Plasma insulin-like growth-factor 1 (IGF-1) concentrations predict early life-history traits in a wild mammal

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Abstract

1. Understanding the physiological mechanisms underpinning plasticity in life-history traits can help us predict individual responses to environmental variability and understand how diverse life-history strategies evolve to be shaped by ecological processes.
2. The hormone insulin-like growth factor 1 (IGF-1) is a key player in the insulin/IGF-1 signaling (IIS) pathway. This nutrient-sensing pathway responds to diverse environmental cues including food availability and has been shown to modulate the association between resource acquisition and allocation of resources to life-history traits like growth, reproduction and survival in the laboratory.
3. We measured IGF-1 concentrations in blood samples from approximately four-month-old wild Soay sheep lambs (n=669), collected over nine summers. We tested whether IGF-1 was positively correlated with proxies of resource availability, and whether IGF-1 was associated with morphological traits measured concurrently and predicted subsequent fitness-related traits.
4. Plasma IGF-1 concentrations were higher in males compared to females, and positively correlated with measures of resource availability in both sexes. IGF-1 was lower in years of high population density when per capita food availability was reduced; in twin lambs who have fewer available resources compared to singletons; and in lambs born to young and old mothers, who have poor maternal provisioning compared to mothers of intermediate age.
5. Higher IGF-1 levels in summer were predictive of higher body mass, faster post-natal somatic growth and increased skeletal size, measured at the same time. These associations were independent of our proxies of resource availability.
6. Lambs with higher summer IGF-1 were more likely to survive their first winter and reproduce the following spring. The association between IGF-1 and reproduction was independent of our resource availability proxies, whereas the association with first-winter survival was not. The association between summer IGF-1 and reproduction was mediated by positive associations with summer body mass.

7. Our study reveals population-level phenotypic plasticity in circulating IGF-1, also finding IGF-1 to predict early life-history traits in a wild mammal population.

Keywords: Hormone, IGF-1, Insulin/Insulin-like Signaling (IIS), Mammal, Wild, Soay sheep (*Ovis aries*)

Introduction

In fluctuating environments, individuals are selected to to adjust their life-history strategy according to prevailing environmental conditions to survive and reproduce. Such phenotypic plasticity is an important mechanism underpinning life-history responses to environmental change (Pigliucci., 2005). Several vertebrate studies have reported the hormone IGF-1 (Insulin-like Growth Factor 1) to be capable of integrating environmental cues and internal signals to coordinate a life-history response (Dantzer & Swanson., 2012). IGF-1 is part of the insulin/insulin-like growth factor 1 signalling (IIS) pathway which is a key nutrient-sensing pathway that responds to changes in food availability (Regan et al., 2020). Numerous studies have reported upregulation of IGF-1 to have a positive impact on life-history traits like growth and reproduction while negatively influencing lifespan (Lodjak & Verhulst., 2020). Tracking individual physiological responses like IGF-1 and its link to life-history variation and fitness outcomes will reveal how individuals have evolved to alter their life-histories to cope with variable environments.

IGF-1 is a key component of the IIS pathway (Dantzer and Swanson 2012). This pathway is highly evolutionarily conserved and plays an important role in energy metabolism and growth by responding to nutrient uptake at the cellular level (Jones & Clemmons., 2005). This pathway is comprised of three peptide hormones (IGF-1, IGF-2, insulin), their cognate receptors and multiple IGF-binding proteins (Dupont & Holzenberger., 2003). Studies across diverse species show that IGF-1 responds to environmental variation and regulates the integration and expression of multiple life-history traits (reviewed in Dantzer & Swanson., 2012; Lodjak & Verhulst., 2020; Junnila et al., 2013; Reinecke., 2010). Although various studies report IGF-1 to respond to diverse environmental cues such as temperature and photoperiod, its link with nutrient availability is extensively studied and robust (Regan et al., 2020; Webster et al., 2001; Taylor et al., 2005, 2008; Dahl et al.,1997; Gabillard et al., 2003; Beckman et al.,1998; Clemmons & Underwood., 1991). In laboratory rodents and primates including humans, studies report individuals on calorie-restricted diets have decreased circulating IGF-1 concentrations (Speakman & Mitchell., 2011; Mattison et al., 2017; Rahmani et al., 2019). Experimental studies in wild bird, fish and reptile populations have similarly found plasma IGF-1 levels to be lower in food-restricted or fasting individuals compared to those exposed to an *ad libitum* diet (Lodjak et al., 2023; Hack et al., 2018; Duncan et

al., 2015). However, these experimentally manipulated diets may not reflect the fluctuating levels of food availability experienced by many wild populations inhabiting highly variable environments. Therefore, it is currently unclear whether consistent patterns in the plasma IGF-1 response to natural variation in food availability will be observed. Here, we investigate whether natural variation in proxies of resource availability predict plasma IGF-1 levels in a wild herbivore.

Across most vertebrate species, IGF-1 is reported to have a critical influence on morphological and life-history traits (Dantzer & Swanson., 2012). Gene ablation studies in laboratory rodents revealed IGF-1 to be a major determinant of body size and somatic growth (Baker et al.,1993; studies within Yakar et al., 2002). IGF-1 has also been shown to regulate bone growth and skeletal muscle size in mouse models (Yakar et al., 2002, 2018). Studies in domesticated and wild vertebrates reveal similar positive associations between IGF-1 and body size or growth rate (Crain et al.,1995; Beccavin et al., 2001; Greer et al., 2011; Lodjak et al., 2014, 2017, 2018; Lewin et al., 2017). Other bone-associated traits such as antler length were also found to be positively correlated with IGF-1 levels in wild vertebrates (Suttie et al., 1991; Ditchkoff et al., 2001). Furthermore, sex differences in plasma IGF-1 levels have been previously reported in laboratory rodents, domestic animals, wild bird and reptile populations. In general, the larger sex showed increased plasma IGF-1 levels (Yuan et al., 2009; Toth et al., 2022; Reda et al., 2024; Baéza et al., 2001; Meter et al., 2022; Roberts et al., 1990). Understanding the physiological mechanisms underpinning early post-natal development can tell us how individuals are able to optimize their physical morphology in response to environmental variation and to achieve favorable life-history outcomes. In this study, we investigate whether plasma IGF-1 concentrations are associated with early-life morphological traits in a sexually dimorphic, ungulate species.

There is convincing evidence of IGF-1 playing a key role in life-history traits like reproduction and survival under laboratory conditions. IGF-1 is required for normal reproductive function in vertebrates; IGF-1 knockout mice had smaller-sized reproductive organs alongside decreased spermatogenesis and ovulation, effectively making them infertile (Baker et al., 1996; D'Ercole., 1999). In laboratory and domesticated mammals, experimental IGF-1 supplementation advanced puberty onset age (Danilovich et al., 1999; Hiney et al., 1996). Mammalian studies also revealed IGF-1 to be associated with earlier sexual maturation and age at first reproduction (Velazquez et al., 2004; Wilson et al., 1998). In addition, extensive biogerontological research has revealed the IIS pathway as an important regulator of ageing and lifespan across species (Mathew et al., 2017). Long-lived humans were observed to have low plasma IGF-1 concentrations (Bonafe et al., 2003). Several studies in laboratory animal models found experimental downregulation of IIS signaling resulted in longer lifespans (Bartke et al., 2005; Berryman et al., 2008; Svensson et al., 2011; Kenyon et al., 1993).

However, the association between IGF-1 and longevity in wild populations is unclear. It is also unclear how IGF-1 impacts survival in the short-term both under laboratory and wild conditions. Here, we investigate whether early-life IGF-1 levels predict short-term reproduction and survival in a long-lived, iteroparous wild mammal.

In long-lived birds and mammals experiencing variable environments, juveniles that are heavier in body mass are generally in good condition and more likely to survive any harsh environments they may experience (Hamel et al., 2009; McMahon et al., 2015). Since individuals in good condition can acquire more resources, they are more likely to invest in current reproduction (van Noordwijk & de Jong., 1986). If so, high IGF-1 levels would predict heavier body mass which in turn would predict increased survival and reproduction in juveniles. Body mass could thus mediate the association between IGF-1 and life-history traits. Additionally, since resource availability could influence IGF-1, body mass and life-history traits independently, conditioning on resource availability is key to understand whether IGF-1 directly influences life-history traits. Despite extensive evidence from the lab and promising studies in some wild bird and reptile populations, the influence of IGF-1 on individual fitness traits of juveniles is virtually unknown in free-ranging mammals. Only one study in a wild hyena population found juvenile females with higher plasma IGF-1 levels to have earlier age at first parturition and reduced longevity after reproductive maturity (Lewin et al., 2017).

In this study, we investigate whether variation in resource availability predicts plasma IGF-1 levels and whether IGF-1 is associated with morphological traits and fitness components in juveniles of a wild vertebrate population, the Soay sheep on St. Kilda. We first investigate whether proxies of resource availability (population density, litter size and maternal age at birth) predict plasma concentrations of IGF-1 in lambs in the summer. We then test whether summer IGF-1 levels positively predict morphological traits like summer body mass, skeletal size, horn length and post-natal growth in lambs. We also hypothesized plasma IGF-1 would be positively associated with the short-term fitness measures of reproduction in the first year and survival over the lamb's first winter. To understand the direct and indirect influence of IGF-1 on morphological and life-history traits, we ran models with different sets of predictors either accounting for proxies of resource availability, summer body mass or both. By doing so, we could disentangle the intricate relationships between IGF-1, resource availability proxies, body mass and life-history traits, enabling us to understand the role of IGF-1 in underpinning life-history variation and shaping adaptive life-history strategies in the wild (Figure 1).

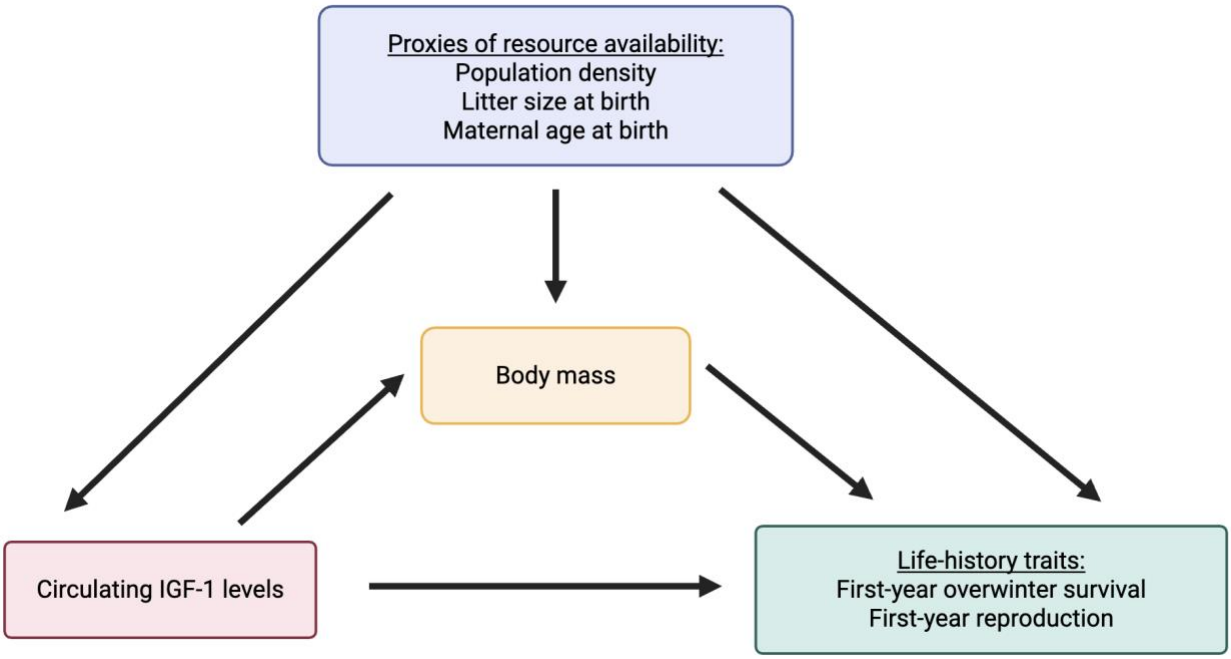

Figure 1: A schematic describing the relationships between IGF-1, proxies of resource availability, body mass and life-history traits. Proxies of resource availability can influence IGF-1 levels, body mass and life-history traits. IGF-1 can have a direct influence on morphological traits such as body mass. IGF-1 can also have a direct influence on life-history traits like survival and reproduction. In addition, IGF-1 could indirectly influence life-history traits through its effects on body mass.

Materials and Methods

Study system and data collection

Since 1985, the Soay sheep resident in the Village Bay area of Hirta (around 30% of the island's population) have been subject to individual-based monitoring (Clutton-Brock & Pemberton, 2004). There are among-year fluctuations in population density with most sheep mortality occurring over February – April and biased towards lambs and males. Regular censusing throughout the year along with mortality searching allows accurate estimation of death dates. The Soay sheep are polygynous with intense male-male competition for access to females. Both males and females are sexually mature in their first year. Male lambs participate in the rut in October-November. Depending on population density, male mating success and female conception rates vary across years. Successful pregnancies may mean ewes giving birth in March – May although still-births or death of foetuses *in utero* (by post-mortem assessment) also occur. The accurate assignment of both parents to offspring is performed using genome-wide SNP markers and the pedigree inference program SEQUOIA (Huisman, 2017). Most lambs

172 are fully weaned by the end of autumn (Clutton-Brock & Pemberton, 2004). Most
173 females produce singleton offspring, but depending on environmental conditions, up to
174 25% can give birth to twins in a year (Clutton-Brock et al, 1991).

175 Around 95% of the lambs born in the study area are caught, weighed and uniquely
176 tagged for identification within a few days of their birth (Clutton-Brock et al., 2003;
177 Robertson et al., 1992). Each August, a fieldwork team visits Hirta and captures as
178 many of the animals resident in the Village Bay area as possible (usually 50-60% are
179 caught within a two-week period). Temporary traps are constructed across the study
180 area and at capture, blood and faecal samples, along with phenotypic measurements
181 such as body weight, foreleg length, and horn length are taken from all individuals
182 (Clutton-Brock, Pemberton, et al., 2003). Blood samples are collected in lithium heparin
183 tubes and kept at 4°C until processing, usually within 24 hours of sampling. The tubes
184 are spun at 1,000g for 10 minutes. The plasma layer is transferred to 1.5 ml Eppendorf
185 tubes and then stored at -20°C.

186

187 *Insulin-like Growth Factor 1 Enzyme-Linked Immunosorbent Assays (IGF-1 ELISAs)*

188 Our initial dataset was comprised of lambs born over 9 breeding seasons, between
189 2014 and 2022 (n=683 individuals). We measured IGF-1 concentrations of these
190 approximately 4-month-old lambs from archived plasma samples. All 683 samples were
191 assigned randomly to different ELISA plates (n=18). We used a commercially available
192 ovine enzyme-linked immunoassay kit (Sheep IGF-1 ELISA Kit, abx576572; Abbexa
193 Ltd) following manufacturer's instructions. Briefly, a 60 ng/ml standard solution was
194 serially diluted six times to obtain a standard curve. Plasma samples were diluted to
195 1:25 in phosphate-buffered saline solution (1X PBS with pH 7.2; Gibco) to ensure our
196 measurements fell within the range of the kit standard curve (0.94 ng/ml to 60 ng/ml).
197 Two blank wells containing the diluent buffer were also included as negative controls.
198 After aliquoting 100µl of standard and blank solutions into the ELISA plate wells, 100µl
199 of the diluted samples was added in duplicate. The plates were then sealed and
200 incubated at 37°C for 1 hour. After discarding the liquid, 100µl of Detection Reagent A
201 (primary antibody) was added to all wells. Plates were once again sealed and incubated
202 for 1 hour at 37°C. Plates were then washed 3 times with 1X Wash Buffer using an
203 automated microplate washer (Skan Washer 400; Molecular Devices). This was
204 followed by the addition of Detection Reagent B (secondary antibody) and incubation for
205 30 minutes at 37°C. Following another wash step (5 times with 1X Wash Buffer), 90 µl
206 of TMB substrate was added to the wells and plates were incubated in the dark for 8
207 minutes following which 50 µl of stop solution was added. Using a microplate reader
208 (FLUOstar Omega; BMG Labtech), the optical density of samples was read at 450 nm.
209 The average concentration of duplicate samples was estimated as the plasma IGF-1

concentration for the individual. Samples were re-run if the difference in optical density (OD) between duplicates was > 0.2 (n=2).

There were 14 samples (out of 683 i.e. 2.05% of full dataset) for which the intra-assay coefficient of variation was >=11% and so, were excluded from further analyses. To determine inter-plate repeatability, we ran one ELISA plate (n=40 samples in duplicate) on consecutive days with samples placed in the same location on both plates. We then fitted a linear mixed effect model only including sample identity as a random intercept in the model. Repeatability was then estimated as the proportion of variance explained by sample identity over the total variance. This inter-plate technical repeatability of the ELISA assays was estimated as 94.524%. We also tested for effects of blood sample collection time and freezer storage time of plasma samples on IGF-1 concentrations (Supplementary Methods & Results).

Definitions of variables

Proxies of resource availability

We considered population density, litter size and maternal age at birth as indirect measures of resource availability. In this population, food is a limiting factor with increased mortality rates during winter when population density is high. Twins are physically smaller at birth and throughout early life compared to singleton lambs. In addition, lambs born to younger and older mothers have lower body mass at birth and poorer survival outcomes in their first year, compared to those born to mothers in their prime (Clutton-Brock & Pemberton., 2004).

Annual population density was estimated as the total number of individuals in the study area alive on October 1st of the calendar year. Litter size was a categorical variable with individuals classified as being born either a singleton or twin. Maternal age at birth was the age of the mother (in years) at offspring birth. We used the average maternal age in the dataset (5.456 years) for those observations where birth year of the mother was unknown (n=44 lambs).

Morphological Traits

Morphological trait data used in this study included a) August body mass – the weight of an individual at capture in August, to the nearest 0.1 kilogram (kg) (n=666 individuals); b) Post-natal growth – defined as August body mass of an individual controlling for birth weight (in kg) and age (in days) (n=545 observations); c) August foreleg length – a proxy for skeletal size, measured as the length of the metacarpal with hoof and knee joint bent away from it, to the nearest millimeter (mm) (n=660 observations); d) August

horn length – for normal-horned individuals, measured along the outer curvature from the base of the horn to the tip, to the nearest mm (n=361 individuals; IGF-1 did not vary depending on individual horn type, see Supplementary Methods & Results - Table S3).

Life-History Traits

We defined first-year reproduction as a binary outcome with individuals who produced an offspring in their first year (determined using the pedigree) assigned '1' and those who did not produce offspring assigned '0'. All female lambs were included in this analysis since reproductive status could be determined even after death by *postmortem* (n=337). For male lambs, only those individuals seen at least once during the rut census were included (n=319). In the complete dataset (n=656 individuals), 68 individuals had offspring that were still-births or foetuses that died *in utero* (10.37%) while 89 individuals produced live offspring (13.57%). There were 134 females and 23 males assigned '1' for reproduction (including foetuses, still births and live offspring) while 499 individuals were assigned '0'. Like reproduction, first-year overwinter survival was a binary response with individuals that survived to June 1st of the following year assigned '1' and those who died before June 1st the following year assigned '0' (n=609 individuals).

Statistical Analyses and Predictions

Do proxies of resource availability predict summer plasma IGF-1 concentrations in lambs?

We first investigated whether our proxies of resource availability predicted summer plasma IGF-1 concentrations (n=669). We hypothesized that IGF-1 levels would be lower in years of high population density and in twins, and also predicted a quadratic association between IGF-1 and maternal age. We ran a linear mixed effects model with population density (linear term), litter size (two-level factor) and maternal age at birth (linear and quadratic terms) as predictor variables and IGF-1 concentration as the response with the latter specified as normally distributed (Figure S1). Sex was included as a categorical predictor to account for differences in levels of circulating IGF-1 between males and females. To account for assay-related variation, ELISA plate number and run date were included as random effects. We also included random effects for sample year and maternal identity to account for repeated measures across years and across mothers. These models were run using the '*rstanarm'* package in R using default weakly informative priors for all parameters. P-values for fixed effects were estimated using the '*parameters'* R package and represent the probability of direction (strongly correlated with frequentist p-value) (Makowski et al., 2019). Conditional and marginal R^2 were estimated using the '*performance'* R package.

Are plasma IGF-1 levels associated with morphological traits?

We hypothesized that summer IGF-1 levels in lambs would be positively associated with the morphological traits of body mass, post-natal growth, skeletal size and horn length (only in normal-horned individuals) measured at the same time. We ran separate linear mixed-effects models with each morphological trait as the response variable. We fitted sex as a categorical predictor and IGF-1 as a continuous fixed effect. Random effects of maternal identity and year were also fitted. These models were fitted using an errors-in-variables modelling approach using '*cmdstanr'* R package (see below for further details).

Since variation in resource availability may drive the association between IGF-1 and morphological traits, we re-ran the above model including population density (linear term), litter size (two-level factor) and maternal age (linear and quadratic terms) as additional predictors to investigate the independent associations between IGF-1 and morphological traits, controlling for our proxies of resource availability. All continuous predictors were standardized to mean = 0 and standard deviation = 1 before including in the model. We also re-ran the foreleg and horn length models including body mass as an additional covariate to understand if IGF-1 predicted these traits independent of summer body mass (Table S6).

Do plasma IGF-1 levels predict first-year reproduction and survival over the first winter?

We hypothesized individuals with increased summer plasma IGF-1 levels would have higher chances of first-year reproduction and overwinter survival. We ran separate generalized linear mixed-effects models for reproduction and survival, fitting them as binary response variables. Sex was included as a categorical predictor and IGF-1 was fitted as a continuous predictor. Maternal identity and year were included as random effects. These models were fitted using an errors-in-variables modelling approach using '*cmdstanr'* R package (see below for further details).

To understand if IGF-1 levels predicted first-year reproduction and survival independent of resource availability, we re-ran the above model including our proxies of resource availability as additional fixed effects. Since variation in body mass could mediate the association between IGF-1 and life-history traits (Figure 1), we also re-ran this model including summer body mass as an additional predictor. All continuous predictors were standardized to mean = 0 and standard deviation = 1 before including in the model. Sample sizes for all analyses and across different categories are described in Table S1 and S2.

Errors-in-variables modelling approach

Measurement error in predictor variables leads to a general attenuation of effects. Given that almost half of the variation in IGF-1 was due to lab-related measurement error (48.445 % of variation explained by ELISA plate number and run date; Table 1), we employed an errors-in-variables modelling approach when investigating whether IGF-1 predicted morphological and life-history traits. This approach accounts for measurement error in the predictors and reduces bias in the estimated effects. In this approach, we assumed that the 'corrected IGF-1' value is a latent variable that can be expressed as –

$$Observed\ IGF1 = Corrected\ IGF1 + Measurement\ noise$$

Corrected IGF-1 values can be estimated according to the above equation and inputted in our subsequent models investigating if $IGF1_{Corrected}$ predicted morphological and life-history traits.

We jointly modelled the measurement error in 'observed IGF-1' and whether 'corrected IGF-1' predicted variation in morphological and life-history traits using Stan (implemented using the '*cmdstanr'* R package version 0.8.1). Prior to model fitting, observed IGF-1 was scaled to have a mean of 0 and a standard deviation of 1. We specified the likelihood for 'observed IGF-1' for an individual i as normally distributed with a mean of μ_{IGF1_i} and a standard deviation σ_{IGF1},

$$IGF1_{Observed_i} \sim Normal(\mu_{IGF1_i}, \sigma_{IGF1})$$

$$\mu_{IGF1_i} = v[ELISA\ Run\ Date_j] + w[ELISA\ Plate_k]$$

Where $IGF1_{obs}$ is the observed IGF-1, v is the intercept varying by ELISA run date $j \epsilon \{1,2,3,4\}$ and w is the intercept varying by ELISA plate $k \epsilon \{1,2,3,\ldots 18\}$.

We defined the relationship between 'observed IGF-1' and 'corrected IGF-1' values as follows –

$$IGF1_{Corrected_i} = IGF1_{Observed_i} - v[ELISARunDate_j] - w[ELISAPlate_k]$$

These 'corrected IGF-1' parameter estimates were fitted as a predictor variable in models where either morphological or life-history traits were the dependent variables:

$$Trait_i \sim Normal(\mu_{Trait_i}, \sigma_{Trait})$$ for morphological traits

(or)

$$Trait_i \sim Bernoulli(\theta_{Trait_i})\ ;\ logit(\theta_{Trait_i}) = \mu_{Trait_i}$$ for life-history traits

$$\mu_{Trait_i} = \alpha + \beta_{IGF1} * IGF1_{Corrected_i} + \beta_{Sex} * Sex_i + y[Birth\ Year_t] + m[Maternal\ Identity_u]$$

Where a trait value for an individual i is either normally distributed with a mean of μ_{Trait} and a standard deviation of σ_{Trait}(for morphological traits) or specified as a Bernoulli distribution with canonical logit link (for life-history traits) where θ_{Trait_i} is the probability of success. The expected trait value μ_{Trait_i}can be expressed as a regression equation with an intercept α, β_{IGF1} as the slope for $IGF1_{Corrected_i}$ and β_{sex} as the slope for Sex_i (coded as a dummy variable with females assigned '1' and males assigned '0'). y is the intercept varying by birth year $t \epsilon \{1,2, \dots 9\}$ and m is the intercept varying by maternal identity $u \epsilon \{1,2, \dots 306\}$.

The weakly-informative prior for the error term, σ_e was defined as a Cauchy distribution with location parameter (mean) = 0 and scale parameter (standard deviation) = 2.5. The random intercepts v and w are assumed to be normally distributed with a mean of 0 and standard deviations σ_v and σ_w respectively, where σ_v, σ_w were also specified as Cauchy distributions (mean=0, sd=2.5).We used non-centered parameterization to define priors for the random intercepts y and m, assumed to be normally distributed with a mean of 0 and standard deviations σ_y and σ_m respectively, specified as Cauchy distributions (mean=0, sd=2.5). Default priors were used for all other parameters in our models. We ran four Markov chains in parallel with 2000 iterations per chain (1000 for warm-up and 1000 for sampling). We checked model diagnostics by evaluating the Rhat parameter equals 1 and the effective sample size > 400 in the bulk and tail of the posterior distribution for all parameter estimates. We also performed posterior predictive checks by comparing distributions of 200 simulated datasets from the fitted model to the observed data (Figure S3). All analyses were run using R version 4.4.1 (2024-06-14) in RStudio (2024.09.0+375).

Results

Proxies of resource availability predict summer IGF-1 concentrations in lambs

We observed lower plasma IGF-1 concentrations in females compared to males (Figures 1A & S2, Table 1). Plasma IGF-1 levels were negatively associated with population density (Figure 1C, Table 1). In addition, being born as a twin was associated with decreased plasma IGF-1 levels in the summer relative to being a singleton (Figure 1B, Table 1). A quadratic relationship between IGF-1 and maternal age was observed; lambs born to younger and older mothers had reduced IGF-1 levels compared to those born to prime-age mothers (Figure 1D, Table 1). The conditional R^2 (variance explained by both fixed and random effects) was estimated as 0.552 (95% CI: 0.501 – 0.598)

while the marginal R^2 (variance explained by fixed effects alone) was 0.121 (0.075 – 0.167).

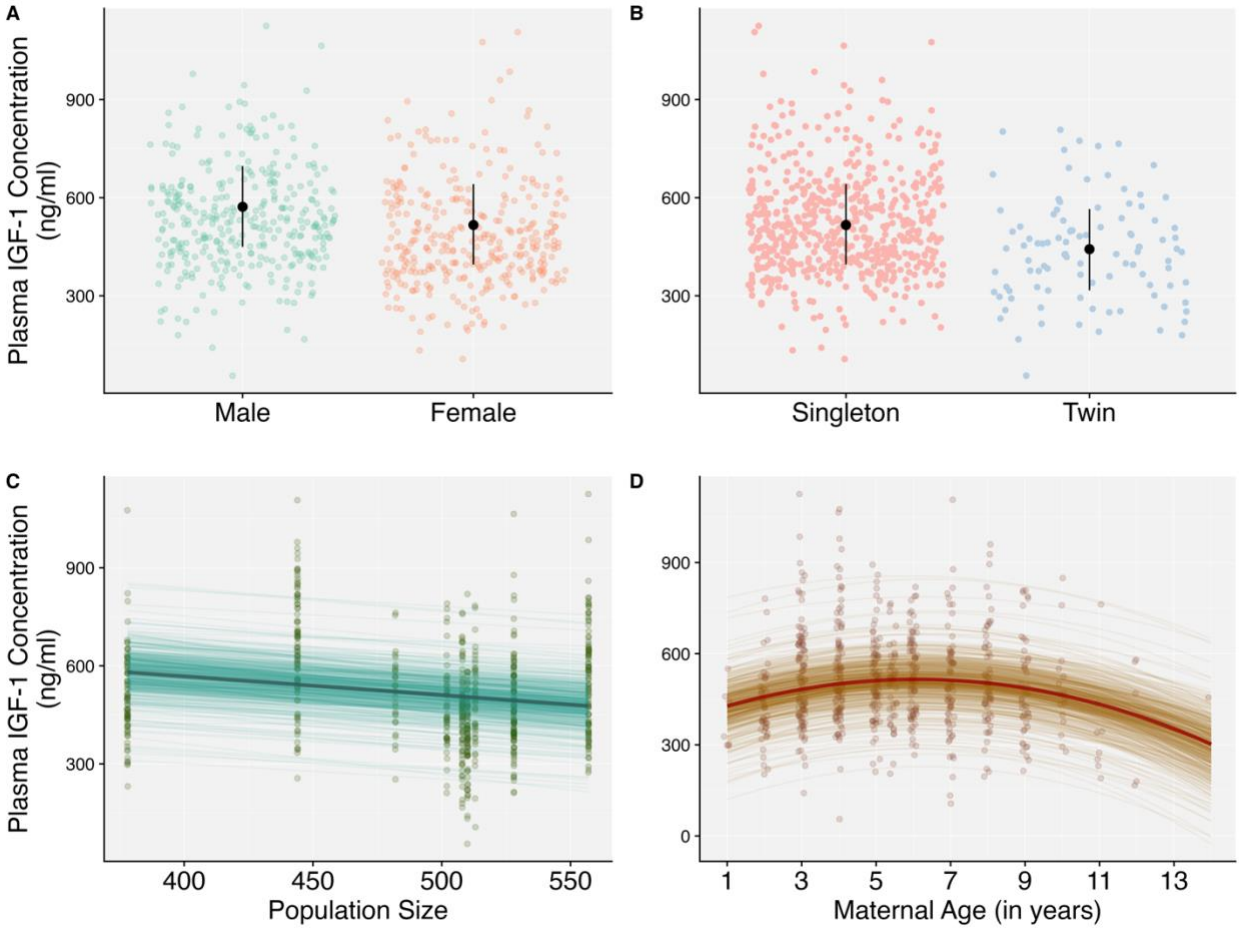

Figure 1: Association between plasma IGF-1 levels and A) Sex, B) Litter size at birth, C) Population density and D) Maternal age at birth in Soay sheep lambs (n=669 observations; Table 1). Black points and error bars represent posterior median and 95% CIs in A and B. Posterior median and 500 draws from joint posterior distribution represented in C and D by dark- and light-shaded lines respectively. Coloured points represent raw data.

Table 1: Result from linear mixed effects model investigating variation in IGF-1 with sex, population density, litter size and maternal age at birth (n=669 observations; population density and maternal age at birth were standardized to mean=0 and standard deviation=1)

Fixed Effect	Posterior Median [95% CI]	p-value
Intercept	572.065 [449.419, 696.938]	**<0.001**
Sex: Female	-56.123 [-73.097, -37.947]	**<0.001**
Twin:1	-73.939 [-100.533, -45.892]	**<0.001**

Population Density	-30.663 [-49.328, -12.597]	**0.011**
Maternal Age (1)	10.136 [0.295, 20.377]	**0.046**
Maternal Age (2)	-18.647 [-25.754, -11.551]	**<0.001**
Random Effect	Posterior Median of Variance [95% CI]	Percentage of Variance
Maternal Identity	2029.170 [835.197, 3250.360]	7.722
Birth Year	206.954 [0.000, 1621.364]	0.788
ELISA Run Date	9551.075 [128.420, 45036.520]	36.345
ELISA Plate Number	3179.780 [1109.484, 7013.365]	12.100
Residual	11312.301 [9874.564, 12915.595]	43.046

Plasma IGF-1 levels are positively correlated with body mass, skeletal size and post-natal growth

Increased levels of plasma IGF-1 were associated with heavier body mass and larger structural size in lambs (Table S6A, S6C). After accounting for variation in birth weight and lamb age at measurement (in days), we still observed a positive association between plasma IGF-1 levels and summer body mass (Table S6B), suggesting that high plasma IGF-1 levels are associated with faster post-natal growth. We also observed a positive correlation between IGF-1 levels and horn length in normal-horned individuals (Table S6D). These positive associations between IGF-1 and all morphological traits were present after controlling for our proxies of resource availability (Figure 2; Table S6). However, the association between IGF-1 and horn length was no longer statistically significant after accounting for summer body mass (Table S6D).

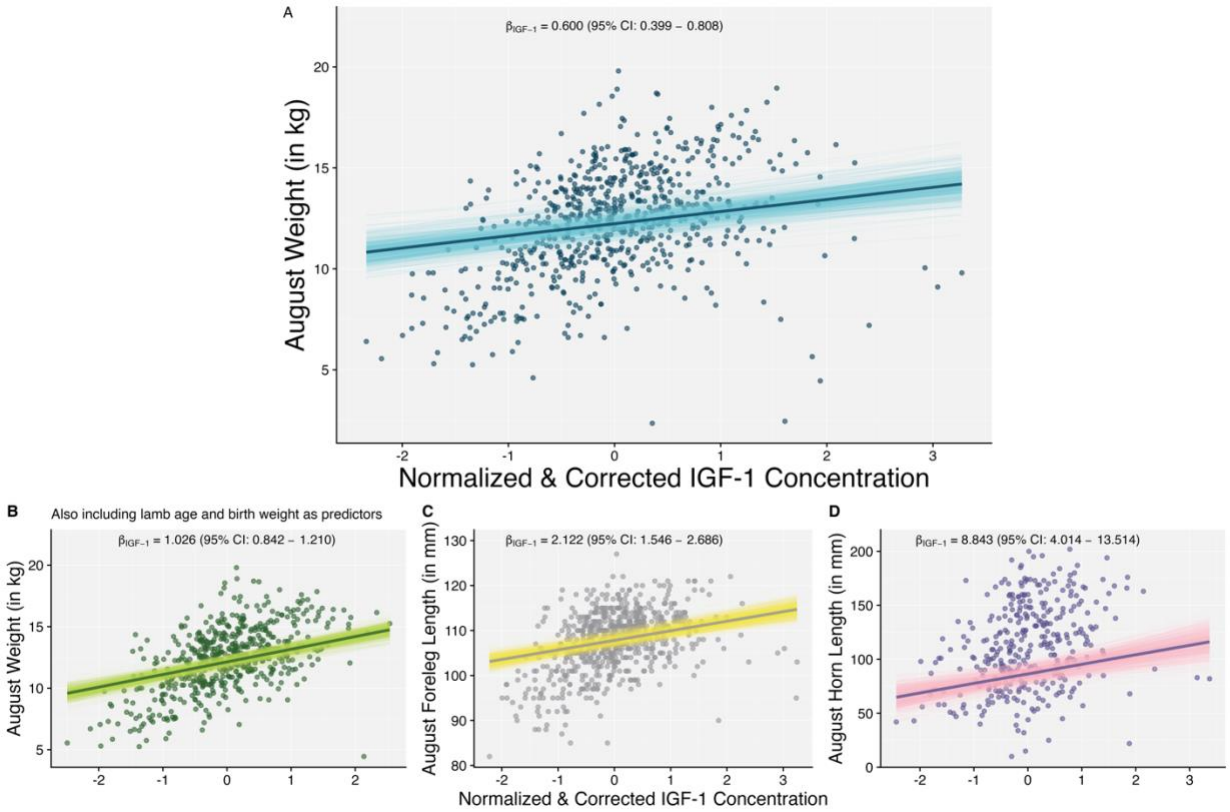

Figure 2: Associations between plasma IGF-1 levels and A) August body mass (n=666); B) Post-natal growth (n=545); C) August foreleg length (n=660); D) August horn length (n=361) in Soay lambs, independent of our proxies of resource availability (population density, sex, litter size and maternal age at birth; Table S6). The slope is predicted with fixed effects set as follows: female sex, singleton litter, average population density and average maternal age at birth. The dark line represents the median of the posterior distribution and the lightly shaded lines are 500 draws from the posterior distribution. Points represent raw data ($IGF1_{Corrected}$ estimated from $IGF1_{Observed}$ which was standardized to mean=0 and standard deviation =1 prior to model fitting).

Plasma IGF-1 concentrations predict first-year survival and reproduction

We found lambs with higher plasma IGF-1 concentrations in the summer were more likely to reproduce in their first year (Table S7A). This association was present after controlling for resource availability proxies (Figure 3A; Table 2). However, after accounting for summer body mass, there was no statistical support for plasma IGF-1 levels positively predicting reproduction (Figure 3B, Table S7A). This suggests the association between IGF-1 and reproduction is mediated by summer body mass.

Lambs with higher plasma IGF-1 had higher survival probabilities over their first winter (Table S7B). The slope between plasma IGF-1 and overwinter survival was positive, however the 95% CIs overlapped zero in models where we controlled for resource availability proxies, body mass or both (Tables 2, S7B; Figures 3C, 3D). Instead, we

found summer body mass to be a better predictor of overwinter survival of lambs than plasma IGF-1 concentrations (Tables 2, S7, S8).

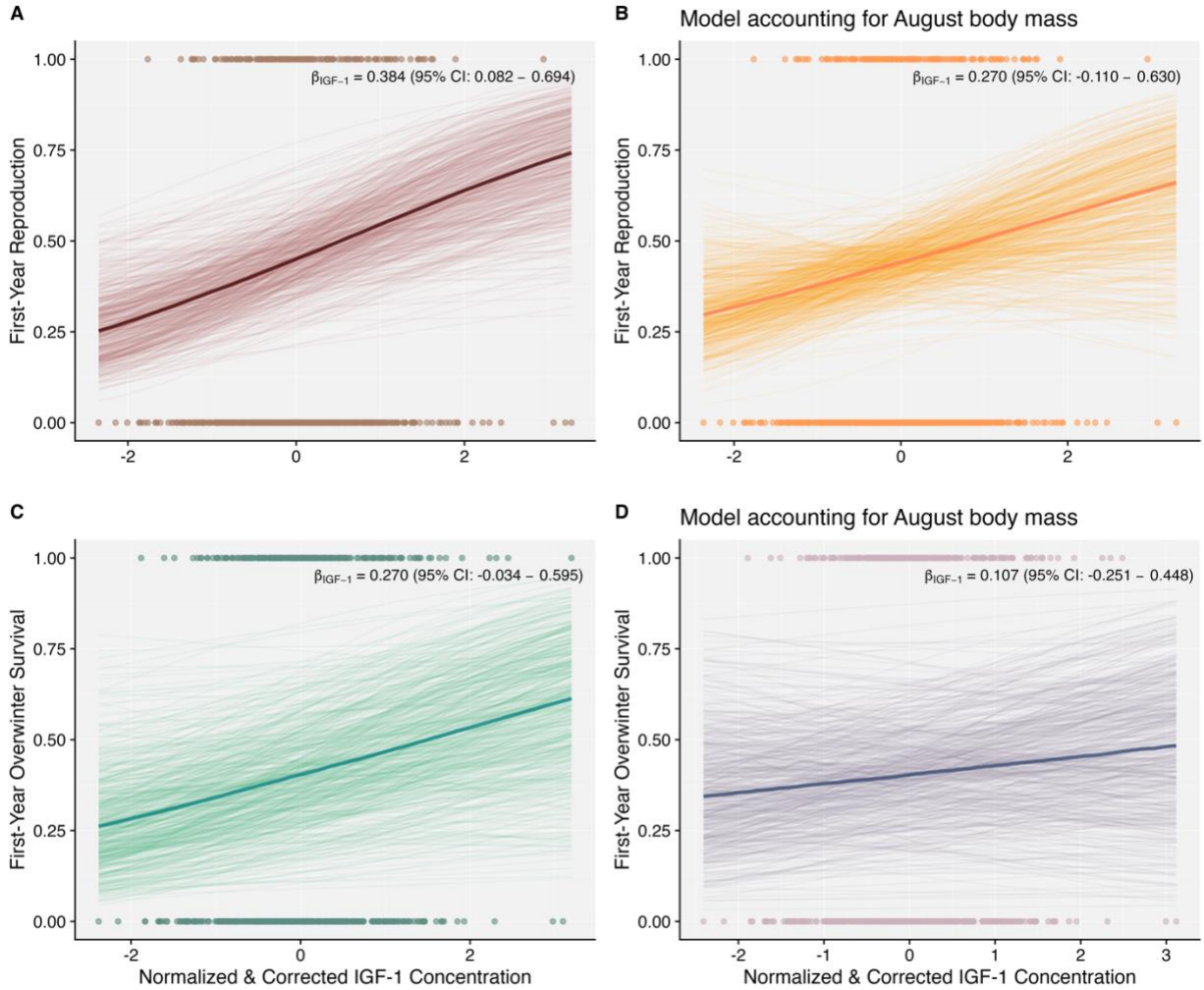

Figure 3: Associations between plasma IGF-1 levels and first-year reproduction (n=656) and first-year overwinter survival probability (n=609) in lambs, independent of resource availability proxies (A and C) or both resource availability and summer body mass (B and D) (Table S7). The slope is predicted with fixed effects set as follows: female sex, singleton litter, average population density and average maternal age at birth. The dark line represents the median of the posterior distribution and the lightly shaded lines are 500 draws from the posterior distribution. Points represent raw data ($IGF1_{Corrected}$ estimated from $IGF1_{Observed}$ which was standardized to mean=0 and standard deviation =1 prior to model fitting).

Table 2: Results from (generalized) linear mixed effects models investigating the associations between circulating IGF-1 levels and summer body mass (n=666 observations), first-year reproduction (n=656 observations) and first-year overwinter survival probability (n=607 observations) in lambs.

	Summer Body Mass	First-Year Reproduction	First-Year Overwinter Survival
Intercept	13.978 (13.141 – 14.849)	-2.596 (-3.467 – -1.764)	-0.908 (-2.282 – 0.296)
IGF-1	**0.600**	**0.384**	0.270

	(0.399 – 0.808)	**(0.082 – 0.694)**	(-0.034 – 0.595)
	-1.096	**2.661**	**0.986**
Sex (Female)	**(-1.404 – -0.789)**	**(2.113 – 3.277)**	**(0.528 – 1.466)**
	-2.983	**-1.399**	**-0.998**
Litter Size (Twin)	**(-3.498 – -2.497)**	**(-2.241 – -0.607)**	**(-1.817 – -0.287)**
	0.063	-0.320	-0.660
Population Density	(-0.827 – 0.959)	(-1.125 – 0.439)	(-1.936 – 0.595)
	0.475	0.112	-0.013
Maternal Age (1)	**(0.297 – 0.651)**	(-0.120 – 0.353)	(-0.283 – 0.241)
	-0.652	**-0.262**	**-0.456**
Maternal Age (2)	**(-0.778 – -0.526)**	**(-0.476 – -0.064)**	**(-0.706 – -0.231)**
Variances			
	1.411	0.120	1.033
Maternal Identity	(0.915 – 2.029)	(0.000 – 0.809)	(0.262 – 2.468)
	1.133	0.792	2.195
Birth Year	(0.382 – 4.376)	(0.172 – 3.711)	(0.729 – 8.578)
	2.875		
Residual	(2.502 – 3.360)		

Discussion

We found proxies of resource availability to predict summer IGF-1 levels in lambs. IGF-1 was negatively associated with population density and was lower in twin lambs compared to singletons. There was a quadratic association between offspring IGF-1 and maternal age. IGF-1 was associated with different morphological traits, positively correlating with body mass, post-natal growth and skeletal size. Higher plasma IGF-1 levels predicted both first-year reproduction and overwinter survival. However, we found no statistical support for the IGF-1–survival association after accounting for either resource availability proxies or summer body mass. IGF-1 predicted first-year reproduction independent of resource availability proxies, but this association was mediated by summer body mass. Our findings demonstrate population-level phenotypic plasticity in plasma IGF-1 due to variation in resource availability proxies. Our results support a potential role for plasma IGF-1 as a physiological marker of total resource budget and a regulator of life-history plasticity in the wild.

Circulating levels of IGF-1 varied predictably with proxies of resource availability. IGF-1 was negatively associated with population density, a proxy for food availability and resource competition. Fewer maternal resources available per capita as a twin than as a singleton meant reduced plasma IGF-1 levels measured in nearly weaned twin lambs compared to singletons. We also observed decreased IGF-1 levels in lambs born to younger and older mothers with poor maternal provisioning compared to lambs born to mothers of intermediate age who can provide more resources to their offspring. Soay lambs rely largely on their mother's milk for their nutritional needs until they become fully weaned in late summer (Clutton-Brock and Pemberton., 2004). In years when population density is high, the amount of food individuals can acquire is low due to increased resource competition (Cote et al., 2004). Reduction in forage biomass and primary productivity due to high numbers of sheep in the study area could then

contribute to low IGF-1 levels (Robertson et al., 1992). In most iteroparous mammal populations, individuals prioritize allocation of resources towards survival over reproduction when resources are scarce (Therrien et al., 2008). As a result, reduced maternal allocation of resources to offspring during gestation and lactation could influence juvenile IGF-1 levels. Young mothers are also resource-poor as they are still growing while older mothers are in poor physiological condition and so are less able to meet the resource demands of gestation and lactation (Hamel et al., 2012; Lumaa & Clutton-Brock., 2002; Gittleman et al., 1988). Previous experimental studies in wild bird and fish populations similarly found plasma IGF-1 concentrations to be reduced in fasting or food-restricted individuals (Schew et al., 1996; Gabillard et al., 2006; Uchida et al., 2003; Wilkinson et al., 2006). Studies also report sibling competition for shared maternal resources negatively influencing IGF-1 levels (Mock & Parker., 1997; Hudson & Trillmich., 2008). In free-living great tits and jackdaws, nestlings from reduced broods had higher plasma IGF-1 levels than those in enlarged or control broods (Lodjak et al., 2014; Lodjak et al., 2023 but see Ridenour et al., 2023). Here, we found increase in resource availability proxies to be associated with higher plasma IGF-1 levels. Both the maternal and external environment may influence food availability, capable of eliciting a plastic IGF-1 response in juveniles of a wild mammal.

Our analyses found support for plasma IGF-1 positively influencing key morphological traits such as body mass, structural size and post-natal somatic growth in Soay sheep. We also found increased levels of IGF-1 in males compared to females. In polygynous mammals with sexual dimorphism like the Soay sheep, males allocate substantially more energy and resources towards growth of their physical characteristics since larger males have a competitive advantage during mating (Trivers., 1972). High IGF-1 levels in male lambs could then be related to their faster growth rates compared to females. Studies across wild bird, reptile and mammal populations reported plasma IGF-1 levels to correlate positively with body mass and growth within species (Crain et al., 1995; Ditchkoff et al., 2001; Toth et al., 2022; Lodjak et al., 2017). Experimental studies in wild and captive bird populations similarly found individuals with increased IGF-1 levels to have higher body mass or faster growth rates, compared to controls (Lodjak et al., 2017; Toth et al., 2022). In two free-living passerine populations, positive associations between plasma IGF-1 and tarsus length - a proxy for structural body size in birds - have also been observed (Lodjak et al., 2014, 2017). The IGF-1/Akt/mTOR pathway is the key mediator of cell proliferation and survival across diverse tissues (Hakuno & Takahashi., 2018). IGF-1 is also part of the growth hormone (GH)/IGF1 axis mediating the effects of GH on somatic growth (Laron., 2001). Given its fundamental role in growth and development, our observation of increased plasma IGF-1 levels in heavier and larger lambs suggests circulating IGF-1 promotes body growth and bone development in Soay sheep. Additionally, we observed consistent positive associations between IGF-1 and all morphological traits even after controlling for resource availability proxies. It is likely that there could be additional variation in resource availability that is not adequately captured using our proxies. For instance, differences in vegetation quality between years or within-year variation in space-use behaviour, home-range quality and local population density may be associated with both IGF-1 and morphological traits (Crawley et al., 2021; Wiersma et al., 2023). Our results suggest IGF-1 could mediate

resource allocation decisions towards key morphological traits, potentially acting as a physiological marker of body size and post-natal somatic growth in wild mammals. Understanding the genetic correlation between IGF-1 and body size in future studies can help reveal the pleiotropic nature of this hormonal pathway in directing organismal development and shaping individual life-histories.

The influence of plasma IGF-1 on short-term survival prospects across both laboratory and wild environments is unclear. We found variation in plasma IGF-1 to predict survival over the lamb's first winter period. However, this association was not independent of resource availability proxies and body mass which suggests that IGF-1 levels do not directly determine early survival of juveniles in this population. In contrast to our results, in wild female spotted hyenas, plasma IGF-1 levels did not predict survival to reproductive maturity but instead, predicted adult survival (Lewin et al., 2017). Reduced IIS activity predicting longer lifespans has been consistently shown in laboratory studies across diverse species (reviewed in Mathew et al., 2017). Comparative studies in wild populations of mammals and birds similarly found higher IGF-1 levels to be associated with fast life-histories (Lodjak et al., 2018; Swanson & Dantzer., 2014 but see Lendvai et al., 2024). We were unable to investigate associations between plasma IGF-1 and adult lifespan in this study since many individuals that survived their first winter are currently alive and have not yet expressed their full lifespan. Repeated measures of plasma IGF-1 concentrations of individuals across their lifespan could help illuminate our understanding of the role of IGF-1 in regulating lifespan and the natural ageing process in wild populations.

High IGF-1 levels predicted increased probability of first-year reproduction in Soay lambs. Although independent of variation in resource availability proxies, this association between IGF-1 and reproduction was explained by variation in summer body mass – individuals with higher plasma IGF-1 concentrations were heavier and so, more likely to reproduce in their first year. IGF-1 is part of the hypothalamic-pituitary-somatotropic (HPS) axis which interacts strongly with the hypothalamic-pituitary-gonadal (HPG) axis, the latter being the key facilitator of reproduction and sexual behaviours in vertebrates (Milman et al., 2016; Sower et al., 2009). It is likely that fertility is mainly regulated by hormones involved in the HPG axes with IGF-1 contributing to this primarily via its influence on body size. Similar to our findings, previous studies in laboratory and wild populations have suggested a size-mediated effect of IGF-1 on reproductive traits (Kroonsberg et al., 1989; Lodjak et al., 2017). In contrast, a study in a wild population of juvenile female hyenas found plasma IGF-1, but not body mass, better predicted age at first parturition although sample sizes were relatively small (n=37; Lewin et al., 2016). A positive association between plasma IGF-1 and reproductive traits has been previously reported in laboratory rodents, cattle, wild reptiles and fish (Sparkman et al., 2010; Campbell et al., 2003; Daftary & Gore., 2005; Patton et al., 2007). But it is unclear in these studies whether resource availability is confounding the association between IGF-1 and reproduction or whether the observed IGF-1 – reproduction association is mediated by effects of IGF-1 on body mass. Our results also suggest IGF-1 being important for early fertility since the reproductive measure used in our analyses included not just successful births but also foetus and

still-births. Previous studies of IGF-1 in dairy cows found positive associations between plasma IGF-1 and early fertility traits like first-service conception rates and pre-implantation embryo development (Patton et al., 2007; reviewed in Velazquez et al., 2005). Our findings reveal body size-mediated effects of IGF-1 on early fertility in a wild mammal. Our results are consistent with the wider literature finding IGF-1 to strongly influence body mass and post-natal growth which in turn influences reproduction of juveniles of this wild sheep population. This reveals support for IGF-1 as an important physiological mechanism underpinning variation in life-history traits in the wild.

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Author Contributions

SR and HF conceived the study; SR performed the laboratory work and statistical analyses with support from YCM and JLP respectively; JMP led pedigree reconstruction; DHN, JMP, JGP, XB are involved in management of the long-term study and fieldwork; SR wrote the first draft of the manuscript with input from HF; all authors contributed to final revisions and editing of the manuscript.

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