://phenome.jax.org; Bogue and Grubb 2004; Grubb et al. 2004; Bogue et al. 2018) to investigate correlations among life history and physiological traits across strains of inbred lab mice. Because a large number of phenotypes are included in this database and a large number of inbred strains are represented, the Mouse Phenome Database provides a unique opportunity for evaluating covariation among life history and metabolic traits within species. To measure reproduction, we assessed individual traits (e.g., age at first reproduction, number of lifetime litters, interbirth interval, and average total number of pups per litter) and used a principal components analysis (PCA) to derive new variables, which we termed "breeding frequency" and "reproductive intensity." Additionally, we were interested in other life history traits, such as average life span and age-specific body size (body mass and body length). Multiple metabolic traits were used, including oxygen consumption, carbon dioxide production, body heat production, food intake, caloric intake, heart rate, and serum concentration of insulin-like growth factor 1 (IGF-1).

Emphasizing these life history, morphological, and metabolic traits (table 1), we conducted a heuristic analysis aimed at describing correlations between these traits that may be indicative of life history trade-offs in females belonging to inbred strains of laboratory mice. We predicted that reproduction-related variables would be negatively correlated with life span, body mass, and body length, as previously described (Promislow and Harvey 1990). Furthermore, we predicted that body size, metabolic rate, and mean serum IGF-1 concentration would correlate with measures of reproduction and longevity. These results would indicate that metabolism and/or IGF-1 plays a role in mediating trait covariation. Together, these results will help elucidate the phenotypic and physiological correlates that accompany intraspecific life history trait variation, thereby informing us about the nature of the architecture underlying these traits in the absence of natural selection.

Methods

Data Collection and Variable Selection

The Mouse Phenome Database by the Jackson Laboratory (http://phenome.jax.org) is a collaborative database of mouse strain characteristics, allowing researchers to explore phenotypic data collected by different investigators (Bogue and Grubb 2004; Grubb et al. 2004; Bogue et al. 2018). All data used in this synthesis were previously published in peer-reviewed journals or were collected by the Jackson Laboratory (table 1). Figure S1 outlines the data included and the selection criteria following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al. 2009; Moher et al.

Table 1: Categories and variables used in this study

Category, variable(s)	Source(s)
Reproduction:	
Dam's age at the birth of her first litter (35)	Jackson Laboratory 2009
Number of litters per dam (35)	Jackson Laboratory 2009
Interval between consecutive litters (35)	Jackson Laboratory 2009
Total number of pups born per litter (35)	Jackson Laboratory 2009
Derived variables:	
PC1: breeding frequency (35)	. . .
PC2: reproductive intensity (35)	. . .
Life span:	
Average life span (32)	Yuan et al. 2007*a*, 2009; Leduc et al. 2010
Body size:	
Body mass at 3 (26), 6 (19), 12 (26), and 20 (18) mo	Ackert-Bicknell et al. 2008
Body length at 3 (21), 6 (19), 12 (26), and 20 (18) mo	Ackert-Bicknell et al. 2008; Center for Genome Dynamics 2009
Metabolism:	
Mass-specific daily oxygen consumption (15)	Seburn 2001
Mass-specific daily carbon dioxide production (11)	Seburn 2001
Mass-specific daily body heat production (11)	Seburn 2001
Mass-specific daily food intake (13)	Seburn 2001
Mass-specific daily caloric intake (13)	Seburn 2001
Heart rate at 6 (23), 12 (24), and 20 (20) mo	Xing et al. 2008, 2009
Serum concentration of IGF-1 at 6 (29), 12 (27), and 18 (16) mo	Yuan et al. 2007*b*, 2012

Note. Categories and sources of the variables used in this analysis are shown here. The number of strains represented by each variable is noted in parentheses. More information (i.e., within-strain means, sample sizes, and standard deviations) and Mouse Phenome Database identifiers are available in the appendix. IGF-1 = insulin-like growth factor 1; PC1 = first principal component; PC2 = second principal component.

2009). Data were obtained in 2016 from the Mouse Phenome Database, and individual records (i.e., variables) were screened to ensure that the measurements were taken from inbred female mice that were older than 6 wk at the time of the measurement. We focused on females because of the high metabolic demand of reproduction in this sex and because there are few data on the breeding performance of males in the Mouse Phenome Database. Studies that included any experimental manipulations of endogenous or exogenous conditions (e.g., high-fat diet or pharmacological treatment) were excluded. Variables were then selected for their biological relevance to our question (e.g., behavioral analyses and histopathology were excluded). Variables were then excluded based on within-strain sample size (inclusion criterion: $n > 7$), inclusion of females in the dataset, and number of strains that the measurements were taken from. No duplicate parameters were included, and in the event of duplicate records, the dataset with the highest within-strain sample size or the greatest number of strains was used. All metabolic data (e.g., oxygen intake, carbon dioxide output, body heat production, food intake, and caloric intake) were previously adjusted to the individual's body mass before use in this dataset.

Data from each variable represent the average measurement for a given strain; each parameter was treated as a discrete and independent variable, as raw data on individuals were not available for all records used. The number of strains that contributes data to each variable varies from 11 to 35 (table 1), and information about each strain as it relates to its potential to have disease phenotypes is available in the appendix. The within-strain sample sizes for each variable range from 7 to 265. For the reproductive variables (e.g., dam's age at the birth of her first litter, number of litters per dam, interbirth interval, and total number of pups per litter), measurements were taken from the same continuously bred females housed in a single colony (Jackson Laboratory 2009). These females were paired for breeding between 6 and 8 wk of age, and data on these variables were collected until the females reached approximately 40 wk of age. It is important to note that while females may remain fertile after 40 wk of age, the Jackson Laboratory reports that the mean maternal age at which they weaned their last litter falls between 5.7 and 8.3 mo (22.8–33.2 wk) for all strains used in this analysis (Flurkey and Currer 2009; Jackson Laboratory 2009). For the remaining variables, data were collected from nonreproductive and nulliparous females (Seburn 2001; Yuan et al. 2007*a*, 2007*b*, 2009, 2012; Ackert-Bicknell et al. 2008; Xing et al. 2008, 2009; Center for Genome Dynamics 2009; Leduc et al. 2010). Although measurements for the same variable were taken at different ages, we treated each age as independent because of the large amount of time between measurements. Further information on the protocols used to collect data included in this analysis is available on the Mouse Phenome Database for each dataset. Homogeneity of residuals was assessed, and data distribution across strains was tested for normality using the Shapiro-Wilk test. Three variables (total number of pups per litter, 3-mo mass, and 12-mo mass) were found to have distributions that deviated from the normal. Normality was not

significantly improved by transforming and therefore remained untransformed.

Despite inbred strains of mice sharing a common evolutionary history, we did not take into account their phylogenetic relatedness. Though the origins of many inbred strains are well known, the origins and relatedness for some strains included in this study remain unclear and may include genetic contamination from other strains, leading to differences in models of hypothesized phylogenetic relatedness that may obscure phylogenetic signal (Atchley and Fitch 1991). In one of the few previous comparative studies of inbred mouse strains, Rhodes et al. (2007) reported in their analysis that the inclusion of phylogenetic signal across strains of inbred mice did not change the results compared to conventional methods, such as those employed here, that ignore the history of strain development (but see Careau et al. 2012, who did report a difference when incorporating phylogenetic signal in their model).

Statistical Analyses

Statistical analyses were performed in R (R Core Team 2013), and graphs were generated in either R or GraphPad Prism (ver. 9.4.0). Data from the reproduction variables were used in a PCA. These variables (e.g., average litter size per dam, number of litters per dam, average interval between consecutive litters, and dam's age at the birth of her first litter; see table 1 for list of variables) were selected so that each represented a different facet of reproduction. Data were centered and scaled before running this analysis to ensure that all variables had equal weights. Resulting PCs were retained after analyzing data with a scree plot. Furthermore, these components were considered to be significant if they had an eigenvalue >1 and explained a large amount of the variance. Scores from these PCs were then extracted and used in further analyses. To explore the relationships among life history components, we created a correlation matrix using Pearson's product-moment correlation coefficient (r) to ensure that important variables and relationships were not removed from the statistical model. Our analyses generated 325 P values, 81 of which were ≤ 0.05 (see the appendix). To control for multiple comparisons, we used the positive false discovery rate procedure as implemented in PROC MULTTEST in SAS (ver. 9.4, Cary, NC), with the positive false discovery rate held at 5%. Based on this procedure, the 56 smallest P values would have adjusted P values <0.05, with the highest unadjusted P value being 0.014. All P values in the text and in the appendix are reported as raw values, without any adjustment for multiple comparisons. We refer to P values <0.014 as significant, while those between 0.014 and 0.05 are referred to as nominally significant. All correlations and raw significance levels between all variables are provided in the appendix.

Results

Reproduction across Strains of Female Inbred Mice

To better represent the multifactorial nature of reproductive performance, we used a PCA with variables that represent different aspects of reproduction. Two PCs were identified, explaining approximately 75% of the variance when combined (table 2). The first PC (PC1) represents a continuum of breeding frequency and explains 40.6% of the variance, and it was heavily weighted by the interval between consecutive litters and the average number of litters per dam for a given strain of mouse. Strains with negative values along this axis represent reproduction characterized by a tendency to have fewer, less frequent litters, whereas strains with positive values along this axis tend to have more litters and a decreased interbirth interval between consecutive litters. Our second PC (PC2) explains 34.6% of the variance in the model. This axis represents reproductive intensity, as it is heavily negatively weighted by the dam's age at the birth of her first litter and positively weighted by the average size of her litter. This axis represents a continuum with strains at negative values first reproducing at older ages, with an average of fewer offspring in each litter. Two other PCs were found, but they were excluded because of their low eigenvalues (>1) and low explanatory power for the model's variance.

Table 2: Breeding frequency and reproductive intensity represent two separate axes of reproductive performance

	Breeding frequency	Reproductive intensity		
	PC1	PC2	PC3	PC4
Overall:				
Percent variance	40.6	34.6	21.2	3.3
Eigenvalue	1.62	1.36	.84	.133
Individual variable weights:				
Litters per dam	.74	−.13	.25	.64
Litter size	.06	.57	.63	−.31
Interbirth interval	−.63	−.37	.47	.56
Age at first birth	.23	−.72	.56	−.41

Note. Breeding frequency (first principal component [PC1]) accounts for 40.6% of the variance across strain averages, and it is negatively weighted by the average interval between consecutive litters and positively weighted by the average number of litters per dam. The second axis represents reproductive intensity (second principal component [PC2]), which accounts for 34.6% of the variance, and it is negatively weighted by the average age of a dam at the birth of her first litter and positively weighted by the average litter size for each dam of a given strain.

The distribution of strains along the breeding frequency (PC1) and reproductive intensity (PC2) axes does not show a clear pattern (appendix) and suggests variation in reproduction and performance across inbred strains of mice. When assessing the relationships among the individual reproductive variables, we revealed two significant relationships (fig. 1; appendix). A nominally significant positive relationship was found between the age of the dam at the birth of her first litter and the average number of litters per dam ($r = 0.40$, $P = 0.017$); that is, strains that first reproduce at older ages tend to have more litters over the course of their reproductive life spans. A significant negative correlation was found between the strain average number of litters per dam and the interval between consecutive litters ($r = -0.58$, $P < 0.001$).

Body Size, Reproduction, and Other Life History Characteristics

Data collected on body mass and body length (from tip of nose to base of tail) at 13 wk (hereafter referred to as 3 mo) and at 6, 12, and 20 mo were used to understand the impact of age on the strength of trait covariation. Body mass and length tended to be positively correlated with one another for the ages measured

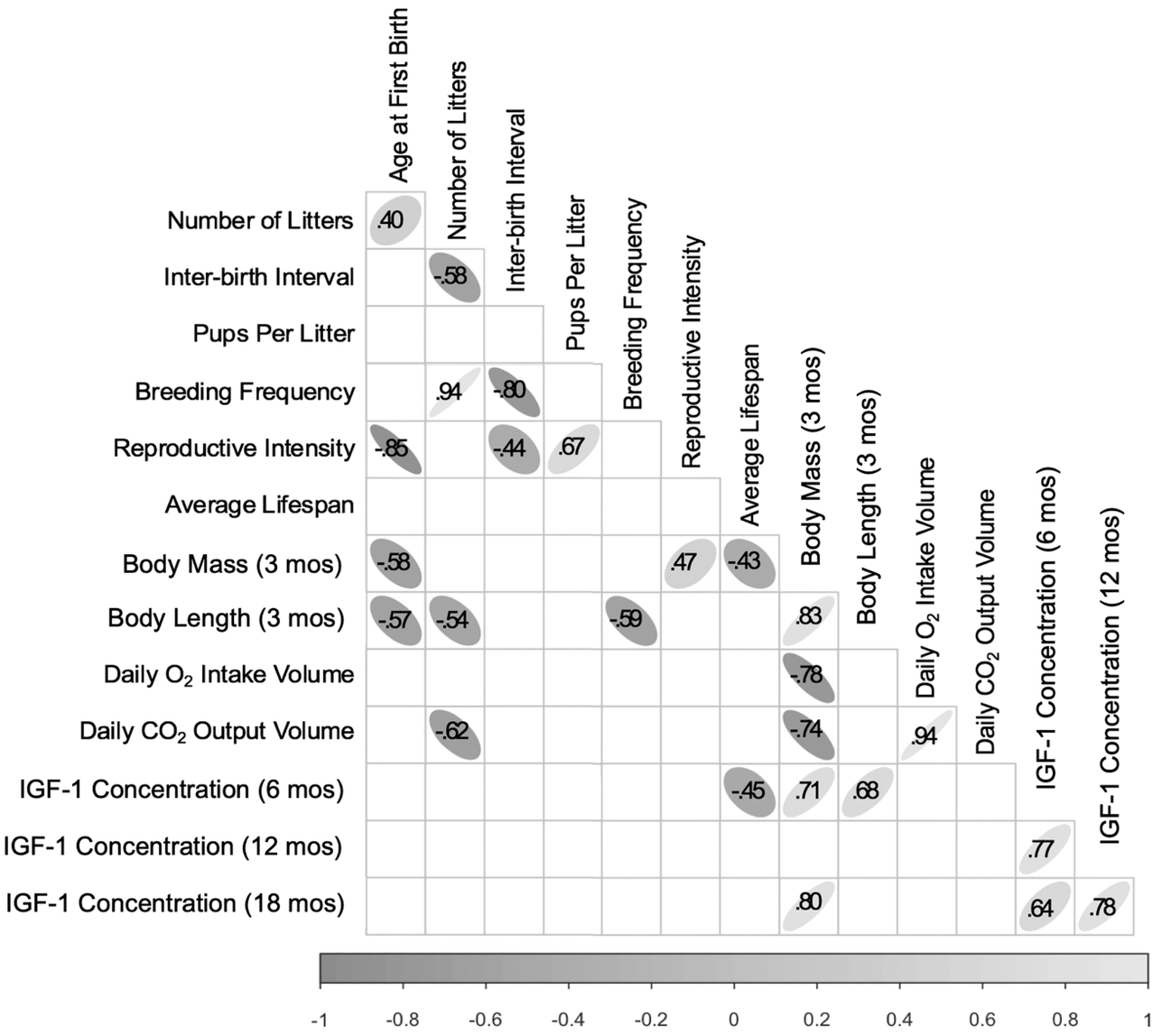

Figure 1. Correlations between reproduction, life span, body size, and metabolism in inbred laboratory mice. Significant ($P < 0.05$) Pearson's product-moment correlation coefficients (r) are given. To control for multiple comparisons, we used the positive false discovery rate procedure, with positive false discovery rate held at 5%. Although we provide the correlation coefficients for correlations with unadjusted P values <0.05, we refer to P values <0.014 as significant and P values between 0.014 and 0.05 as nominally significant. The ovals under the values range from dark (more negative) to light (more positive) and from narrow (strong correlation) to wide (weak correlation). IGF-1 = insulin-like growth factor 1.

(fig. 1; appendix). A significant negative relationship was found between the average age of females when they first gave birth and the average body mass at 3 mo of age ($r = -0.58$, $P = 0.008$); similarly, there was a nominally significant negative relationship between the age of females when they first gave birth and their body length at 3 mo of age ($r = -0.57$, $P = 0.03$). No significant relationships were found between the average age of females when they first gave birth and their body length or mass at 6, 12, or 20 mo of age (fig. 1). Body length at 3 mo of age was nominally negatively correlated with breeding frequency (PC1; $r = -0.59$, $P = 0.02$) and average number of litters per dam ($r = -0.58$, $P = 0.038$), but these relationships were not present at any other age or with body mass at any age. Reproductive intensity (PC2) was nominally positively correlated with body mass at 3 mo of age ($r = 0.47$, $P = 0.03$) but not at any other age or with body length at any age (table 3). Average interbirth interval and litter size were not found to be related to body mass or length at any age.

The strains' average life spans of females were nominally significantly correlated with average body masses at 3 mo ($r = -0.43$, $P = 0.042$), 6 mo ($r = -0.48$, $P = 0.015$), and 12 mo ($r = -0.41$, $P = 0.03$; fig. 1; table 3; appendix). Average life span was not related to average body mass at 20 mo or to body length at any age. No significant relationships were found between the strains' average life spans and any of the reproductive variables, including breeding frequency and reproductive intensity.

Physiological and Metabolic Traits Associated with Life History Characteristics

Metabolic rate is hypothesized to play a role in establishing patterns of life history trait covariation along the fast-slow continuum (Ricklefs and Wikelski 2002; Jimenez 2016, 2021). Here, we explored relationships between mass-specific metabolic variables (e.g., average daily oxygen consumption, average daily carbon dioxide production, body heat production, food and caloric intake, and heart rate at 6, 12, and 20 mo), reproduction, life span, and body size. These metabolic variables were collected when the individuals were approximately 9 wk old. Excluding heart rate, which did not appear to be related to any variables in this analysis, the variables representing metabolic rate tended to be highly correlated with one another; for example, daily oxygen intake volume and daily carbon dioxide production volume were tightly correlated ($r = 0.98$, $P < 0.0001$). Additionally, the mass-specific daily food and caloric intake volumes were nominally positively correlated with mass-specific daily oxygen intake volume (for food intake volume: $r = 0.63$, $P = 0.02$; for caloric intake volume: $r = 0.63$, $P = 0.02$) and mass-specific daily carbon dioxide production volume (for food intake volume: $r = 0.64$, $P = 0.04$; for caloric intake volume: $r = 0.63$, $P = 0.048$).

Mass-specific daily oxygen intake volume and mass-specific daily carbon dioxide production volume tended to be negatively correlated with body size (fig. 1; table 3; appendix). Specifically, body mass at 3 mo was negatively correlated with mass-specific daily oxygen intake volume ($r = -0.78$, $P = 0.005$) and nominally correlated with mass-specific daily carbon dioxide production volume ($r = -0.74$, $P = 0.03$), mass-specific daily food intake volume ($r = -0.72$, $P = 0.02$), and mass-specific daily caloric intake volume ($r = -0.72$, $P = 0.02$). Body length at 3 mo was also negatively related to mass-specific daily food intake volume ($r = -0.90$, $P = 0.01$) and nominally related to mass-specific daily caloric intake volume ($r = -0.90$, $P = 0.02$). Though not significant, a trend was present between mass-specific average daily oxygen consumption and reproductive intensity (PC2; $r = -0.51$, $P = 0.065$), where strains with higher mass-specific daily oxygen consumption tended to also reproduce at older ages and have smaller average litter sizes. Similarly, mass-specific average daily carbon dioxide production volume was nominally negatively related to the average number of litters for a given strain ($r = -0.62$, $P = 0.05$), indicating that a higher metabolic rate was correlated with fewer litters across the reproductive life span. Excluding these relationships, we found no other correlations between metabolic variables and reproductive traits or average life span.

The hormone IGF-1 has been identified as a putative link connecting pace of life and metabolic rate because of its pleiotropic effects (Ricklefs and Wikelski 2002; Dantzer and Swanson 2012). Our analysis revealed significant relationships between IGF-1 concentration and body size and life span. No significant relationships were found between IGF-1 and reproduction or metabolism (other than IGF-1 concentration at other ages). In general, the concentration of IGF-1 in serum was positively correlated with body mass and length (table 3). Concentrations of serum IGF-1 at the different ages tended to be highly positively correlated with one another. At 6 mo of age, a strain's average serum concentration of IGF-1 was nominally negatively correlated with its average life span ($r = -0.40$, $P = 0.027$), but this relationship was not present at any other age. We did not find any other significant correlations between the concentration of IGF-1 and the reproductive or metabolic variables included in this study.

Discussion

At a cursory glance, insights gained from comparing inbred strains of laboratory animals typical of biomedical research may seem irrelevant for understanding natural populations. We argue the opposite: the high phenotypic diversity captured across the numerous strains of laboratory mice can be valuable for understanding topics central to evolutionary biology. Phenotypic diversity produced by artificial selection provides an excellent opportunity to evaluate the interactions among traits that would otherwise not persist in the wild (Grafen 1988; Conner 2003; Fuller et al. 2005; Swallow et al. 2009). We used phenotypic data collected from strains of inbred mice in this heuristic descriptive analysis to understand how life history traits (e.g., body size, reproduction, and life span) and metabolic traits (e.g., daily energy expenditure [DEE] and IGF-1 concentration) covary at the intraspecific level.

Interspecific analyses have identified body size as a key determinate of where species fall along the fast-slow life history

Table 3: Relationships of body size with life span, reproductive performance, metabolism, and insulin-like growth factor 1 (IGF-1) in inbred laboratory mice

		Fitness-related variables		Metabolic variables		Serum IGF-1 concentrations (ng/mL)		
	Average life span (d)	Age at first birth	Reproductive intensity	Daily O_2 (mL/kg/h)	Daily CO_2 (mL/kg/h)	6 mo	12 mo	18 mo
Body mass (g):								
3 mo[a]	**−.44 (.02)**	**−.61 (<.001)**	**.64 (.001)**	**−.76 (<.001)**	**−.74 (.01)**	**.73 (<.001)**	.40 (.064)	.36 (.102)
6 mo	**−.36 (.05)**	**−.57 (<.001)**	**.54 (.011)**	**−.74 (.003)**	**−.79 (.007)**	**.59 (.008)**	**.71 (.001)**	**.71 (.001)**
12 mo	**−.41 (.03)**	−.28 (.23)	.26 (.27)	**−.65 (.02)**	**−.82 (.007)**	**.53 (.006)**	**.54 (.006)**	**.72 (<.001)**
20 mo	−.17 (.38)	−.08 (.74)	.14 (.57)	−.47 (.15)	−.57 (.11)	.37 (.121)	.35 (.146)	**.55 (.018)**
Body length (cm):								
3 mo[a]	−.3 (.14)	**−.67 (<.001)**	**.72 (<.001)**	**−.67 (.008)**	−.59 (.16)	**.72 (<.001)**	.34 (.198)	.22 (.419)
6 mo	−.28 (.12)	**−.56 (<.001)**	**.57 (.007)**	**−.72 (.008)**	**−.78 (.01)**	**.78 (<.001)**	**.79 (<.001)**	**.73 (.001)**
12 mo	−.29 (.13)	−.35 (.13)	.37 (.10)	−.57 (.07)	**−.74 (.03)**	**.71 (<.001)**	**.75 (<.001)**	**.72 (<.001)**
20 mo	−.27 (.15)	−.12 (.62)	.11 (.66)	**−.76 (.01)**	**−.85 (<.001)**	**.66 (.003)**	**.67 (.003)**	**.81 (<.001)**

Note. Pearson's product-moment correlation coefficients (r) for body mass and length versus several life history and metabolic variables and IGF-1 at three different ages. P values are given in parentheses, and significant ($P \leq 0.05$) relationships are shown in bold. Reproductive intensity was the second principal component.

[a]Animals were 13 wk of age at the time that measurements were taken, which we refer to as 3 mo.

continuum (Promislow and Harvey 1990). Our intraspecific analysis revealed that body size correlated with multiple life history and metabolic variables but that these relationships were not static across the life span and that the strongest correlations tended to appear earlier in life. Specifically, we found that females from strains that were smaller at 3 mo of age tended to start reproducing later, have fewer litters over the course of their reproductive life span, and have decreased overall reproductive output (as indicated by our two PCs, breeding frequency and reproductive intensity) compared to their larger conspecifics. Likely, the decreased reproductive output in these strains is due to shorter reproductive life spans resulting from both delayed maturation and shorter life spans, as body mass was not correlated with the interval between two consecutive litters. We are, however, limited in our ability to definitively speak to the reproductive life span of these strains, as those data were not collected and breeding data were collected only until dams reached 40 wk of age, which captured the majority, but not all, of their potential reproductive life spans (Flurkey and Currer 2009). Previous intraspecific analyses, including comparisons across breeds of domesticated dogs (Jimenez 2016, 2021), found similar patterns, suggesting that body size plays a role in determining the latency to sexual maturity and the number of offspring in each reproductive bout rather than in regulating the overall number of reproductive events (Frisch 1987; Chehab et al. 1997). Together, our results suggest that body size early in life, which is most likely a proxy for developmental rate, is linked to reproduction and performance.

Despite finding relationships linking body size to both longevity and reproduction, we did not find any evidence for a trade-off between strain average measurements of reproductive traits and longevity, regardless of the broad variation in reproductive traits across strains of inbred mice (appendix). However, although we did not find evidence for a direct trade-off between reproduction and life span, our results suggest that there is a mediating factor that links both traits, as females from strains with smaller average masses tended to have decreased reproductive outputs as well as longer life spans. Likely, this body condition acts as the mediating factor between reproductive performance and longevity, as it has been widely documented that both traits are condition dependent (Clutton-Brock 1984; Benton et al. 2008; Hamel et al. 2008, 2010). The notion that the large energetic demand of reproduction necessarily incurs costs to somatic investment, and therefore to longevity, is pervasive within the field of biology, despite empirical studies not always supporting this assumption (Zhang and Hood 2016). This finding demonstrates that reproductive performance does not necessarily trade off with longevity but rather that persistent costs may be revealed only under certain environmental conditions not present in the benign environment of these laboratory populations.

However, there are several alternative explanations for our findings. First, natural selection has shaped both pace-of-life and life history trade-offs in wild animals; conversely, the relaxed selection coupled with inbreeding may have removed the underlying architecture in inbred laboratory conspecifics. For example, Miller et al. (2000) posited that the development of inbred strains of mice may have selected against alleles that delay aging and instead favor rapid maturation with higher early reproductive rates and diminished longevity. Second, many inbred strains of mice have associated disease phenotypes resulting from the expression of rare and deleterious alleles that are in part a result of inbreeding itself (for a list of pertinent disease phenotypes for the strains that we used in the present study, see the appendix). Many of these diseases manifest later in life, thereby truncating a strain's average longevity, and there is potential for strains to have accelerated senescence that occurs independently from the life history relationships that we explore in the present study. Nonetheless, we believe that the relationship between longevity and reproductive performance in these strains of mice warrants further exploration.

At the proximate level, life history variation is mediated by physiological components, such as pleiotropic hormones and metabolic rate (Ketterson and Nolan 1992; Hau et al. 2011; Garland et al. 2016), as a consequence of selection linking shared developmental and physiological networks (Davidowitz et al. 2012). Metabolic rate has been implicated as a mechanism underlying the observed relationships between body size and life history traits, such as longevity and reproductive performance. At both the inter- and intraspecific levels, larger animals tend to have lower mass-specific metabolic rates than smaller animals (Promislow and Harvey 1990; Careau et al. 2013; Jimenez 2016). This pattern was reflected in our results, as mass-specific DEE (i.e., mass-specific daily oxygen intake volume and mass-specific daily carbon dioxide output volume) tended to be negatively related to body size. DEE was not found to be related to longevity or reproduction, which concurs with findings from previous studies (Derting and McClure 1989; Earle and Lavigne 1990; Hayes et al. 1992). Thus, despite the presence of a relationship between DEE and body size, DEE does not appear to mediate the relationships between body size and other life history characteristics, or alternatively, it may have a mediating role that becomes apparent only under specific conditions. It is important to note that the data that we included for this analysis were reported by the Jackson Laboratory's Mouse Phenome Database as mass-specific values rather than as absolute values, and thus, we are limited in our understanding on whether these relationships are still present after accounting for covariation with mass (Hayes and Shonkwiler 1996; Hayes 2001). Additionally, the data used in the present analysis represent strain averages, and much of the reproductive data (e.g., total number of pups born per litter) represent averages across the life span. Reproductive performance is not static across the life span, and litter size varies with parity in many species, including mice (Zhang and Hood 2016; Vargovic et al. 2022). The findings from this work, as well as from previous work on domesticated animals (Jimenez 2016, 2021), may represent an uncoupling of the relationships between metabolic rate and life history traits, since domesticated animals tend to have abundant resources and do not face the same challenges as their nondomesticated counterparts.

Similar to the hypothesized mediating role of metabolism in inter- and intraspecific life history trait variation, pleiotropic hormones allow for coordinated responses in multiple tissue and organ systems. IGF-1 responds to the nutritional status of

the individual and exerts pleiotropic effects on metabolism, development, growth, body size and composition, onset of sexual maturity, reproduction, and life span (Bartke 2005; Yuan et al. 2012). This hormone has been suggested to play a role in the inter- and intraspecific variation of life history traits in several different taxa, including mammals (Dantzer and Swanson 2012; Swanson and Dantzer 2014), passerine birds (Lodjak et al. 2018), and reptiles (Schwartz and Bronikowski 2016). For example, the negative relationship between IGF-1 and life span has been exploited in mutant strains of mice, such as the Snell, Ames, or growth hormone receptor knockout mice; these strains have attenuated insulin/IGF-1 signaling as well as small body sizes and increased life spans (Bartke and Brown-Borg 2004). Given the coordinating role of this hormone, it is feasible that IGF-1 underlies the observed relationships at the intraspecific level. Consistent with previous findings, such as those of Harper et al. (2003), our results indicate an age-dependent inverse relationship between life span and serum IGF-1 concentration at 6 mo of age but not at any other age. The time frame of the age-dependent relationship between IGF-1 and life span mimics the relationships between body mass and life span and reproductive output, providing further evidence of the importance of IGF-1 in the proximate regulation of life history variation.

Taken together, this study suggests that the intraspecific relationships among life history traits, and the physiological mechanisms behind those relationships, are not always consistent with predictions from interspecific studies. Differences between inter- and intraspecific patterns of life history trait covariation, as previously predicted (Harvey et al. 1989), are most pronounced in the relationships between body size and longevity and reproductive performance. Despite the reversal in the direction of the relationships between body size and reproduction and life span, the overall relationships between mass-specific metabolic rate and IGF-1 concentration match previous interspecific findings. It is not known whether these deviations from the predicted interspecific findings are caused by the domestication process, representing an uncoupling between metabolism and key life history traits or whether these same deviations are present in nondomesticated populations. Given the importance of understanding physiological and metabolic mechanisms that support life history variation (Ricklefs and Wikelski 2002), this study highlights the importance of conducting intraspecific analyses of life history and metabolic trait patterns of covariation.

Acknowledgments

We thank Dr. Theodore Garland Jr. for his help with and feedback on our statistical analyses. We thank the Hood and Hill labs and Drs. Tonia Schwartz, Dan Warner, Sarah Zohdy, and James Wright for their comments on an earlier version of the manuscript. We also thank two anonymous reviewers for their thoughtful comments. This work was supported by the National Science Foundation Graduate Research Fellowship and Postdoctoral Research Fellowship in Biology (1907314 to C.C.J. and IOS1453784 and OIA1736150 to W.R.H.).

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