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JOANNES VAN CANN (Orcid ID : 0000-0002-1394-804X)

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TITLE: Intergenerational fitness effects of the early life environment in a wild rodent

AUTHORS: Joannes Van Cann[1]*, Esa Koskela[1], Tapio Mappes[1], Angela Sims[1], Phillip C. Watts[1,2]

Authors after the first author are listed in alphabetical order

[1] Department of Biological and Environmental Science, University of Jyväskylä, FI-40014 Jyväskylä, Finland

[2] Ecology and Genetics, University of Oulu, FI-90014, Oulu, Finland

*email: joannes.j.vancann@jyu.fi

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Summary

1. The early life environment can have profound, long-lasting effects on an individual's fitness. For example, early life quality might (1) positively associate with fitness (a silver spoon effect), (2) stimulate a predictive adaptive response (by adjusting the phenotype to the quality of the environment to maximize fitness) or (3) be obscured by subsequent plasticity. Potentially, the effects of the early life environment can persist beyond one generation, though the intergenerational plasticity on fitness traits of a subsequent generation is unclear.

2. To study both intra- and inter-generational effects of the early life environment, we exposed a first generation of bank voles to two early life stimuli (variation in food and social environment) in a controlled environment. To assess possible intra-generational effects, the reproductive success of female individuals was investigated by placing them in large outdoor enclosures in two different, ecologically relevant environments (population densities).

3. Resulting offspring were raised in the same population densities where they were conceived and their growth was recorded. When adult, half of the offspring were transferred to opposite population densities to evaluate their winter survival, a crucial fitness trait for bank voles.

4. Our setup allowed us to assess: (1) do early life population density cues elicit an intra-generational adaptive response i.e. a higher reproductive success when the density matches the early life cues and (2) can early life stimuli of one generation elicit an intergenerational adaptive response in their offspring i.e. a higher growth and winter survival when the density matches the early life cues of their mother.

5. Our results show that the early life environment directly affects the phenotype and reproductive success of the focal generation, but adaptive responses are only evident in the offspring. Growth of the offspring is maintained only when the environment matches their mother's early life environment. Furthermore, winter survival of offspring also tended to be higher in high population densities if their mothers experienced an competitive early life. These

results show that the early life environment can contribute to maintain high fitness in challenging environments, but not necessarily in the generation experiencing the early life cues.

KEYWORDS: early life, intergenerational plasticity, maternal effect, population density, predictive adaptive response, protein restriction, silver spoon, social environment

INTRODUCTION

Many organisms adjust their phenotype in response to environmental stimuli (Burton & Metcalfe, 2014; Nettle, Frankenhuis, & Rickard, 2013; Paaby & Testa, 2018). The early life environment is of particular importance as it can have a profound, and often irreversible, impact upon the phenotype (Burton & Metcalfe, 2014). A high quality early life environment can elicit high adult fitness – the so called 'silver spoon effect' (Grafen, 1988; Monaghan, 2008) or 'condition transfer' (Bonduriansky & Crean, 2018) which appears to be a common phenomenon in animals (Cartwright, Nicoll, Jones, Tatayah, & Norris, 2014; Lindström, 1999; Wong & Kölliker, 2014). Alternatively, either a high or a low quality early life environment might stimulate a certain phenotypic trajectory that maximizes the fitness in a matching (i.e. high or low quality) environment – a 'predictive adaptive response' (Duckworth, Belloni, & Anderson, 2015; Galloway & Etterson, 2007; Gluckman, Hanson, & Spencer, 2005). For example, in the marine polychaete *Ophryotrocha labronica*, maternal temperature during oogenesis can lead to increased temperature tolerance when the offspring are reared in a similar ('matching') environment (i.e. an environment with thermal variation; Massamba-N'Siala, Prevedelli, & Simonini, 2014). The evolutionary benefits of a predictive adaptive response are unclear when the future environment is not predictable, as the early life environment can stimulate a phenotype that performs poorly in later conditions (Bateson, Gluckman, & Hanson, 2014; Vickers et al., 2000).

Traditionally the focus of early life effects has been on within-generational plastic responses because considering the length of time between the environmental cue and the expressed phenotype, the effects might be expected to be more apparent within (F1 early environment affecting F1 fitness) than between generations (F1 early environment affecting F2 fitness) (Burton & Metcalfe, 2014). Indeed, laboratory studies on rodents (Bateson et al., 2014; Vickers et al., 2000) and insects (Raveh, Vogt, & Kölliker, 2016; Vijendravarma, Narasimha, & Kawecki, 2010) show how the similarity in nutritional environment during early (development) and late (mature) life (i.e. occurring within one generation) determines the fitness of phenotype. With this in mind, it is intriguing that the phenotypic consequences of an F1 individual's early life environment can persist to the next generation (F2) (Burton & Metcalfe, 2014; Donelson, Salinas, Munday, & Shama, 2018; Donohue, 1999), as depending on environmental autocorrelation, intergenerational effects can either limit or enhance the ability of an individual to express the optimal phenotype (Guillaume, Monro, & Marshall, 2016; Heckwolf, Meyer, Döring, Eizaguirre, & Reusch, 2018). Of course, the F2 adult phenotype might be plastic (Ergon, Lambin, & Stenseth, 2001; Piersma & Drent, 2003) (i.e. able to reversibly change the phenotype based on immediate environmental cues) and capable of mitigating the consequences of the early life environment (Beaman, White, & Seebacher, 2016). The processes that impact phenotype have obvious eco-evolutionary relevance and yet it has proved difficult to quantify their relative impact in natural populations (Monaghan, 2008). The challenge in identifying the eco-evolutionary relevance of the early life environment (Mousseau & Fox, 1998) on subsequent generations lies in assessing the fitness consequences, which in turn depend on the degree of environmental variation.

Numerous examples exist of F1 early life exposure resulting in intergenerational F2 responses. For example, F1 early life ambient temperature for certain fish species (*Acanthochromis polyacanthus* Donelson, Munday, McCormick, & Pitcher, 2012; *Gasterosteus aculeatus* Shama & Wegner, 2014; Shama et al., 2016) and lizards (*Lacerta vivipara* Marquis, Massot, & Le Galliard, 2008) can lead to changes in offspring body size. Evidence in mammals for intergenerational phenotypic effects of F1

early life environment on F2 is derived largely from biomedical studies of humans (Gluckman et al., 2005) and laboratory rodents (Bateson et al., 2014), whereby conditions experienced during pregnancy can impact the birth characteristics and health of both the focal generation (F1) and the next generation (F2) (Lumey & Stein, 1997; Painter et al., 2008; Rickard et al., 2012). Intergenerational effects may occur through several different pathways, such as differential parental investment into F2 offspring and/or by direct environmental influence on the F2 through epigenetic processes that occur during prenatal or early life (Burton & Metcalfe, 2014). Despite unambiguous evidence of intergenerational early life effects in humans and laboratory animal models, it is unclear whether intergenerational effects have fitness consequences in natural settings (Sheriff & Love, 2013) and the extent to which any (mal)adaptive effects are mediated in different ecological circumstances. For example, intergenerational phenotypic effects could allow populations to cope with climate change (Donelson et al., 2018) by facilitating individuals to rapid changes in temperature and precipitation (e.g. Marquis et al., 2008; Shama & Wegner, 2014).

The bank vole *Myodes glareolus* has several life-history traits that make it an ideal species to study the within- and between-generation consequences of the early life environment through the maternal line: females are promiscuous, males do not display paternal care, and females are territorial during the breeding season (Gromov & Osadchuk, 2013). The maternal environment is therefore presumed to be the main contributor to the early life environment of the next generation (but see Vaiserman, Koliada, & Jirtle, 2017; Weyrich et al., 2016 for potential environmental paternal effects in other study systems). Furthermore, varying (early life) environments are relevant to bank voles as natural populations typically undergo cyclic fluctuations in density (Kallio et al., 2009; Korpela et al., 2013; Korpimaki et al., 2005; Prévot-Julliard, Henttonen, Yoccoz, & Stenseth, 1999). As a consequence, density-related factors, such as nutritional quality (Helle, Koskela, & Mappes, 2012) and population density itself (Prévot-Julliard et al., 1999) impact several life-history traits including maturation, reproductive success and susceptibility to the costs of reproduction (Koskela, Jonsson, Hartikainen, & Mappes, 1998; Mappes et al., 2008; S. C. Mills et al., 2007; Prévot-Julliard et al.,

1999). Some life-history traits follow a delayed density pattern and a predictive adaptive response has previously been hypothesized to be partly responsible (Oksanen, Koivula, Koskela, Mappes, & Soulsbury, 2012). An important aspect of the bank vole's life cycle is the overwintering survival where populations can easily decrease by 50% during winter (Kallio et al., 2009). For voles born during the summer the first mating opportunity is after the winter, making winter survival a key fitness trait. Intra-generationally, it has been shown that bank voles born in a certain density have a higher winter survival if the adult winter density matches that early life density (Oksanen et al., 2012). So far, no efforts have been made to investigate potential intergenerational effects of the early life density. In theory, intergenerational effects that 'prepare' offspring for an increasing population density could be beneficial for bank voles due to the cyclicity of the population fluctuations.

Our aim was to quantify the role of the early life environment in mediating fitness traits in natural conditions both within and between generations and in different environments. We predict that (1) if early life environmental cues have a silver spoon effect (Grafen, 1988; Monaghan, 2008), then a low quality early life reduces adult fitness independent of the adult environmental quality; (2) if early life cues elicit a predictive adaptive response (Gluckman et al., 2005), then a low quality early life leads to a lower adult fitness only if the adult environmental quality does not match the early life quality and (3) if the phenotype is plastic and can compensate for any effects of the early life environment, then our treatments will have little to no effect on adult fitness. To test these predictions, we varied the early life environment, which is the intra-uterine development and nursing period of female bank voles (termed F1), by exposing them to two population density-related cues in a factorial setup in the laboratory (Fig. 1a). The chosen early life cues were (1) social confrontation, relevant to bank voles as gravid female bank voles fiercely defend their territories (Gromov & Osadchuk, 2013; Koskela, Juutistenaho, Mappes, & Oksanen, 2000; Koskela, Mappes, & Ylönen, 1997), and (2) variation in dietary protein, as the nutritional environment is related to population density (Brook & Bradshaw, 2006; Forbes et al., 2014; Tanner, 1966) and protein is an

important component of the bank vole diet (Hansson, 1971). To test the effects of the early life in either a matching or a non-matching adult environment, the F1 animals were released into experimental field-enclosures at two different population densities, where they freely competed and reproduced (Fig. 1b). Reproduction of F1 in the field produced a second generation (F2) whose growth and overwintering survival was quantified at different population densities, allowing us to test whether there was an intergenerational response (Fig. 1c). We quantified the phenotypes (i.e. fitness-related traits - growth, reproductive characteristics and survival) of the focal (F1) and second (F2) generations at both low and high population densities under a full factorial design (Fig. 1).

METHODS

Starting colony

Three hundred and eighty two bank voles females (F0) (Table S1) were bred in spring of 2014 (first replicate) and 2015 (second replicate) from a random mix of first or second generation wild-caught animals that had been trapped in Central Finland (62°8379 N; 26°8209 E). All bank voles were kept in polyethylene cages (43x26x15 cm) and maintained on a 16L:8D photoperiod at 20±2°C, with wood shavings and hay provided as bedding. Water was provided *ad libitum* and prior to the experiment standard food (Labfor 36; Lactamin AB, Stockholm, Sweden) was provided *ad libitum*. Animals were chipped with electronic Trovan tags (EID Aalten BV, Aalten, Holland) for identification.

Early life environment– laboratory manipulation

All F0 females were randomly assigned to four groups in a two by two factorial design (Fig. 1; Table S1): (1) a control group (PR-SC-; Fig. 1), (2) a protein restricted group (PR+SC-), (3) a social confrontation group (PR-SC+) and (4) a group which received both protein restriction and social confrontation (PR+SC+). There were no significant differences in average body mass (one way ANOVA; $F_{3,477}$=0.359; p=0.783) between groups. Mature males (from the laboratory stock, non-kin with the females) were randomly grouped with F0 females.

At the start of the breeding, F0 females receiving the PR- treatment received a control diet (18% protein; 3.1 kCal/g; Envigo, WI, USA) that has a similar protein content as found in the wild (Droždž, 1968) while females from the PR+ treatment were given a restricted protein diet (9% protein; 3.2 kCal/g; Envigo, WI, USA). After seven days, males were removed and females receiving the SC+ treatment started receiving social confrontation. Social confrontation consisted of confronting each female in a new, empty cage with another SC+ female every second day (Marchlewska-Koj, Kruczek, Kapusta, & Pochroń, 2003) for 10 minutes. New combinations of females were used every day to avoid habituation. A more detailed explanation of the social confrontation treatment can be found in the supplementary information. All treatments were carried out throughout the pregnancy and continued until the pups (F1) had weaned (20 days post-partum). Upon weaning, F1 individuals were transferred to separate cages per litter where they received water and standard food *ad libitum* (Labfor 36; Lactamin AB, Stockholm, Sweden). At the age of 30 days, litters were separated per sex until they were released to the field enclosures.

Population density treatments – field experiments

At the age of two months, i.e. the beginning of July 2014 or 2015 for individuals born in 2014 or 2015 respectively, fitness of F1 females from all treatment groups was assessed by releasing them to field enclosures twice for approximately three weeks (Fig. 1b). F1 individuals mated and carried litters in the first three weeks and nursed their litters in the second three weeks. Twenty three enclosures (40m x 50m) were used, located in Central Finland (62°37'30"N 26°14'38"E and 62°39'23"N 26°09'32"E; Fig. S2). Enclosures were fenced with 1.25m high galvanized sheet metal buried 0.5 m in the ground, which prevented immigration and emigration of bank voles but did not prevent predation by avian predators. Trapping was performed by placing 20 Ugglan live traps (Grahnab, Hillerstorp, Sweden) per enclosure, organized in a grid, baited with sunflower seeds and potato. Traps were not set and contained no food during any other period. Throughout the field experiments, individuals relied on natural resources for food and water.

Over two years, F1 females were released in enclosures in one of two population densities (termed 'population density 1'; PD1): (1) a low population density treatment, consisting of four female individuals (one from each early life treatment group), or (2) a high population density treatment, consisting of eight female individuals (two from each early life treatment group). Densities corresponded to the variation of natural bank vole populations over the multiannual density cycle (Rikalainen, Aspi, Galarza, Koskela, & Mappes, 2012; Yoccoz, Stenseth, Henttonen, & Prévot-Julliard, 2001). In total, the two replicates consisted of nineteen low and twelve high density enclosures. After one day, experimentally naive males, previously caught from wild populations, were added to the enclosures to produce a 1:1 sex ratio, and all individuals were allowed to mate. Individuals were exhaustively trapped (individuals not caught were considered dead) and brought to the laboratory just before their parturitions, where they could give birth to the F2 generation (Fig. 1b).

Intergenerational effect on F2 phenotype – field experiments

After parturitions, F1 mothers and their new-born F2 litters were returned to the same densities as before. Releases were done by placing the cage in which the mother gave birth in the enclosure on its side, giving the mother opportunity to relocate her nest (after which the cages were removed). This method to trap late pregnant bank vole females to give birth in the lab and then promptly return them with their new-born pups back to the enclosures makes it possible to determine the phenotypes of new-born pups (Koskela, Juutistenaho, Mappes, & Oksanen, 2000; Oksanen, Koskela, & Mappes, 2002). New experimentally naïve males, not used for the experiment so far, were added after one day, in a 1:1 sex ratio. At weaning (ca. three weeks old), the F2 individuals were exhaustively trapped and brought to the laboratory where they were weighed and kept in standard cages until tested for winter survival. All F1 mothers and naïve males were also trapped and not used subsequently in the experiment.

Intergenerational effects on F2 survival – winter survival

When F2 individuals were at least 50 days old their winter survival was assessed in outdoor enclosures in either low or high population densities (termed 'population density 2' (PD2); Fig. 1c). Half of the F2 individuals were designated to the density treatment by matching their early life density (PD1), and half were designated by not matching their early life density. This reciprocal transplant experiment meant that every F2 individual now had three factors for which their winter survival could be tested: (1) the intergenerational effects of the F1 early life (PR and/or SC), (2) the intra-generational effect of the density in which the F2 was conceived and raised (PD1) and (3) the direct effect of the density in which an individual resides during the winter (PD2). There were 10 low density populations consisting of 8 individuals (one female and one male F2 individual from each F1 early life treatment group) and 5 high density populations with 16 individuals in each (two female and two male F2 individuals from each F1 early life treatment group). Enclosures never contained individuals from the same litter. The winter survival experiment began in October, when the temperature started dropping below zero (average temperature at day of release was 6°C), and long-term survival was determined by trapping all enclosures exhaustively in April, as the snow started melting and this means the onset of the next breeding season.

Morphological measurements

All body masses were measured using electronic scales. Body mass of F0 was measured at the start of the experiment, at the birth of F1 and at F1's weaning age (20 days). F1 body mass was recorded at birth and as adults (30 days). F2 individuals' body mass was recorded at the age of recapture (25 days).

Statistical analyses

Statistical analyses were performed using R v.3.4.2 (R Core Team, 2017). All analyses of body mass and the F2 winter survival (logit link) were performed using the package lme4 (Bates, Mächler, Bolker, & Walker, 2015), and p-values were calculated with the package lmerTest (Kuznetsova, Brockhoff, & Christensen, 2017) using Satterthwaite's method for approximating degrees of freedom. The litter size (number of offspring) that F1 produced in the field was analysed as a zero-truncated Poisson generalized mixed model using glmmTMB (Brooks et al., 2017) (log link). Whether or not a F1 mother reproduced at all ("Reproduced"; binomial yes/no; logit link) was analysed using glmmTMB (Brooks et al., 2017). All model selections began with a full model that had stepwise reduction until the model with the lowest AIC was achieved, after which the model fit was examined. The F1 early life treatments, PR and SC, and their interaction term (PR x SC) were purposely retained during model selection. For the F1 enclosure experiments, density (PD1) was always included as a fixed factor in the model. For the analysis of F2 winter survival, the full model included the F2 winter density (PD2), as well as the F2 summer density (PD1), in which the F2 were conceived and raised, as fixed factors (in addition to PR, SC and PR x SC). For all analyses, sex (Koivula, Koskela, Mappes, & Oksanen, 2003; Koskela, Mappes, Niskanen, & Rutkowska, 2009; Schulte-Hostedde, 2007) and the litter size the individual was born in (Koivula et al., 2003; Mappes & Koskela, 2004; Oksanen et al., 2002; Schroderus et al., 2012) were included as covariates in the full model. As individuals were born in different years and weeks, all F1 analyses included the 'batch number' as a random factor. F2 individuals were released in two groups during the first year and this was included as a random factor for the summer F2 analyses. All analyses also included 'litter number' as a random factor, which groups siblings to account for litter effects (either for F1 or F2 individuals). All field enclosure analyses included 'enclosure number' as a random factor, which accounts for local differences between the enclosures. Random factors were always included in the initial full model and retained during model selection. Standard deviations of all included random factors are reported in the supplementary tables (Tables S4, S5 and S6).

RESULTS

Early Life Environment

Both the social confrontation and protein restriction treatments affected the phenotype of F1 individuals (Table 1). In total, 643 F1 individuals (Table S2) were born to 158 F0 mothers. A restricted protein diet significantly lowered both the F1 birthmass (mean±SD(g), PR-: 1.90±0.23; PR+: 1.83±0.22) as well as the F1 adult body mass (mean±SD(g), PR-: 16.71±2.21; PR+: 16.11±2.48) compared with the control group (Fig. S1). F1 individuals receiving the SC treatment had a significantly lower adult body mass (mean±SD(g), SC-:16.57±2.51; SC+:16.21±2.21), while not having a significantly different body mass at birth (mean±SD(g), SC-:1.85±0.23; SC+:1.88±0.23), compared with the control group. The final model did not reveal a significant interaction of the PR and SC treatment indicating that their effects were independent of each other (Tables 1 and S3).

F1 reproductive success

Neither a restricted protein or social confrontation early environment had a significant influence on the reproductive success of F1 females in the field (Tables 1 and S4). Only PD1 density had a significant effect on the probability of breeding with high density populations significantly lowering the chance of reproduction. 88% of all F1 females originally released survived during the six weeks in the field enclosures (no difference in survival between treatments: one way ANOVA; $F_{3,168}$=0.407; p=0.748), of which 105 (68%) were gravid.

Intergenerational effects on F2 phenotype

A high population density had a negative effect on the adult body mass of the F2 individuals if the mother did not receive the SC treatment (SC-; low density: mean±SD(g)=12.57±1.08; SC-; high density: mean±SD(g)=11.12±1.98; Tables 2 and S5; Fig. 2a), but if the mother did receive the SC

treatment, this negative effect associated with a high population density disappeared (SC+; low density: mean±SD(g)=12.41±1.33; SC+; high density: mean±SD(g)=12.06±1.53). Hence, if the mother received a high density related cue during her early life (*i.e.* social confrontation), her offspring were not affected by a high population density. Litter size in which the F2 individual was born had a significant negative correlation with the F2 body mass which is common in bank voles (Mappes & Koskela, 2004; Schroderus et al., 2012) (Table S5).

Intergenerational effects on F2 survival

F2 Individuals in high population densities had a lower winter survival, but this was somewhat countered if their mothers had received social confrontation during their early life. Of the 160 F2 individuals that went to the enclosures in October, 37 survived (23%) until the start of the next breeding season in April (and no unknown immigrants were captured). The density in which the F2 were conceived and raised (PD1) had no significant effect on winter survival (Tables 2 and S6). However, the early life treatment of their F1 mothers had a near statistically significant (p=0.0537) interaction effect with density on the winter survival (PD2) (Tables 2 and S6; Fig. 2b) indicating that effects of the maternal early life persisted to the F2 generation and provided a fitness benefit if the winter environment matched that of the maternal early life environment. Neither the restricted protein treatment, nor its interaction with SC, presented a statistically detectable effect upon F2 winter survival.

Table 1: Phenotypic and reproductive characteristics of F1 individuals in relation to manipulation of early life environment and population density (PD1). Reduced table of body mass of F1 individuals at birth (*n*=643) and at 30 days old (*n*=565) in the laboratory and F1 reproductive success (littersize and reproduced (*n*=172)) in the field enclosures. PR= protein restriction; SC= social confrontation; PD1= population density in which F1 females reproduced; HD= high population density. Note that estimated values for reproduced represent the probability of not breeding. Bold *p*-values indicate $p < 0.05$. Est is estimated value; Std error is standard error; x indicates interaction between variables. Full results including random effects are provided in tables S3 and S4.

		Est	Std error	DF	t value	p
F1 mass at birth	PR (+)	-0.1124	0.0394	144	-2.8540	**0.0050**
	SC (+)	-0.0213	0.0404	143	-0.5280	0.5982
	PR x SC	0.0601	0.0551	145	1.0900	0.2774
F1 mass at 30d	PR (+)	-1.0768	0.4024	137	-2.6760	**0.0084**
	SC (+)	-0.8706	0.4157	136	-2.0940	**0.0381**
	PR x SC	0.6812	0.5623	138	1.2110	0.2278
Reproduced	PR (+)	-0.6638	0.4752		-1.3970	0.1624
	SC (+)	-0.2307	0.4657		-0.4950	0.6204
	PD1 (HD)	0.9005	0.3794		2.3740	**0.0176**
	PR x SC	-0.0093	0.6781		-0.0140	0.9891
Litter size	PR (+)	-0.1002	0.1195		-0.8390	0.4016
	SC (+)	-0.2177	0.1288		-1.6910	0.0909
	PD1 (HD)	-0.1013	0.0856		-1.1830	0.2369
	PR x SC	0.2147	0.1716		1.2510	0.2109

Table 2: Adult body mass and winter survival of F2 individuals in relation to: early life treatments of their F1 mothers (PR and/or SC), their own early life (PD1) population density and their adult/winter (PD2) population density. Reduced results of 25 day body mass (*n*=414) and winter survival (*n*=160). PR= protein restriction; SC= social confrontation; PD1= population density in which the F2 individuals were raised; PD2= population density during winter survival; HD= high population density; Lsize= size of litter in which the F2 individual was born. Bold *p*-values indicate $p < 0,05$. Est is estimated value; Std error is standard error; x indicates interaction between variables. Full results including random effects are provided in tables S5 and S6.

		Est	Std error	DF	t value	p
F2 Mass at 25 days	PR (+)	-0.2998	0.3459	75	-0.8670	0.3888
	SC (+)	-0.9242	0.8082	75	-1.1440	0.2564
	PD1 (HD)	-1.7794	0.4303	59	-4.1350	**0.0001**
	Lsize	-0.4591	0.1139	94	-4.0310	**0.0001**
	PR x SC	-0.1284	0.4970	77	-0.2580	0.7969
	PD1 x SC	1.0753	0.5085	77	2.1150	**0.0377**
F2 Winter survival	PR (+)	0.1178	0.6447		0.183	0.8551
	SC (+)	0.3216	0.6691		0.481	0.6307
	PR x SC	-0.6692	0.8195		-0.817	0.4141
	PD2 (HD)	-1.3193	0.8055		-1.638	0.1014
	SC x PD2	1.7024	0.8824		1.929	0.0537

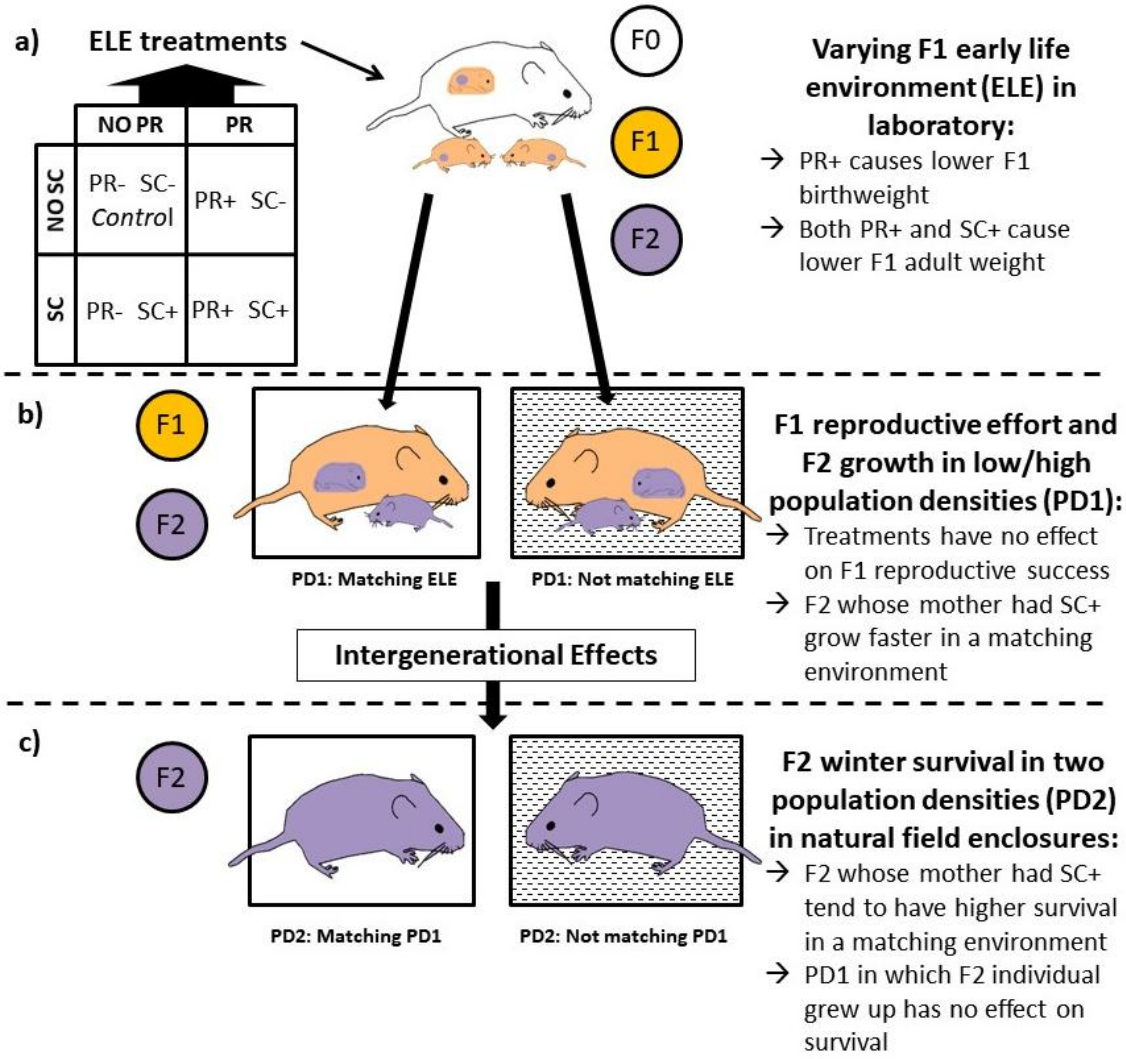

Fig. 1: Overview and summary of the experimental design to investigate the effects of population density related cues during the early life environment (ELE) of F1 on the morphology and reproductive success of F1, as well as the intergenerational effects on the phenotype and winter survival of F2. a) early life treatments (protein restriction (PR) and/or social confrontation (SC) in a factorial setup) are presented to the F1 individuals during the intra-uterine development and nursing period. b) The (adaptive) response is tested by placing the female F1 in natural outdoor enclosures in different population densities (low/high population density; blank square is population density that matches the ELE and shaded square is population density that does not match the ELE). c) Winter survival of F2 offspring is tested in a reciprocal transplant experiment where the population density (low/high population density; PD2) matches or does not match the population density in which the

F2 individual was born (blank square represents a PD2 that matches the PD1 and shaded square represent a PD2 that does not match the PD1). The setup allows winter survival of F2 to be tested for: the population density during the winter (PD2; (c)), the population density in which the F2 was born and grew up in (PD1; (b)), and the intergenerational effects of the maternal F1 ELE (a). Uncoloured voles indicate F0 individuals; orange colour indicates F1 as pups and adults; purple indicates F2 as egg cells, pups and adults.

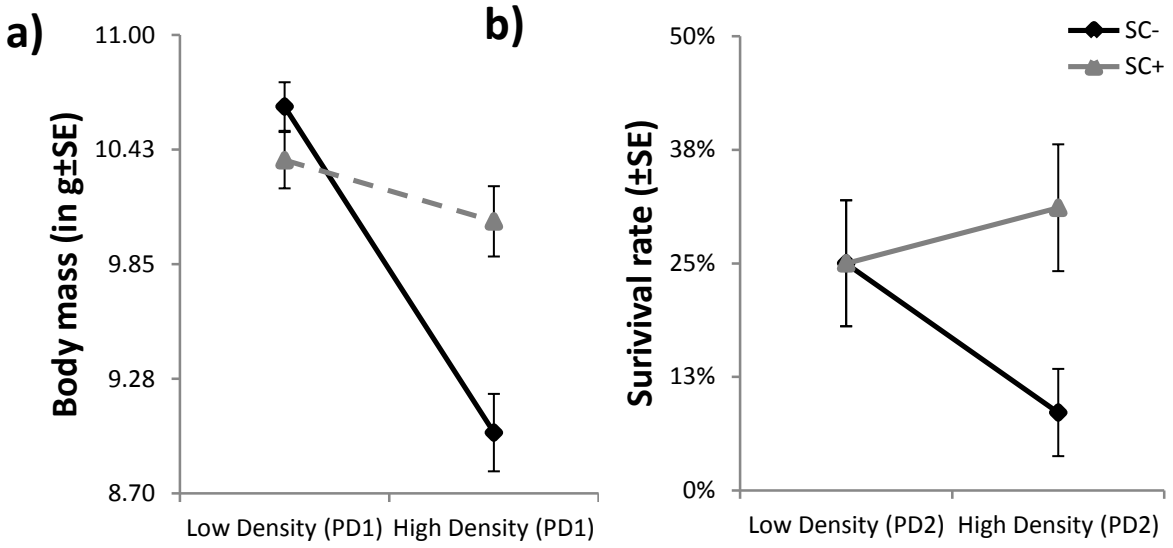

Fig. 2: Variation in F2 bank vole fitness traits (adult body mass and survival) whose maternal early life environment either had frequent social confrontation or not, competing in different population densities during the summer (PD1) and winter (PD2). a) 25 day old body mass of 414 F2 individuals (111 SC- and 121 SC+ in low density; 91 SC- and 91 SC+ in high density) in the field during the summer; b) winter survival percentage of 160 F2 individuals (40 SC- and 40 SC+ in low density of which 10 SC- and 10 SC+ survived; 35 SC- and 45 SC+ in high density of which 3 SC- and 14 SC+ survived). Diamond shaped black dots represent the average value for SC- F2 individuals. Triangular shaped grey dots represent average value for SC+ F2 individuals.

DISCUSSION

The early life environment, defined here as the period between fertilization and weaning, can have a profound influence on the adult phenotype and thus impact fitness in different ways. For example, the quality of the early life environment may associate with fitness (silver spoon effect) or an individual's fitness might be conditional upon the match in the environment experienced during early and late life (predictive adaptive response) or even a combination of both silver spoon effects and a predictive adaptive response (Bonduriansky & Crean, 2018). What is unclear, however, is the extent to which the early life experienced by the target individuals (i.e. first generation) (Burton & Metcalfe, 2014) can have intergenerational effects on the fitness of the next generation and whether these effects can be adaptive or not (Monaghan, 2008; Nussey, Wilson, & Brommer, 2007). This is especially important as we try and predict animal population response under climate change and extreme weather events (Donelson et al., 2018; Ghalambor, McKay, Carroll, & Reznick, 2007; Yeh & Price, 2004). By manipulating dietary protein and social confrontation during the early life of female bank voles we show that (1) maternal early life effects can persist to the subsequent generation (F2) where it influences adult body mass in an adaptive manner; moreover (2) winter survival of the F2 offspring tends to depend on the maternal early life environment (F1), rather than its own early life environment.

Social confrontation was exerted on pregnant bank voles during the period that wild female bank voles would be most likely to aggressively defend their territory. The effects of social confrontation on body mass were similar to a previous study in bank voles (Marchlewska-Koj et al., 2003), but did not have any effects on the reproductive success. Social confrontation during early life also had a notable intergenerational phenotypic effect on the F2 that persisted to the adult stage. F2 individuals were captured from the field not long after they are old enough to be independent from the mother, hence their body mass is largely dependent on the feeding of the mother. The ability of F2 to cope with the high population density could therefore be due to increased maternal care,

signifying that there would be a predictive adaptive response (Nettle et al., 2013) in the F1 maternal behaviour, although further investigation is needed to confirm this.

Social confrontation during the early life of the F1 generation had a nearly statistically significant positive effect (p = 0.0537) on the F2 winter survival, indicating a predictive adaptive response in F2 winter survival. In contrast, the early life environment of the F2 (i.e. PD1 density) had little effect on winter survival, implying that the maternal early life environment is of greater importance for the F2 winter survival than the F2 individuals' own early life environment. Two mechanisms could be mediating this effect (Burton & Metcalfe, 2014): (1) F1 mothers from the SC+ treatment changed some aspect of their parental care, leading to a higher survival rate of their offspring or (2) SC+ during the early life of F1 had *in utero* effects on the F2 egg cells. An example of the second possibility occurs in laboratory rats where *in utero* exposure to social stress has been linked to lower mass at birth and subsequent cardiometabolic diseases (Drake & Walker, 2004). While it might be intuitive to argue that the difference in F2 body mass relates to their winter survival, and hence maternal care would be the most likely mechanism, body mass in bank voles is not always related to winter survival (Helle et al., 2012). The specific mechanism by which the F2 survival is increased could due to selective predation, e.g. Tengmalm's owls (*Aegolius funereus funereus*) have been shown to prefer lighter prey that are in good condition (Koivunen, Korpimäki, Hakkarainen, & Norrdahl, 1996). Differences in physiology e.g. metabolic rate (Boratyński & Koteja, 2009) might also contribute to the difference in survival rate.

It is important to note that, while SC+ F2 individuals had higher survival in the high density environment (i.e. a matching environment) compared to SC- individuals, SC+ individuals did not have a lower survival in the low density environment (i.e. a mismatching environment) compared to SC- individuals (Fig. 2b). This response is not fully in line with a predictive adaptive response (*sensu* Gluckman et al., 2005) and perhaps indicates a co-occurrence of more than one type of response (Bonduriansky & Crean, 2018). It is possible that the SC+ individuals were able to plastically adapt to

the less competitive, low density environment; while the SC- individuals were not able to plastically adapt to the more competitive, high density environment. Alternatively, it is possible that the costs of living in a mismatched low density environment were too small to be detected, at least in the variables measured in this study.

Body size in female bank voles is positively correlated to fitness-related traits such as a faster onset and higher probability of breeding (Mappes & Koskela, 2004; Mappes, Ylonen, & Viitala, 1995). Additionally, dietary protein content has a major impact on mammalian phenotypes, such as mass at birth (Zambrano et al., 2005), hypertension (Harrison & Langley-Evans, 2009), and epigenetic patterns (Burdge et al., 2007; Lillycrop, Phillips, Jackson, Hanson, & Burdge, 2005). Changes in epigenetic patterns could potentially lead to intergenerational effects (Bonduriansky & Day, 2009; Burton & Metcalfe, 2014; Heard & Martienssen, 2014; Skvortsova, Iovino, & Bogdanovi, 2018; Youngson & Whitelaw, 2008). In our study, protein restriction during the early life of bank voles elicited negative effects on F1 body size both as new-borns and as adults. However, we did not find any impact on the reproductive success in F1 and no detectable impact on the F2 adult phenotype or overwintering survival probability. This is in contrast with laboratory rats (Pinheiro, Salvucci, Aguila, & Mandarim-de-Lacerda, 2008), where protein restriction increased F2's mass at birth and decreased male F2 adult body mass. While we did not find intergenerational effects due to protein restriction, we might have overlooked other phenotypic traits, such as pathogen susceptibility (Monaghan, 2008), which can affect fitness-related traits in F2 besides winter survival, e.g. reproduction (Hakkarainen et al., 2007; Kallio, Helle, Koskela, Mappes, & Vapalahti, 2015; J. N. Mills, 2006). We propose that a protein restricted early life impacts bank vole phenotype, but it is of little consequence to fitness in natural settings. As such, protein restriction cannot be considered to have a 'silver spoon effect', at least not for the fitness traits measured here.

Conclusion

High population density related cues experienced during the early life environment influence the phenotype of both the generation that experiences it (F1), and their offspring (F2). Social confrontation during the early life of the F1 individuals caused a predictive adaptive response that enabled their offspring to better compete (i.e. grow and survive) in a high population density. That the juvenile environment of F2 was less important for winter survival than the prenatal/early life environment of their F1 mothers, underlines the eco-evolutionary importance of intergenerational effects. Protein restriction during the early life of F1 had a negative effect on the body mass, but otherwise did not lead to a silver spoon effect or a predictive adaptive response. Protein restriction might affect other fitness-related traits or its impact can be overcome later in life via plasticity. This study provides clear evidence of the maternal early life environment having direct adaptive influences on the phenotype and fitness of the subsequent generation in an ecologically relevant setting of intraspecific competition at different population densities.

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AUTHORS CONTRIBUTION

J.V.C., E.K., T.M., A.S and P.W. designed the research and wrote the paper. J.V.C., E.K., T.M. and A.S performed the research and analysed the data.

DATA ACCESSIBILITY

The datasets generated during and analysed during the current study are available in the Zenodo repository via the link https://doi.org/10.5281/zenodo.1040834 (Van Cann et al., 2019).

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