Compensatory Growth Is Accompanied by Changes in Insulin-Like Growth Factor 1 but Not Markers of Cellular Aging in a Long-Lived Seabird

Aubrey E. Sirman,[1,*] Jacob E. Schmidt,[1] Mark E. Clark,[2] Jeffrey D. Kittilson,[1] Wendy L. Reed,[3] and Britt J. Heidinger[1]

1. Biological Sciences Department, North Dakota State University, Fargo, North Dakota 58108; 2. Biology Department, University of Minnesota, Duluth, Minnesota 55812; 3. Swenson College of Science and Engineering, University of Minnesota, Duluth, Minnesota 55812

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ABSTRACT: Developing organisms often plastically modify growth in response to environmental circumstances, which may be adaptive but is expected to entail long-term costs. However, the mechanisms that mediate these growth adjustments and any associated costs are less well understood. In vertebrates, one mechanism that may be important in this context is the highly conserved signaling factor insulin-like growth factor 1 (IGF-1), which is frequently positively related to postnatal growth and negatively related to longevity. To test this idea, we exposed captive Franklin's gulls (*Leucophaeus pipixcan*) to a physiologically relevant nutritional stressor by restricting food availability during postnatal development and examined the effects on growth, IGF-1, and two potential biomarkers of cellular and organismal aging (oxidative stress and telomeres). During food restriction, experimental chicks gained body mass more slowly and had lower IGF-1 levels than controls. Following food restriction, experimental chicks underwent compensatory growth, which was accompanied by an increase in IGF-1 levels. Interestingly, however, there were no significant effects of the experimental treatment or of variation in IGF-1 levels on oxidative stress or telomeres. These findings suggest that IGF-1 is responsive to changes in resource availability but is not associated with increased markers of cellular aging during development in this relatively long-lived species.

Keywords: telomeres, telomere dynamics, growth rates, insulin-like growth factor 1, compensatory growth, nutritional stress.

Introduction

Developing organisms often flexibly modify growth in response to environmental conditions. For example, when food becomes scarce, growth is often slowed and then resumed again or even accelerated once resources become more readily available (Metcalfe and Monaghan 2001). Matching the pace of growth to resource availability may be adaptive in the short term but is also often accompanied by long-term costs. These costs can occur as a result of an initial developmental setback, as a consequence of later increasing the pace of growth to catch up to the original growth trajectory, or both (Metcalfe and Monaghan 2001). Regardless, the mechanisms that mediate these plastic growth adjustments and the long-term costs associated with them are less well understood.

In vertebrates, one mechanism that may be important in this context is insulin-like growth factor 1 (IGF-1). IGF-1 is a highly conserved metabolic hormone that is part of the insulin/insulin-like signaling pathway (e.g., IGF-1, IGF-2, and insulin) and is regulated by the somatotropic (growth hormone/IGF-1) axis. IGF-1 is sensitive to a range of environmental stimuli (Dantzer and Swanson 2012; Regan et al. 2020), including changes in resource availability, and is expected to play a conserved role in regulating growth in vertebrates (Bruggeman et al. 1997; du Dot et al. 2009; Killpack and Karasov 2012; although see Schew et al. 1996; Schaetzlein et al. 2004). For example, domesticated sheep that are selected for higher IGF-1 levels grow faster (Kenyon et al. 2009), and knockout mice with disrupted IGF-1 signaling are smaller at birth and grow more slowly during postnatal development than controls (Baker et al. 1993; Liu et al. 1993; Ducos et al. 2003).

IGF-1 may also be involved in mediating long-term costs of plastic growth adjustments, and this could occur through many routes. For example, growth is a metabolically demanding activity that can generate reactive oxygen species

* Corresponding author. Present address: Arrupe College, Loyola University, Chicago, Illinois 60611; email: asirman@luc.edu.

ORCIDs: Sirman, https://orcid.org/0000-0002-1277-4850; Clark, https://orcid.org/0000-0003-4802-8478; Reed, https://orcid.org/0000-0001-9222-5386; Heidinger, https://orcid.org/0000-0003-0064-209X.

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(ROS), which when not sufficiently quenched can result in oxidative damage to macromolecules, including DNA, and accelerate the pace of biological aging (Von Zglinicki 2002). Consistent with this idea, in addition to growing more slowly, knockout mice with experimentally reduced IGF-1 have greater resistance to oxidative stress and live an average of 26% longer than controls (Ducos et al. 2003). Recent in vitro evidence also suggests that elevated IGF-1 shortens telomeres (Matsumoto et al. 2015), highly conserved noncoding segments of DNA that enhance genome integrity and are often positively related to longevity (Monaghan 2010). Telomeres also often shorten in response to stress and metabolically demanding activities, such as rapid growth (Monaghan and Haussmann 2006; Geiger et al. 2012; Pauliny et al. 2015).

Taken together, these studies suggest that IGF-1 may be involved in mediating plastic growth adjustments and contribute to long-term costs associated with changes in growth profiles. However, much of the research supporting these ideas comes from domestic animals, and whether this is also true in nonmodel organisms is less well understood. Here, we experimentally tested the hypothesis that organisms plastically modify their growth rate and IGF-1 levels in response to reduced food availability and that these growth modifications increase oxidative stress and telomere loss, potential biomarkers of cellular and organismal aging. To test these ideas, we experimentally manipulated nutritional stress by restricting resource availability in captive Franklin's gulls (*Leucophaeus pipixcan*) for a 10-day period during postnatal development. We predicted that (1) IGF-1 levels and growth rates would be reduced during the 10-day restriction period in experimental chicks relative to controls and that (2) experimental chicks would experience greater oxidative stress and telomere loss than controls because of the initial developmental insult and/or increasing the pace of growth following the restriction period.

Methods

Study System, Egg Collection, and Incubation

This study was conducted between May and August 2015 in a population of Franklin's gulls that breed in Rush Lake, North Dakota (Clark and Reed 2012). Franklin's gulls breed in small to large colonies in prairie marshes in the interior of North America. Breeding is highly synchronous, and adults will lay single three- to four-egg clutches (Burger and Gochfield 2020). Maximum life spans have not been recorded for Franklin's gulls, but maximum life spans of the closest relatives (lava gull [*Leucophaeus fulginosus*] and laughing gull [*L. atricilla*]; Pons et al. 2005) can exceed 30 years. To minimize disturbance and time spent in the colony, the first eggs of clutches were collected just after laying on two occasions that spanned the breeding season, May 7 ($n = 25$ early-season eggs) and May 25 ($n = 25$ late-season eggs), and measured (egg length [±0.1 mm] and breadth [±0.1 mm]) in the laboratory within 8 h of collection. Eggs were then randomly assigned to an incubator maintained at 37.5°C and 65% relative humidity with automatic egg turners (Brinsea Mini EX high-performance egg incubator).

Incubators were then placed in environmental chambers maintained at 24°C that were equipped with full-spectrum light bulbs set to timers. Consistent with previous studies in this system, eggs collected earlier in the season on May 7 were incubated under a shorter-day photoperiod (14L:10D 24-h cycle), and eggs collected later in the season on May 25 were incubated under a longer-day photoperiod (18L:6D) to mimic seasonal variation in day length (Clark and Reed 2012). After 21 days of incubation, eggs were removed from automatic turning and checked daily for signs of hatching. Average time to hatch was 24.2 days ± 0.27 and is comparable to what is observed in the wild (Burger and Gochfield 2020). Hatching success was high (21/25 eggs [84%] for the May 7 collection date and 20/25 [80%] for the May 25 collection date) and was mostly synchronous, but not all chicks hatched on the same day or time, with a mean hatch spread of 36.4 h ± 3.53.

Experimental Design

After hatching, chicks were immediately removed from the incubator, weighed, and placed in a brooder for approximately 12 h. After 12 h in the brooder, chicks were randomly assigned to either a control or experimental treatment using a random number generator (see description below) and divided by treatment into smaller rearing groups. Each rearing group contained three or four chicks of the same treatment and of similar ages (±1 day posthatching). In total, there were six control rearing groups and six experimental rearing groups with 38 chicks (May 7 collection: $n = 20$, 10 control and 10 restricted chicks; May 25 collection: $n = 18$, nine control and nine restricted chicks). At hatching, body mass did not differ significantly between treatment groups ($F_{1,33} = 0.016$, $P = .89$). Since Franklin's gull chicks are semiprecocial at hatching (Burger and Gochfeld 2009), we waited 7 days before starting the experimental treatment to ensure that the chicks were able to feed on their own. During this 7-day prerestriction period (fig. 1), all chicks were fed ad lib. while they learned to eat and acclimate to their assigned rearing groups. All chicks were fed moistened dry cat food (Royal Canin Mother and BabyCat 34; 34% minimum crude protein, 24% minimum crude fat, 3.5% maximum crude fiber, 4,406 kcal/kg) on the basis of success in previous studies (Reed and Clark 2016).

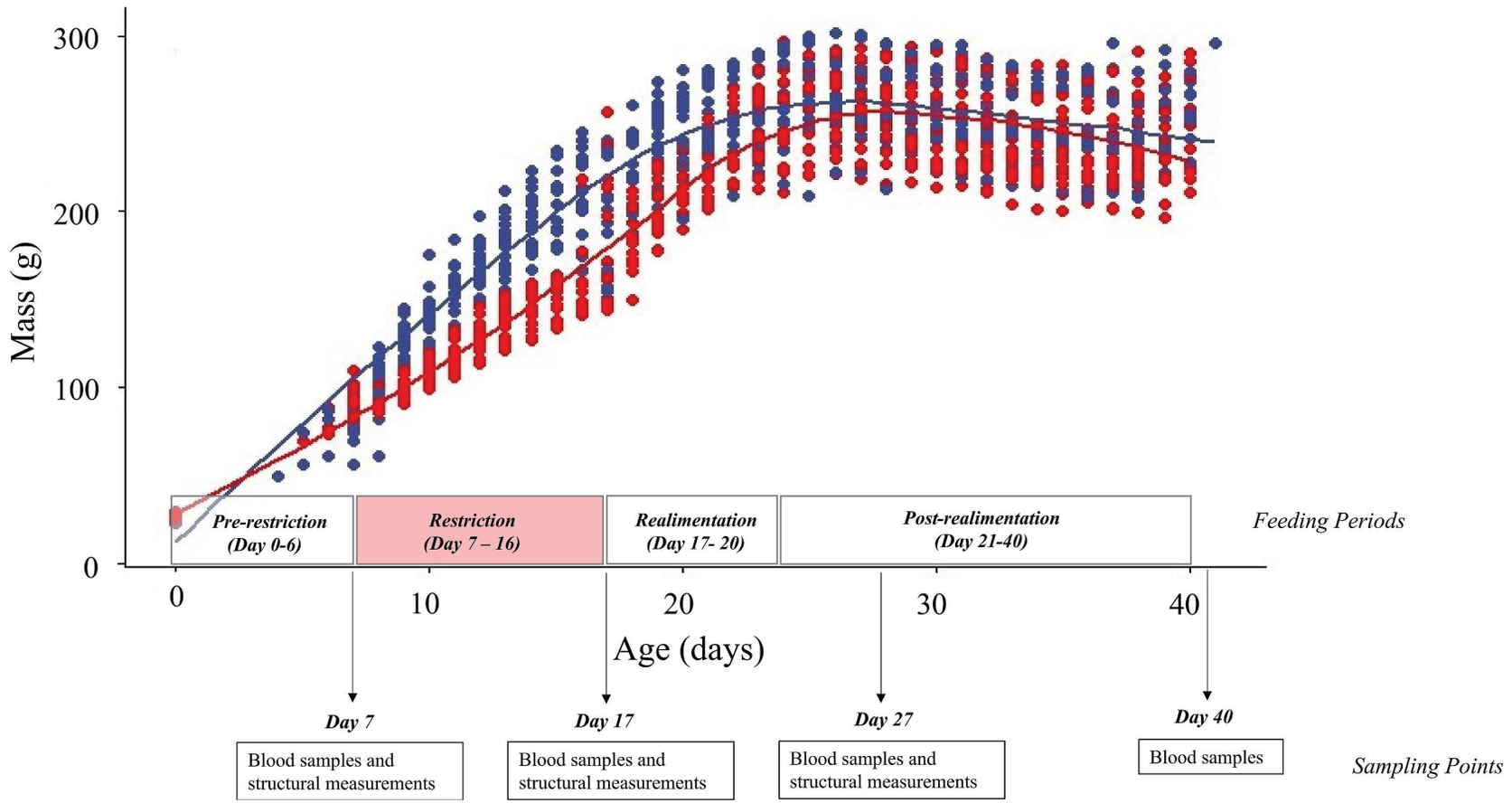

Figure 1: Franklin's gull (*Leucophaeus pipixcan*) daily chick body mass growth (g) measured prior to feeding throughout the experiment. Control chicks are depicted in blue and received food ad lib. across all feeding periods. Experimental chicks are depicted in red and received only 60% of the food consumed by control chicks during the restriction period but received ad lib. access to food during all other feeding periods. Structural measurements were collected on days 7, 17, and 27 posthatching, and blood samples were collected on days 7, 17, 27, and 40 posthatching.

To experimentally manipulate growth trajectories, we restricted the food intake of experimental chicks relative to controls for a 10-day period (restriction period; fig. 1). Between days 7 and 16 posthatching, control chicks continued to be fed ad lib., and experimental chicks received 60% of this ad lib. control food intake. At each feeding, the amount offered to experimental chicks was calculated as 60% of the food intake consumed by the oldest control group. The oldest control group was fed first to determine the amount of food that would be offered to experimental chicks. During all feedings, all of the chicks in both treatment groups were fed individually, separated by dividers, to accurately measure how much food was consumed, to confirm that each chick received the same amount of food at each feeding within a rearing group, and to reduce within-group competition for food. This level of food restriction is consistent with other food restriction studies that have been conducted in seabirds and is expected to be within the range of natural conditions experienced by the chicks (Kitaysky et al. 1999, 2001). Throughout the restriction period, we confirmed that food-restricted chicks were maintaining, rather than losing, weight, and no health problems were observed during the 10-day treatment period in either control or experimental chicks. Following this 10-day restriction period, experimental chicks resumed ad lib. feeding, and all chicks in both treatment groups received food ad lib. for the remainder of the study.

The ability to quantify and detect compensatory growth is compromised by including measurements collected from individuals nearing asymptotic size (Hector and Nakagawa 2012). In Franklin's gulls, chicks begin to reach asymptotic size at 20 days (Reed and Clark 2016); thus, we defined the realimentation period as from the time when the experimental chicks resumed ad lib. feeding following restriction to 20 days posthatching (fig. 1). We then defined the time after the realimentation period until the end of the experiment as the postrealimentation period (fig. 1).

Sample Collection

To assess the potential effects of the treatment on growth, IGF-1, oxidative stress, and telomeres, we collected daily body mass measurements (to the nearest 0.1 g) and structural size measurements (culmen, head-to-bill length, wing chord to the nearest 0.1 cm) and blood samples at key sampling points: on day 7 posthatching, just prior to the restriction period; on day 17 posthatching, at the end of the restriction period; and on day 27 posthatching, during the postrealimentation period. We also collected a final blood sample at the end of the experiment on day 40 posthatching to measure telomere loss and assess the potential effect of IGF-1 on telomere length and loss at the time of sampling (fig. 1).

All measurements and blood samples were collected at 7 a.m. prior to feeding. Blood samples were collected from the chicks after fasting overnight and prior to the first feeding of the morning via venipuncture of the alar vein. All blood samples were stored on ice immediately after collection for less than an hour. Samples were then centrifuged at 10,000 *g* for 10 min, and separated red blood cells and plasma fractions were stored at −80°C until further analysis.

Hormone Measurement

IGF-1 levels were measured using an enzyme-linked immunosorbent assay multispecies IGF-1 kit from Immunological and Biochemical Test Systems (distributed by Eagle BioSciences). To measure total IGF-1 concentrations, 20-μL plasma samples were acid extracted to free the IGF-1 fraction from binding proteins. The acid extraction releases the bound IGF-1 fraction from the binding proteins (Clemmons et al. 1997). This is significant because most (~95%) of the circulating IGF-1 is bound to binding proteins and thus not biologically active (Radecki et al. 1997; Yakar et al. 2002) To acid extract our samples, we followed the acid extraction protocol provided by the kit. Specifically, for our samples and standards, we added 50 μL of 1M HCl, incubated them at room temperature for 15 min, and then added 10 μL of neutralization buffer to stop the reaction. Following the acid extraction, the neutralized samples and standards were added to each well with slight modifications to the initial sample and standard volumes. We then added 100 μL of the conjugate and incubated the samples and standards at room temperature for 2 h, following kit protocol. After 2 h, we discarded the solution and washed the wells with a buffer. We then added 150 μL of the enzyme complex and incubated samples and standards for 1 h at room temperature. After incubation, we discarded the solution. After washing the wells with buffer, we added 100 μL of substrate and incubated the plate for 15 min at room temperature before stopping the reaction. The plate was read at 450 nm, and 620 nm was used as the reference wavelength to obtain absorbance values. We validated this kit for use in Franklin's gulls using a serial plasma dilution (for details, see the supplemental PDF). Samples were assayed in duplicate. The mean intra-assay coefficient of variation was 2.18%, and the mean interassay coefficient of variation was 2.70%. We used a pooled plasma sample across all plates to calculate the interassay variation. The sensitivity of the assay was 1.0 ng/mL, and all samples had detectable IGF-1 levels.

Telomere Measurements

Relative telomere length was measured in red blood cells, which are nucleated in birds and are highly proliferative

and well suited for longitudinal analysis. DNA was extracted from red blood cells using Macherey Nagel NucleoSpin Blood kits, following the manufacturers protocol. DNA concentration was assessed using a NanoDrop 8000 spectrophotometer (ThermoScientific). Relative telomere lengths were measured on days 7 and 40 posthatching using quantitative polymerase chain reaction (qPCR) on an Mx3000P instrument (Stratagene; Cawthon 2002; Schmidt et al. 2016). We calculated the relative telomere length (T/S) of the samples as the ratio of the telomere repeat copy number (T) to that of a single copy control gene (S), relative to the reference sample.

We used the following gull-specific glyceraldehyde-3-phosphate dehydrogenase (GAPDH) forward and reverse primers as the single-copy control gene (Integrated DNA Technologies): 5′-CGGAGCACCGCTTACAATTT-3′ (forward) and 5′-GCATCTCCCACTTGATGTTG-3′ (reverse). The following primers were used to measure telomeres: 5′-CGGTTTGTTTGGGTTTGGGTTTGGGTTTGGGTTTGGGTT-3′ (TEL1b) and 5′-GGCTTGCCTTACCCTTACCCTTACCCTTACCCTTACCCT-3′ (Tel2b).

Reactions for GAPDH and telomeres were run on separate plates. The total volume for each reaction was 25 μL and contained 20 ng of DNA and either GAPDH or telomere primers at a 200 nM forward/200 nM reverse concentration mixed with 12.5 μL of PerfeCTa SYBR Green Supermix, Low ROX (Quantabio). The thermal profiles for the qPCRs were as follows: for GAPDH, 10 min at 95°C followed by 40 cycles of 30 s at 95°C and 30 s at 60°C; for telomeres, 10 min at 95°C followed by 27 cycles of 15 s at 95°C, 30 s at 58°C, and 30 s at 72°C. The number of PCR cycles (C_t) required for the products to accumulate enough fluorescence to cross a threshold was determined. Individuals with relatively long telomeres were characterized by low C_t values, and individuals with relatively short telomeres were characterized by high C_t values. Each sample was run in triplicate, and the average values were used to determine the T/S ratio according to the following formula: $2^{\Delta\Delta C_t}$, where $\Delta\Delta C_t = (C_t^{\text{Telo}} - C_t^{\text{GAPDH}})$ reference $- (C_t^{\text{Telo}} - C_t^{\text{GAPDH}})$ (Agilent 2012). Water was used as a nontemplate control sample on each plate. The repeatability of the T/S ratio was calculated by running 20 Franklin's gull samples in random well locations across two plates. The intraclass correlation coefficient (two-way, single-measurement, absolute-agreement random effects model) was 0.863 ($P < .001$; 95% confidence interval [CI]: 0.692 to 0.943). The average plate efficiencies for telomeres were 102.2% (±0.45) and 93.8% (±0.42) for GAPDH.

Oxidative Stress Measurements

We measured total antioxidant capacity in the plasma using the OXY-Adsorbent test (Diacron International) and protein carbonyls, a well-established biomarker of oxidative damage to proteins (Enzo Life Sciences). Protein carbonylation occurs when ROS or lipid peroxidation products add carbonyl groups (C = O) to proteins and is often irreversible (Halliwell and Gutteridge 1985). Antioxidant capacity was measured in plasma following established methods previously described in birds (Costantini et al. 2008). We diluted 10 μL of plasma into 990 μL of distilled water (a 1∶100 dilution). We then mixed 5 μL of this solution with 195 μL of the HCOI solution provided in the kit. We measured the absorbance at 490 nm (Bio-Rad xMark microplate spectrophotometer) and calculated total antioxidant capacity in mmol/L HOCI neutralized. All samples were run in a single assay in duplicate. The mean intra-assay coefficient of variation was 4%, and the interassay coefficient of variation was 17.7%. Protein carbonyls were measured in red blood cells as a parameter of oxidative damage, following the standard kit protocol for samples containing 0.4–80 mg/mL protein. We then diluted our samples following the kit protocol and added 200 μL of each diluted sample to our 96-well plate, leaving samples to incubate overnight at 4°C. We then washed the plate with 300 μL of wash buffer and added 200 μL of diluted blocking solution, allowing incubation for 1 h at 37°C. Following the incubation, we washed the plate with buffer as before and added 200 μL of the diluted anti-DNP antibody, allowing samples to incubate for another hour at 37°C. We then washed the plate as described above and added 200 μL of diluted streptavidin-HRP, incubating the plate for a final time at 37°C. The plate was then washed for a final time using 300 μL of wash buffer and 200 μL of the chromatin reagent was added, allowing the color to develop at room temperature. Absorbances were read at 450 nm, and the carbonyl content was calculated for each sample. All samples were run in duplicate. The mean intra-assay coefficient of variation was 7%, and the interassay coefficient of variation was 12.5%.

Statistical Methods

In total, 38 gull chicks were included in the experiment ($n = 18$ experimental and $n = 20$ controls). As expected, prior to the start of the experiment, control and experimental chicks did not significantly differ in body mass ($F_{1,33} = 0.69$, $P = .41$), structural size ($F_{1,33} = 0.39$, $P = .54$), IGF-1 level ($F_{1,32} = 0.38$, $P = .53$), antioxidant capacity ($F_{1,30} = 0.19$, $P = .67$), protein carbonyl content ($F_{1,25} = 0.12$, $P = .73$), or telomere length ($F_{1,32} = 0.86$, $P = .36$).

We assessed the potential effect of the experimental treatment on chick body mass growth during three distinct feeding periods: restriction, realimentation, and postrealimentation (fig. 1). The ability to quantify compensatory growth

is compromised by including measurements collected from individuals nearing asymptotic size (Hector and Nakagawa 2012); thus, we defined the realimentation period as the time between the end of the restriction period on day 17 and day 20 (Reed and Clark 2016). We used linear mixed effects models to assess the potential influence of the treatment on body mass growth rate. To measure body mass growth rate, we calculated the daily mass growth rate for each individual in grams per day as $Mass_{i+1} - Mass_i$, where $Mass_i$ is the body mass (in grams) at age i of the individual on a specific day. For each individual during each feeding period (i.e., restriction, realimentation, and postrealimentation), we then used the median of the daily mass growth rates during the respective period to quantify individual growth rate over the period. We used the median rather than the mean absolute growth rate to minimize the potential effects of outliers when obtaining individual daily mass measurements from chicks. The model for growth included treatment, feeding period (restriction, realimentation, and postrealimentation), sex, collection date, and a treatment × feeding period interaction as fixed effects and chick ID as a random effect (table 1). Tukey's post hoc tests were used to assess the effects of the treatment on growth during the different feeding periods. Specifically, we compared median absolute growth of treatment groups at the start of the experiment (restricted control vs. restricted restriction; table 1) to confirm there were no differences in growth at the start of the experiment. We then compared median absolute growth of control and restricted groups at the end of the restriction period (realimentation control vs. realimentation restricted; table 1) to identify whether our food restriction impacted chick growth. We

Table 1: Effect of experimental food restriction on median absolute growth rate and structural growth in Franklin's gull chicks

Dependent variable	$\beta \pm$ SE	F	P
1. Median absolute growth rate:			
Independent variable/factor:			
Intercept	−1.19 ± .28	…	…
Treatment[a]	.78 ± .28	16.17	<.001**
Feeding period	…	7,899.09	<.001**
Sex[b]	.23 ± .28	.682	.41
Collection date[c]	.41 ± .28	2.19	.15
Feeding period × treatment	…	1,310.22	<.001**
Post hoc analysis (selected pairwise comparisons):			
Restriction control vs. restriction restricted	6.66 ± .29	…	<.001**
Realimentation control vs. realimentation restricted	−9.63 ± .36	…	<.001**
Restriction control vs. realimentation restricted	4.00 ± .33	…	<.001**
Postrealimentation control vs. postrealimentation restricted	−.78 ± .28	…	.12
2. Structural growth (PC1):			
Independent variable/factor:			
Intercept	−1.25 ± .05	…	<.001**
Treatment[a]	−.02 ± .05	4.47	.04*
Sampling period		3,184.63	<.001**
Sex[b]	.05 ± .06	7.17	.01*
Collection date[c]	−.06 ± .05	1.39	.23
Treatment × sampling period		6.55	.002*
Post hoc analysis (selected pairwise comparisons):			
Day 7 control vs. day 7 restricted	.02 ± .06	…	.99
Day 17 control vs. day 17 restricted	.23 ± .06	…	.005*
Day 27 control vs. day 27 restricted	.06 ± .06	…	.89

Note: Model 1 includes treatment, feeding period, sex, and collection date as well as an interaction between treatment and feeding period. Fitted model 2 includes treatment, sampling period, sex, and collection date as well as interactions between treatment and sampling period and between sampling period and sex. All nonsignificant ($P < .05$) interactions were removed from the final models. Tukey's post hoc tests were used to examine multiple comparisons between feeding periods. Parameter estimates ± standard errors are reported.

[a] Estimate is for the control treatment compared with the experimental treatment.

[b] Estimate is for females compared with males.

[c] Estimate is for the early collection date (May 7) compared with the late collection date (May 25).

* $P < .05$.

** $P < .001$.

also compared median absolute growth rates of control chicks during the restriction period and restricted chicks during the realimentation period (restriction control vs. realimentation restricted; table 1) to determine whether restricted chicks grew faster than control chicks at a time when control chicks should have been growing at their fastest. Finally, we compared median absolute growth rates of control chicks and restricted chicks during the postrealimentation feeding period (postrealimentation control vs. postrealimentation restricted; table 1).

Although body mass was measured daily, structural growth was measured only at three sampling points. To evaluate how the treatment impacted chick structural size throughout the experiment, we collected structural measurements (wing chord, culmen length, and head-to-bill length) at three different sampling points: day 7 posthatching (prior to the start of the restriction period), day 17 posthatching (at the end of the restriction period), and day 27 posthatching (during the postrealimentation period; fig. 1). To reduce the dimensionality of these measurements and to calculate a single value for overall size at a specific sampling point, we used a principal component analysis (PCA) and defined structural growth as the first principal component. PC1 explained 96.4% of the variance (table 2). This model included treatment, sampling point (day 7, day 17, and day 27), sex, collection date, and all significant two-way interactions as fixed effects and chick ID as a random effect (table 2). Tukey's post hoc tests were used to assess the effects of the treatment on growth during the different structural size sampling points.

We used a linear mixed effects model to evaluate the potential influence of the treatment on IGF-1 levels at three sampling points: before the experimental food restriction (on day 7 posthatching), at the end of the experimental food restriction (on day 17 posthatching, when we predicted that IGF-1 levels would be lower in experimental chicks relative to controls), and 10 days after the restriction period (on day 27 posthatching, when we predicted that the IGF-1 levels of experimental chicks would have returned to those of controls). The model included IGF-1 levels at these three sampling points as the dependent variable and treatment, mass at the time of sampling, sampling point (day 7, day 17, and day 27), collection date, and sex as fixed effects. Chick ID was included as a random effect. This model also included a significant treatment × sampling period interaction term (table 3). Tukey's post hoc tests were used to assess the effects of the treatment on IGF-1 levels at the different sampling points.

We also examined the potential effects of the treatment and IGF-1 levels on telomere dynamics using linear models. Telomeres were measured on days 7 and 40 posthatching, and the change in telomere length was calculated as telomere length on day 40 minus the telomere length on day 7, corrected for the regression to the mean (Verhulst et al. 2013). The final telomere model included telomere length on day 7 or telomere length on day 40 posthatching as the dependent variable and treatment, IGF-1 levels at the time of telomere sampling (day 7 or 40 posthatching), and sex as fixed effects. We also fitted a third model to include change in telomere length as the dependent variable and treatment, IGF-1 levels across the experimental timeline (day 7, day 17, and day 40), collection date, and sex as fixed effects (table 4).

Table 2: Loadings for principal component analysis (PCA) on Franklin's gull chick structural growth variables and the percentage of structural growth variation explained by the PC1 axis

Structural growth variable	PC1
% of variance explained	96.4
Head to bill (mm)	.991
Wing chord length (mm)	.982
Culmen length (mm)	.973

We examined the effects of treatment and IGF-1 levels on oxidative stress (antioxidant capacity and protein carbonyls) using linear models. We ran a linear model that included antioxidant capacity or protein carbonyl on day 7 or 40 posthatching as the dependent variable and treatment, IGF-1 levels on day 7 or 40 posthatching at the time of oxidative stress sampling, collection date, and sex as fixed effects (table 5).

Data were analyzed using R version 4.0.2 statistical software (R Development Core Team 2020). The lmer function in the R package lme4 was used to run linear mixed effects models (Bates et al. 2018). To meet linear mixed effects model assumptions for normality, all IGF-1 and telomere data were log transformed. The emmeans function in the R package emmeans was used to run all post hoc comparisons (Lenth et al. 2019). The PCA was performed using SPSS 28. In all models, we initially included all two-way interactions between fixed effects. Nonsignificant interaction terms were removed, and final models were determined based on Akaike information criterion scores.

Results

Body Mass and Structural Growth

The experimental treatment significantly affected absolute growth rates. There was a significant interaction between treatment and feeding period on median absolute growth rate ($F_{3,\,1,240.40} = 1{,}310.22$, $P < .0001$; fig. 2*A*). During the restriction period, experimental chicks had significantly reduced median absolute growth rates compared with

Table 3: Effect of experimental food restriction on Franklin's gull insulin-like growth factor 1 (IGF-1) concentrations

Dependent variable	$\beta \pm$ SE	F	P
1. IGF-1:			
Independent variable/factor:			
Intercept	5.12 ± .17	...	...
Treatment[a]	−.08 ± .10	5.47	.02*
Sampling mass	−.003 ± .002	2.72	.10
Sex[b]	.20 ± .07	8.10	.006**
Sampling period	...	3.70	.03*
Collection date[C]	−.09 ± .06	2.06	.16
Treatment × sampling period	...	5.43	.006**
Post hoc analysis (selected pairwise comparisons):			
Day 7 control vs. day 7 restricted	.08 ± .10	...	.97
Day 17 control vs. day 17 restricted	.52 ± .16	...	.02*
Day 27 control vs. day 27 restricted	−.06 ± .10	...	.99

Note: Linear mixed effects model 1 included treatment, sampling mass, sex, collection date, and sampling period as well as an interaction between treatment and sampling period as fixed effects and chick ID as a random effect. Tukey's post hoc tests were used to examine multiple comparisons between feeding periods, and preselected pairwise comparisons are reported. Parameter estimates ± standard errors are reported.

[a] Estimate is for the control treatment compared with the experimental treatment.

[b] Estimate is for females compared with males.

[c] Estimate is for the early collection date (May 7) compared with the late collection date (May 25).

* $P < .05$.

** $P < .001$.

controls (Tukey's HSD, $t_{47.1} = 22.62$, $P < .0001$; fig. 2*A*; table 1) and gained on average 7.15 ± 0.37 (95% CI: 6.39 to 7.91) grams per day, while control chicks gained on average 13.81 ± 0.36 (95% CI: 13.09 to 14.53) grams per day. In contrast, during the realimentation period, experimental chicks experienced significantly greater median absolute body mass growth rates compared with controls (Tukey's HSD, $t_{102.8} = -26.82$, $P < .0001$; fig. 2*A*). During this time, experimental chicks more than doubled their daily mass gain by gaining on average 17.81 ± 0.94 (95% CI: 15.92 to 19.71) grams per day, while control chicks gained on average only 8.16 ± 0.72 (95% CI: 6.66 to 9.65) grams per day. The median absolute growth rates of experimental chicks during the realimentation period were also significantly higher than those of controls during the restriction period (Tukey's HSD, $t_{74.0} = 12.13$, $P < .0001$; fig. 2*A*), when control chicks were growing at their fastest rate. Therefore, during the realimentation period, experimental chicks grew significantly faster than controls at a time when controls were growing their fastest, demonstrating that food-restricted chicks underwent compensatory growth. During the postrealimentation period, median absolute body mass growth rates did not differ significantly between experimental and control chicks (Tukey's HSD, $t_{37.2} = -2.81$, $P = .12$; fig. 2*A*). During this time, body mass declined in both groups; experimental chicks lost an average of −0.10 ± 0.26 (95% CI: −0.63 to 0.43) grams per day, and controls lost an average of −0.89 ± 0.25 (95% CI: −1.39 to −0.39) grams per day.

Food restriction also significantly negatively impacted chick structural size. We observed a significant interaction between treatment and sampling point ($F_{2,72} = 6.55$, $P = .002$; fig. 2*B*). By the end of the restriction period (day 17 posthatching), experimental chicks were significantly structurally smaller than control chicks (Tukey's HSD, $t_{67.8} = 3.77$, $P = .004$; fig. 2*B*). However, by day 27 of the postrealimentation period there were no significant differences in structural size between treatments (Tukey's HSD, $t_{67.8} = 1.05$, $P = .89$; fig. 2*B*), and experimental chicks were ultimately able to reach the structural size of control chicks within 10 days following the food restriction. Males were also significantly structurally larger than females regardless of treatment ($F_{1,34} = 7.18$, $P = .01$). By the end of the postrealimentation period, there was no significant effect of the treatment on final mass ($F_{1,33} = 1.52$, $P = .23$).

IGF-1 Levels

There was a significant interaction between experimental treatment and sampling point on IGF-1 levels ($F_{2,84.85} = 5.43$, $P < .006$). Specifically, IGF-1 levels were significantly lower in restricted chicks on day 17 following food restriction compared with control chicks (Tukey's HSD, $t_{101.3} = 3.24$, $P = .02$; fig. 3; table 3). However, by day 27

Table 4: Effect of experimental food restriction on Franklin's gull chick relative telomere length and change in telomere length

Dependent variable, independent variable/factor	$\beta \pm$ SE	F	P
1. Relative telomere length (day 7):			
Intercept	−.42 ± .84	…	…
Treatment[a]	−.10 ± .11	.95	.34
IGF-1 on day 7	.14 ± .17	.17	.68
Sex[b]	−.03 ± .11	.32	.57
Collection date[c]	.22 ± .11	4.08	.06
2. Relative telomere length (day 40):			
Intercept	.59 ± .31	…	…
Treatment[a]	−.02 ± .10	.22	.64
IGF-1 on day 40	−.06 ± .05	2.56	.12
Sex[b]	−.03 ± .10	.30	.59
Collection date[c]	.13 ± .10	1.77	.19
3. Change in relative telomere length:			
Intercept	.19 ± 1.48	…	…
Treatment[a]	.20 ± .14	1.59	.22
IGF-1 on day 7	−.13 ± .22	.46	.50
IGF-1 on day 17	.22 ± .21	.59	.45
IGF-1 on day 40	−.03 ± .07	.87	.36
Sex[b]	−.20 ± .13	2.45	.12
Collection date[c]	.03 ± .13	.05	.82

Note: Models 1 and 2 include treatment, sex, collection date, and insulin-like growth factor 1 (IGF-1) levels on day 7 or 40 posthatching. Model 3 includes treatment, sex, collection date, and IGF-1 on days 7, 17, and 40 posthatching. All two-way interactions were nonsignificant ($P < .05$) and were removed from the final models. Parameter estimates ± standard errors are reported.

[a] Estimate is for the control treatment compared with the experimental treatment.

[b] Estimate is for females compared with males.

[c] Estimate is for the early collection date (May 7) compared with the late collection date (May 25).

posthatching, following realimentation, IGF-1 levels no longer differed between treatment groups (Tukey's HSD, $t_{102.6} = -0.61$, $P = .99$; fig. 3; table 3). There also was a significant effect of sex on IGF levels where males had higher IGF-1 levels than females regardless of treatment ($F_{1, 40.87} = 8.10, P = .006$).

Telomere Dynamics

There were no significant effects of the treatment ($F_{1, 30} = 0.22$, $P = .64$) or IGF-1 levels on day 40 posthatching ($F_{1, 30} = 2.55$, $P = .12$) on final telomere length. There were also no significant effects of the treatment ($F_{1, 27} = 1.59$, $P = .22$) or IGF-1 levels on day 7 posthatching ($F_{1, 27} = 0.46$, $P = .50$), day 17 posthatching ($F_{1, 27} = 0.59$, $P = .45$), or day 40 posthatching ($F_{1, 27} = 0.87$, $P = .36$) on the change in telomere length (table 4).

Oxidative Stress

On day 40 posthatching, there were no significant effects of the treatment ($F_{1, 29} = 0.29$, $P = .59$), IGF-1 levels ($F_{1, 29} = 0.002$, $P = .97$), or collection date ($F_{1, 29} = 0.10$, $P = .75$) on antioxidant capacity (table 5). There were also no significant effects of the treatment ($F_{1, 23} = 2.0$, $P = .17$), IGF-1 posthatching ($F_{1, 23} = 1.31$, $P = .26$), or collection day ($F_{1, 21} = 0.01$, $P = .92$) on protein carbonyl content at 40 days posthatching (see table 5). On

Table 5: Effect of experimental food restriction on oxidative stress in Franklin's gulls

Dependent variable, independent variable/factor	$\beta \pm$ SE	F	P
1. Total antioxidant capacity on day 7 posthatching:			
Intercept	50.10 ± 129.28	…	…
Treatment[a]	−4.81 ± 17.93	.19	.67
IGF-1 on day 7	26.68 ± 26.25	.85	.36
Sex[b]	−13.78 ± 18.92	.47	.50
Collection date[c]	−5.21 ± 18.72	.08	.78
2. Total antioxidant capacity on day 40 posthatching:			
Intercept	−183.55 ± 54.3	…	…
Treatment[a]	−11.14 ± 17.21	.29	.59
IGF-1 on day 40	2.37 ± 9.15	.002	.97
Sex[b]	−18.85 ± 17.72	1.31	.26
Collection date[c]	5.70 ± 18.05	.10	.75
3. Oxidative damage—protein carbonyl content on day 7 posthatching:			
Intercept	−.003 ± .22	…	…
Treatment[a]	.01 ± .03	.12	.73
IGF-1 on day 7	.04 ± .04	.56	.46
Sex[b]	.04 ± .03	.62	.44
Collection date[c]	.07 ± .03	5.36	.03*
4. Oxidative damage—protein carbonyl content on day 40 posthatching:			
Intercept	.38 ± .12	…	…
Treatment[a]	−.05 ± .04	2.01	.17
IGF-1 on day 40	−.03 ± .02	1.31	.26
Sex[b]	.04 ± .04	.92	.35
Collection date[c]	.004 ± .04	.01	.92

Note: Linear models include treatment, age of the chick at sampling, sex, collection date, and insulin-like growth factor 1 (IGF-1) levels on day 7 or 40 posthatching. All nonsignificant interaction terms were removed from the final models ($P < .05$). Parameter estimates ± standard errors are reported.

[a] Estimate is for the control treatment compared with the experimental treatment.

[b] Estimate is for males compared with females.

[c] Estimate is for the early collection date (May 7) compared with the late collection date (May 25).

* $P < .05$.

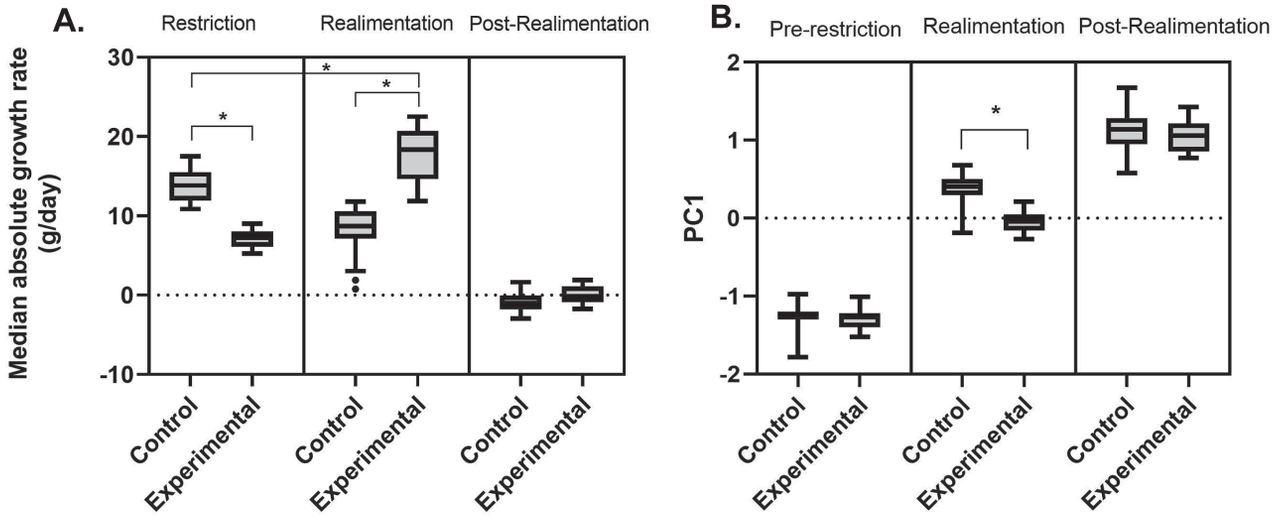

Figure 2: *A*, Median absolute growth rate. *B*, Loadings for the first principal component (PC) for structural growth variables during the prerestriction, restriction, and postrealimentation sampling periods (mean, Tukey's HSD). *P* values are based on Tukey's HSD post hoc test, and asterisks indicate significant differences ($^{*}P < .05$).

day 7 posthatching, there were also no significant differences in antioxidant capacity with respect to collection date ($F_{1, 31} = 0.08$, $P = .78$); however, chicks whose eggs were collected on May 25 had significantly more protein carbonyl content than chicks whose eggs were collected on May 7 ($F_{1, 26} = 5.36$, $P = .03$).

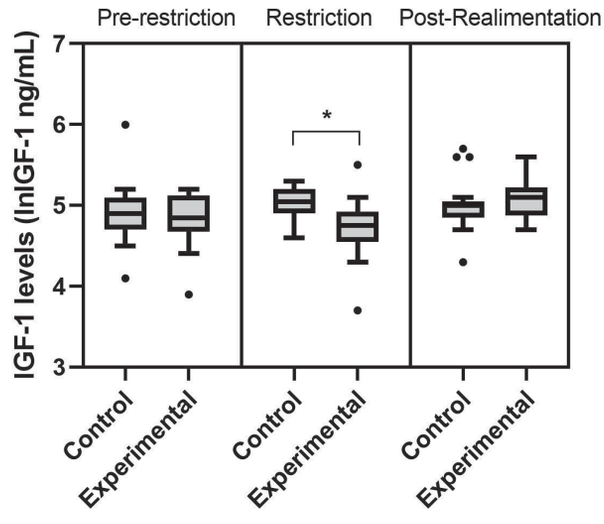

Figure 3: Relationship between insulin-like growth factor 1 (IGF-1) levels, treatment group, and sampling point in Franklin's gull (*Leucophaeus pipixcan*) chicks. Restricted chicks had significantly lower IGF-1 levels on day 17 compared with control chicks ($P = .01$). IGF-1 levels did not significantly differ between treatments on day 7 ($P = .96$) or 27 ($P = .99$) posthatching. *P* values are based on Tukey's HSD post hoc test, and asterisks indicate significant differences ($P < .05$).

Discussion

Organisms are often capable of plastically modifying growth in response to environmental conditions, but the underlying mechanisms are not well understood. Here, we experimentally demonstrated in captive Franklin's gulls that during a period of food restriction, IGF-1 levels, body mass, and structural growth were significantly reduced relative to controls. These results are consistent with our predictions and previous research in other developing vertebrates (Schew et al. 1996; McMurtry 1998; Ronning et al. 2009; Richmond et al. 2010*a*, 2010*b*). During the realimentation period, the IGF-1 levels of experimental chicks returned to those of controls, and experimental chicks underwent rapid compensatory growth. The absolute body mass growth of experimental chicks during the realimentation period was significantly faster than that of the controls during both the realimentation period and the restriction period, when controls grew the most rapidly. Consequently, experimental chicks were able to catch up to controls, and there were no significant differences in the body mass or structural size between these two groups within 10 days of returning to ad lib. feeding. Surprisingly, however, there were no significant effects of the experimental treatment or of variation in IGF-1 levels on two potential markers of cellular and organismal aging, oxidative stress (antioxidant capacity and protein carbonyl content) or telomeres (telomere length or the change in telomere length). Taken together, these results are

consistent with the idea that IGF-1 may be involved in mediating plastic growth adjustments in response to changes in resource availability but does not appear to come at a cost to cellular aging during postnatal development in this relatively long-lived species.

Previous research in vertebrates suggests that diverse developmental stressors, including nutritional deficits, can increase oxidative stress (Aiken et al. 2013) and telomere loss and result in shorter telomeres (Herborn et al. 2014; Verhulst et al. 2014; Noguera et al. 2015; Young et al. 2017), and these effects may occur as a direct consequence of the nutritional insult, as a consequence of the costs associated with more rapid compensatory growth, or both (Metcalfe and Monaghan 2001). Thus, it is interesting that although the experimental food restriction did induce rapid compensatory growth, there were no significant effects on oxidative stress or telomeres, and several nonexclusive factors could have contributed to these results.

One possibility is that although the treatment induced compensatory growth, it was not severe enough to induce oxidative stress and telomere loss. Importantly, the degree of food restriction used in this study was intended to induce physiologically relevant nutritional stress, and it is similar to what has been used in other studies in developing seabird chicks (Kitaysky et al. 2001, 2006; Will et al. 2014) and has previously been shown to increase glucocorticoid stress hormone levels in many seabird species, including black-legged kittiwakes (*Rissa tridactyla*; Kitaysky et al. 1999), red-legged kittiwakes (*Rissa brevirostris*; Kitaysky et al. 2006), and rhinoceros auklets (*Cerorhinca monocerata*; Will et al. 2014). Thus, we expect that in addition to inducing compensatory growth, this dietary restriction regime was stressful for the chicks.

It is also possible that any effects of nutritional stress and compensatory growth on cellular aging are delayed and the timescale of this study (~30 days) was too short to detect them. In zebra finches, although there was no significant effect of compensatory growth on telomeres at the end of postnatal growth (15 days posthatching), there was a significant effect at a later sampling point (120 days posthatching; Salmón et al. 2021). However, because telomeres were not measured between days 15 and 120, it is unclear when these effects became evident. Importantly, many studies have detected effects of developmental stressors, including nutritional stress, on telomere loss within the time span of this study (i.e., within 30 days or less; Nettle et al. 2013; Boonekamp et al. 2014; Stier et al. 2015; Heidinger et al. 2016), including in several closely related gull species (Foote et al. 2011; Mizutani et al. 2016; Young et al. 2017). Therefore, we have good reason to expect we would have been able to detect effects of compensatory growth on oxidative stress and telomeres within the time span of this study.

In this study, we measured oxidative stress and telomeres in red blood cells because it is a highly proliferative tissue that can be nondestructively sampled and is well suited for longitudinal analyses (Nussey et al. 2014) and because blood cell telomeres are often positively related to longevity (Heidinger et al. 2012, 2021; Wilbourn et al. 2018). Telomere dynamics are expected to be highly correlated among tissue types (Daniali et al. 2013). However, we have previously reported in this species that although telomeres are positively correlated among several tissues (red blood cells, heart, skeletal muscle, and liver) at the end of prenatal development, this is no longer the case at the end of postnatal development (Schmidt et al. 2016). Thus, future studies should also explore whether the effects of variation in nutritional stress and compensatory growth on oxidative stress and telomeres vary among tissues, as some tissues may be more vulnerable to developmental insults than others (Jennings et al. 1999).

Another possibility is that some seabirds may have evolved mechanisms that buffer them against the developmental costs of frequent fluctuations in food supply (Lack 1968; Stier et al. 2019). For example, chicks may plastically up-regulate antioxidant defenses (Beaulieu et al. 2011) or telomerase, an enzyme that can extend telomere length, to mitigate these effects (Noguera et al. 2022). We did not find any evidence that experimental gull chicks upregulated antioxidant defenses, but we did not measure telomerase levels. Interestingly, there is also evidence in two closely related gull species, black-legged kittiwakes (*Rissa tridactyla*; Young et al. 2017) and black-tailed gulls (*Larus crassirostris*; Mizutani et al. 2016), that the effects of nutritional stress on telomere loss depends on brood size. Thus, the effects of nutritional stress on oxidative stress and telomeres may depend critically on what other stressors the chicks are experiencing.

We also did not find any effect of variation in IGF-1 levels on oxidative stress or telomeres. Recent evidence suggests that IGF-1 may be one mechanism that could impact telomere dynamics. For example, Matsumoto et al. 2015 demonstrated that exogenous IGF-1 induced telomere shortening in skin fibroblasts in humans with acromegaly, a condition that increases growth and reduces longevity. The mechanisms by which IGF-1 induces telomere shortening are not well understood, but there is some evidence to suggest that activation of the IGF-1 pathway may enhance ROS production, ultimately damaging telomeres (Handayaningsih et al. 2012; Matsumoto et al. 2015). However, we did not find any evidence that IGF-1 levels were predictive of oxidative stress, telomere length, or the change in telomere length in Franklin's gull chicks.

Overall, our results are consistent with the idea that IGF-1 is a conserved hormonal mechanism that accompanies plastic growth modifications in response to nutritional stress, but

our experimental restriction did not induce costs to oxidative stress or telomeres in this species. It may be that some long-lived species, like Franklin's gulls, are capable of upregulating mechanisms such as telomerase (Noguera and Velando 2021) that buffer against the long-term costs of nutritional stress exposure during postnatal development. It may also be that the effects of nutritional stress and compensatory growth are context dependent and only evident when individuals also experience additional developmental stressors. Future research should investigate the mechanistic role of IGF-1 in mediating the trade-off between growth adjustments and cellular aging in species with varying life history strategies by experimentally manipulating IGF-1 levels.

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Statement of Authorship

A.E.S. participated in the study design; carried out the experiment, data analysis, hormone measurement, and analysis; and drafted the manuscript. J.E.S. participated in the study design, carried out the experiment, and conducted the telomere analysis. M.E.C. participated in the study design, made substantial contributions to the statistical analyses, and critically revised the manuscript. J.D.K. played a crucial role in the development of the hormone and telomere analyses and advised on sample collection. W.L.R. participated in the study design and critically revised the manuscript. B.J.H. conceived of the study, participated in the study design, and helped draft and revise the manuscript. All authors gave final approval for publication and agree to be held accountable for the work performed herein.

Data and Code Availability

The datasets and code supporting this article have been uploaded to the Dryad Digital Repository (https://doi.org/10.5061/dryad.crjdfn33p; Sirman et al. 2023).

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Captive Franklin's gull (*Leucophaeus pipixcan*) chicks at approximately day 7 posthatch (*left*) and day 17 posthatch. Photo by Aurelia Kucera.