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ORIGINAL PAPER

The demographic consequences of fertility reduction in rats and voles

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Abstract
Rodent population control is a global problem, complicated by evolved non-responsiveness to rodenticide treatment. Contraceptives could help mitigate this challenge, but questions remain about their efficacy, especially for rodenticide-resistant populations. We used an age-dependent demographic model to generate two hypotheses: Fertility reduction applied early in female lifetimes (1) is more effective in controlling rodent populations than when applied later in female lifetimes, and (2) is effective in controlling rodent populations that are expanding. Compared to controls, fertility reduction applied early, in mid-life, and late in female lifetimes, decreased, matched, and accelerated, respectively, the rates of population growth. Fertility reduction was effective in reducing population size only when sustained over multiple generations and was ineffective when application was episodic. Substituting classic *Rattus norvegicus* and *Microtus agrestis* life history data into our simulation framework confirmed that early fertility reduction was effective in controlling population growth, including expanding populations in both species. These simulations generated two additional hypotheses for field applications of fertility control: Over treatment durations, (3) the fraction of the population consisting of juveniles, and (4) the overall population size, will both decrease. We tested these predictions using a 12-month contraceptive bait application on rats in two urban US locations (Washington, DC) where rodenticides were already deployed. Consistent with our predictions, these populations showed marked decreases in the proportion of juvenile to adult rats, and in the total number of rats observed in camera traps over the study period. Our results support fertility control as an effective method for managing rodent populations.

Keywords Contraceptives · Population control · Pest management · Rodent life history

Key message

- Evolved resistance to rodenticides complicates rodent population control.
- Contraceptives could help, but their efficacy on rodenticide-resistant populations is poorly known.
- Our demographic models show how contraceptives can control expanding rat and vole populations.
- These models also predict observed reductions in contraceptive-treated populations of urban rats.
- Our results support fertility control as an effective method for managing pest populations.

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Introduction

Rats are significant pests, associated with the destruction of crops and the spread of disease worldwide (Leslie et al. 1952; Singleton and Petch 1994; Meerburg et al. 2009; Diaz et al. 2010; Buckle 2012; Pyzyna et al. 2014). The development of methods for controlling rat populations has fostered a rich literature on rat population biology that continues to expand (Emlen et al. 1948; 1949; Clark and Price 1981; Sridhara and Krishnamurthy 1992; Quy et al. 1993; Singleton et al., 2003; Keiner 2005; Abdelkrim et al. 2005; Pagès et al. 2013; Buckle and Smith 2015). Methods for rat population control have mainly involved anticoagulant rodenticides (Greaves and Ayres 1967; Pelz

et al. 2005). However, this emphasis has led, not only to widespread mortality among secondarily exposed rodent predators (Geduhn et al. 2015; Ruiz-Suarez et al., 2014) but also to the evolution of resistance within rat populations to these chemical treatments (Boyle 1960; McNichol 1985; Rost et al. 2004; Pelz et al. 2005; Ishizuka et al. 2008). Populations of rats that are resistant to multiple chemical treatments are widespread in Europe, Asia, Australia and North America (Pelz et al. 2005). Evolved resistance to chemical control in rats, as well as in other pest- and pathogenic species, is now recognized as one of the most significant problems of modern times (Garrett 1994; Palumbi 2001; Rost et al. 2004; Pelz et al. 2005; Ishizuka et al. 2008; Davies and Davies 2010; Frieri et al. 2016; Gould et al. 2018).

Recent attempts to control rat populations have included fertility management. Most of these studies have advocated sterilization to control fertility (Knipling and McGuire 1972; Norbury 2000; Shi et al. 2002; Jacob et al., 2006a, b; Massawe et al. 2018). However, existing sterilization methods can be labor intensive (e.g., immunocontraception [Tyndale-Biscoe 1994; Kirkpatrick 2007], surgical sterilization [Jacob et al. 2004, 2006b; Massawe et al. 2018]) or may impose recognized or unknown ecological risks (chemical sterilants [Norbury 2000], CRISPR-Cas9 gene drives [Drury et al. 2017]). Furthermore, in most applications, sterility is imposed upon such a large fraction of the population that only non-responsive individuals contribute to future generations. Thus, resistance to sterilants evolves for the same reasons that resistance evolves to rodenticides (Kirkpatrick 2007; Drury et al. 2017; Magiafoglou et al. 2003; Shuster et al. 2018). Theoretical frameworks used to understand the effects of sterilization and other forms of fertility control on rat population growth have predicted that fertility management will be ineffective in controlling rat populations, particularly those undergoing expansion (Knipling and McGuire 1972; Hone 1992, 2004). However, theoretical analyses of this and related phenomena are comparatively few (Stenseth et al. 2001; 2003; Davis et al. 2003; Magiafoglou et al. 2003; Jacob et al. 2004; Arthur et al. 2005; Ransom et al. 2014).

This paper further explores the demographic consequences of fertility reduction in rodents. We have shown elsewhere that the opportunity for selection ($I = VW/W^2$, where VW=variance in fitness; W=mean fitness; Crow 1958; Shuster and Wade 2003) favoring resistance imposed by rodenticides and sterility inducers is among the most powerful evolutionary forces known ($I > 1.0 \times 10^5$; Shuster et al. 2018). We have also shown that, compared to how selection favors resistance to rodenticides and sterilants, the opportunity for selection favoring resistance to contraceptives, which reduce fertility rather than attempt to extirpate pest populations, is likely to be no greater than that expected by chance alone ($I < 0.05$; Shuster et al. 2018). These results argue that in addition to providing a means for arresting rodent population growth, fertility reduction represents a sustainable, non-lethal method for rodent pest control.

Here, we explore how contraceptives could control rat populations by manipulating key life history parameters. We begin by generating a simple age-dependent demographic model to illustrate general patterns of life history variation as they might apply to this process. Although the basic principles illustrated in these preliminary simulations are well-established and widely appreciated (Caswell 2018), we revisit them here to show how manipulating population fertility can influence, not only the rates at which populations grow, but also how age-specific fertility reduction can influence the rates as which populations decline, depending on when and how strongly fertility is reduced. Our analysis focuses on age-dependent effects because the relevant details of rat life history in this context are well known (Leslie and Ranson 1940; Leslie et al. 1952) and because age-dependent, rather than density-dependent factors, appear to adequately explain major elements of rat population dynamics (Leslie et al. 1952; Knipling and McGuire 1972; Hone 1992; Shi et al. 2002; Wolff 2003; Ransom et al. 2014). We emphasize that the goal of fertility control in general, and of our analysis, is not to extirpate rodent populations by reducing their population sizes to zero. This policy imposes the same intensity of selection that favors the evolution of resistance to rodenticide treatment (Shuster et al. 2018). Instead, we illustrate that fertility control can reduce rodent populations to numbers at which these species are no longer recognized as pests.

We use the results of our preliminary simulations to generate two model hypotheses that we test using classic life history data for *Rattus norvegicus* (Leslie et al. 1952) and *Microtus agrestis* (Leslie and Ranson 1940). These model hypotheses, in turn, generate two empirical hypotheses that we test using field data obtained from a 12-month study of rat populations from two urban US populations (Washington, DC: Oglethorpe Street, Reservoir Road) between November 2019 and October 2020. Before fertility control was applied, these populations had been treated for an unspecified duration and with limited success with conventional second-generation anticoagulant rodenticides (SGARs).

Our Model Hypothesis 1 states that fertility reduction, applied early in female life history, will be more effective in controlling rodent population growth than fertility reduction applied in mid-life or later in life. This hypothesis is not new (Leslie et al. 1952; Hone 1992, 2004; Stenseth et al. 2001; 2003; Davis et al. 2003; Caswell 2018), but an explicit study of age-specific fertility control on rodent populations, to our knowledge, does not exist. Moreover, contraceptives have age-specific- as well as reversible effects on treated populations, that rodenticides and sterilants do not. An Empirical

Hypothesis 1 arising from our Model Hypothesis 1 states that when fertility control is deployed, the fraction of juveniles comprising the urban rat population will decrease over time.

Our Model Hypothesis 2 states that fertility reduction applied early in female life history will be effective in controlling rodent populations that are expanding. Rat populations that have become resistant to rodenticides are known to increase in size despite attempts to control them with lethal methods (Shi et al. 2002). Sterilants have been considered ineffective in regulating such populations because the inertia of population growth is presumed to exceed the power of this method to control increases in population size (Hone 1992; 2004). Our results explore how fertility reduction using contraceptives could overcome this apparent limitation. Empirical Hypothesis 2 arising from our Model Hypothesis 2 is, when fertility control is deployed, urban rat populations that appear nonresponsive to rodenticides and are expanding, will decrease in size over time.

Materials and methods

Preliminary simulations

We began by examining the effects of five conditions to simulate the effects of fertility control on a hypothetical breeding population of 100 iteroparous mammals. We compared (1) overall fertility reduction, with (2) age-specific fertility reduction, to compare the use of contraceptives that may not have age-specific effects. We next examined (3) episodic application of age-specific fertility reduction, to simulate the periodic or intermittent application of fertility control. We refined our analysis by (4) progressively reducing age-specific fertility one offspring at a time from 6 to 2 offspring (17% increments from 0 to 68%). Lastly, we explored (5) the reduction of age-specific fertility on expanding populations, to examine the effect of fertility control on populations that are increasing in size. Such conditions are likely when pesticides or other population control measures have been applied, but because the population has evolved resistance to these measures, it has resumed its expansion.

We used a life table modelling framework (Leslie et al. 1952; Ricklefs 2006; Table 1) because we found it more transparent to our specific manipulation of age-specific fertility than the projection matrix approach (Caswell 2018). After adjusting the proportions required for estimates of survival, both methods generated identical results (Supplementary Information, Tables SI 1–3). We identified five age classes (x = 0 to 4) using population census data, $c_{(x)}$, at time t = 0 for an initial, pre-breeding population of 100 hypothetical female mammals (Table 1). We included survival probabilities, $l_{(x)}$, where $l_{(0)} = 0.5$, $l_{(1)} = 0.8$, $l_{(2)} = 0.5$ and $l_{(3,\,4)} = 0$. We next identified the distribution of surviving individuals, where the number of survivors at age x, $s_{(x)}$, equaled the product $[c_{(x-1)}\ l_{(x-1)}]$. We included age-specific fertility, $m_{(x)}$ where $m_{(0)} = 0$, $m_{(1)} = 1$, $m_{(2)} = 3$, $m_{(3)} = 2$, $m_{(4)} = 0$; ($\Sigma m_{(x)} = 6$) as well as the distribution of offspring produced, where offspring number at age x, $o_{(x)}$, equaled the product $[s_{(x)}\ m_{(x)}]$.

We entered the sum of all offspring produced in generation t = 0 for the census of individuals of age = $x_{(0)}$ at t + 1, or $\Sigma\ o_{(x)} = c_{(0)[t+1]}$, and entered the surviving individuals in generation t = 0 in generation t + 1 as $s_{(x)[t=0]} = c_{(x)[t+1]}$. We calculated the proportion of the total population in each age class, x, at generation t + 1, $P_{(x)[t=1]}$, as $c_{(x)[t+1]} / \Sigma\ c_{(x)[t+1]}$. We calculated the finite rate of increase of the population, λ, as the sum of the population census at generation t + 1 divided by the sum of the population census at time [t = 0], or $\Sigma\ c_{(x)[t+1]} / \Sigma\ c_{(x)[t-1]}$. We calculated the intrinsic rate of increase of the population as ln(λ) = r (Table 1).

Manipulating age-specific fertility

Control

We began our preliminary analysis with a control simulation that allowed the conditions described above to proceed for 12 reproductive events (generations).

Age-specific fertility reduction 1

We reduced female lifetime fertility by half (from 6 to 3 progeny) and imposed this condition at early (x = 1), middle (x = 2) and late (x = 3) ages within female lifetimes, such that the numbers of offspring produced by surviving females at age(x) = 1, 2, and 3, were [0,1,2]; [1,0,2]; [1,2,0], respectively. We assumed that fertility treatment could be precisely manipulated to have these age-specific effects, acting only on females of the prescribed age and not persisting within females that survived beyond that age. Contraceptives produce similar age-specific effects in laboratory trials, although the duration of infertility among individual females varies more than we assume here (Mayer et al. 2002; 2004; Dyer and Mayer 2014; Dyer et al. 2013; Siers et al. 2017).

Episodic fertility reduction

To explore the effect of episodic reduction in fertility, we imposed the conditions described above (a) during generation 1, and (b) during generations 1 and 2.

Table 1 Life table for a hypothetical iteroparous mammal with an initial population size of 100 females

Age (x)	Census (t = 0)	Survival $l_{(x)}$	Survivors $s_{(x)}$	Fertility $m_{(x)}$	Offspring $o_{(x)}$	Census (t + 1)	%
0	20	0.5		0	0	74	0.66
1	10	0.8	10	1	10	10	0.09
2	40	0.5	8	3	24	8	0.07
3	30	0	20	2	40	20	0.18
4	0	0	0	0	0	0	0.00
Totals	100		38		74	112	1
						λ =	1.12
						r =	0.11

Female age class (= x); female survival = $l_{(x)}$; number of female survivors in each class = $s_{(x)}$, age-specific female fertility = $m_{(x)}$, number of female offspring = $o_{(x)}$; % of female census at t + 1; finite rate of increase = λ; intrinsic rate of increase = r = ln(λ); projection matrix for this table on SI Table 1, Supplementary Information

Age-specific fertility reduction 2

To explore the combined effects of age-specific reproduction and progressive fertility reduction, we began with an initial lifetime fertility of 6 offspring per female, adjusted so that no reproduction occurred at early, middle and late ages (Early: 0,0,6; Mid-life: 3,0,3; Late: 6,0,0). We then progressively reduced female fertility within the remaining reproductive ages from 6 to 2 offspring. We emphasize that the goal of this approach was to explore the combined effects of age-specific fertility as well as fertility reduction on population growth. We accomplished this by beginning each treatment with identical fertility ($\Sigma m_{(x)} = 6$ progeny) and then reducing fertility stepwise. Although the approach of collapsing lifetime fertility into particular ages is clearly artificial (e.g., Early: 0,0,6; Mid-life: 3,0,3; Late: 6,0,0), this scheme allowed us to isolate the relative influences of age-specific fertility and fertility reduction on the rate of population growth. To demonstrate that this approach did not generate spurious results, we compared the results of these starting conditions to the control described above. We predicted that collapsing lifetime fertility into early, middle and late ages as described above would decrease, match and increase population growth rates relative to this control.

Expanding populations

We applied the above scheme to an expanding population, i.e., a population under the same conditions as the control population and allowed it to grow for 12 generations (with λ, and r [= log(λ)] equaling 1.49, 0.4 respectively as in Table 1. We then imposed the age-specific fertility reduction scheme described above.

Application to rats

We next generated a life table for brown rats, *Rattus norvegicus*, using published data from Leslie et al. (1952) to generate a stable age distribution for females, using the authors' original schedules of age-specific fertility and survival, and a gross reproductive rate (GRR) of 31.2 offspring per female lifetime (Table 2; SI Table 2). We note that following Leslie et al. (1952), to account for juvenile mortality, our first time-step included 90 days, whereas successive time steps included 60 days each. Although these intervals differed in duration, no reproduction occurred within the first interval, making the effect of this difference equivalent across each of our simulations. We test the validity of this assumption below.

Control

We generated a control simulation using these classic data (Leslie et al. 1952) and allowed this hypothetical population to grow for 12 generations, as described in the preliminary simulations above.

Model hypothesis 1

We tested this hypothesis, that fertility reduction early in life is most effective in controlling rat population growth (Leslie et al. 1952; Caswell et al. 2018) in three sets of simulations in which the fertility of female rats was reduced in early life, [ages 1 (90–149 days), 2 (150–209 days), 3 (210–269 days)], in mid-life [ages 4 (270–329 days), 5 (330–389 days), 6 (390–449 days)], and late in life [ages 7 (450–509 days), 8 (510–569 days), 9 (570–630 days)].

Table 2 Life table for brown rats (*Rattus norvegicus*) with an initial population size of 1,000 females

Age (x)	Days	Census (t = 0)	Survival $l_{(x)}$	Survivors $s_{(x)}$	Fertility $m_{(x)}$	Offspring $o_{(x)}$	Census (t + 1)	%
0	0-	751.4	0.751		0.00	0	2178	0.77
1	90-	147.0	0.196	565	3.18	1795	565	0.20
2	150-	60.2	0.410	29	5.47	157	29	0.01
3	210-	24.7	0.410	25	5.87	145	25	0.01
4	270-	10.1	0.409	10	5.40	55	10	0.00
5	330-	4.1	0.406	4	4.61	19	4	0.00
6	390-	1.6	0.390	2	3.28	5	2	0.00
7	450-	0.6	0.375	1	2.13	1	1	0.00
8	510-	0.2	0.333	0	1.04	0	0	0.00
9	570-	0.1	0.500	0	0.22	0	0	0.00
10	630-	0.0	0.000	0	0.00	0	0	0.00
Totals		1000		635	31.20	2178	2813	1.00
							λ =	2.81
							r =	1.03

The census of females at each age(x), is given in 60 day intervals (except for age 0); female age class (= x); female survival = $l_{(x)}$; number of female survivors in each class = $s_{(x)}$, age-specific female fertility = $m_{(x)}$, number of female offspring = $o_{(x)}$; % of female census at t + 1; finite rate of increase = λ,; intrinsic rate of increase = r = ln(λ); projection matrix for this table on SI Table 2, Supplementary Information

In each simulation, we reduced female lifetime fertility (GRR-31.2 pups) by 3, 6 and 9 pups (approximately 10, 20, and 30%). We reduced the number of pups in the three earliest age classes for early life reductions, and the number of pups produced in the latest age classes, for later life reductions. We reduced the fertility of the most extreme age class to zero before moving to the next age class and reduced the fraction of offspring produced in that age class until we obtained the required whole number of pups. For example, to reduce the fertility of the youngest females by 3 pups, we changed the value of $m_{(1)}$ from 3.18 to 0.18 (Table 2). To reduce female fertility by 6 pups, we changed the value of $m_{(1)}$ from 3.18 to 0.0 and reduced the value of $m_{(2)}$ from 5.47 to 2.65. To reduce the fertility of these females by 9 pups, we changed the values of $m_{(1)}$ and $m_{(2)}$ to 0.0 and reduced the value of $m_{(3)}$ from 5.87 to 5.52 (Table 2). Note that this procedure simulated the actual effects of fertility control (Mayer et al. 2002; 2004; Dyer and Mayer 2014; Dyer et al. 2013; Siers et al. 2017) and were not equivalent to sterilization (Knipling and McGuire 1972; Jacob et al. 2004, 2006a) because surviving females regained their fertility as they aged.

Model hypothesis 2

We tested this hypothesis, that early fertility reduction will be effective in controlling rat populations that are expanding, also in three sets of simulations, establishing conditions identical to those for the control population, allowing the population to expand for 12 generations, and then applying the conditions for fertility reduction described above. We included fertility reduction of 40% in this simulation to show the effects of this level of fertility control on the expanding population.

Application to voles

To investigate the generality of our approach, we next created a life table for field voles, *Microtus agrestis*, a widely distributed and often economically important pest species in Europe and northern Asia, using laboratory data from populations collected in Wales and Scotland (Leslie and Ranson 1940). As above, we used these authors' original schedules of age-specific fertility and survival, and a gross reproductive rate (GRR) of 12.67 offspring per female lifetime (Table 3). Each time step in this life table was equivalent in duration (56 days) thus this application provided an opportunity to compare the effect of the longer initial time step used above for *R. norvegicus* in these simulations. In general, field voles have shorter life spans, smaller litter sizes and more rapid generation times than brown rats.

Control

Our life table for voles (Table 3; SI Table 3) had the same general characteristics as those described above for *R. norvegicus* (Table 2). We generated a control population and allowed it to grow for 12 generations as described above.

Table 3 Life table for field voles (*Microtus agrestis*) with an initial population size of 1,000 females

Age (x)	Days	Census (t = 0)	Survival $l_{(x)}$	Survivors $s_{(x)}$	Fertility $m_{(x)}$	Offspring $o_{(x)}$	Census (t = 1)	%
0	0-	577	0.577		0.00	0	669	0.57
1	56-	255	0.442	333	0.65	217	333	0.28
2	112-	107	0.420	113	2.39	270	113	0.10
3	168-	41	0.383	45	2.97	133	45	0.04
4	224-	14	0.341	16	2.47	39	16	0.01
5	280-	5	0.357	5	1.70	8	5	0.00
6	336-	1	0.200	2	1.08	2	2	0.00
7	392-	0	0.000	0	0.67	0	0	0.00
8	448-	0	0.000	0	0.43	0	0	0.00
9	504-	0	0.000	0	0.30	0	0	0.00
10	560-	0	0.000	0	0.00	0	0	0.00
Totals		1000		513	12.67	669	1182	1.00
							λ =	1.18
							r =	0.17

The census of females at each age(x), is given in 56 day intervals; female age class (= x); female survival = $l_{(x)}$; number of female survivors in each class = $s_{(x)}$, age-specific female fertility = $m_{(x)}$, number of female offspring = $o_{(x)}$; % of female census at t + 1; finite rate of increase = λ,; intrinsic rate of increase = r = ln(λ); projection matrix for this table in SI Table 3, Supplementary Information

Model hypothesis 1

We tested this hypothesis by reducing female fertility by 10% (1.27 pups), 20% (2.53 pups) and 30% (3.8 pups) and applied these reductions to total female fertility in early life, mid-life and late life as described above.

Model hypothesis 2

We tested this hypothesis by allowing the simulated vole populations to expand for 12 generations and then applied the conditions for fertility reduction described above. As with the *R. norvegicus* simulations, we allowed the populations to expand for 12 generations, and examined fertility reduction of 40% (5.07 pups) for *M. agrestis*.

Field tests of empirical hypotheses

Our demographic model generated two empirical hypotheses predicting the outcomes of fertility control when deployed upon actual rodent populations. Empirical Hypothesis 1 states that the proportion of juvenile to adult rats will decrease from their initial values over time, as is expected if population control occurs through reduced fertility. Empirical Hypothesis 2 states that with continued application, the entire rat population will also decrease as fertility control reduces the total number of rats. We tested these predictions using a field deployment of Contrapest (CP, EPA registration #91,601–1), a proprietary fertility control product containing 4-vinylcyclohexene diepoxide (VCD) and triptolide, known to control rodent fertility under laboratory conditions (Dyer et al. 2013; Witmer et al. 2017; Siers et al. 2017). We report the results of a 12-month CP application in two locations near Washington, DC, USA (Oglethorpe Street, Reservoir Road) between November 2019 and October 2020. Prior to and during CP deployment, SGARs were used by local businesses and residents to control brown rats (*Rattus norvegicus*) in the study areas. Although we were unable to influence how these potentially confounding effects on fertility control were manifest, we considered the delivery of rodenticides to be similar before our study began and throughout its duration.

Bait stations, camera traps, and rat abundance

We placed Bell Laboratories Protecta Evo Express Bait Stations, near rat burrows or areas of conspicuous rat activity in each study location and replenished them to their 400 ml capacity with liquid CP bait each month for the study duration. Total bait consumption was recorded in both locations each month from November 2019 to April 2020 before pandemic-associated service personnel changes discontinued this record. We used a Reconyx HyperFire HC600 motion-sensitive digital camera mounted over the central station in each bait station array to record the observed the numbers of juvenile and adult rats in each location throughout the study. Each month, we recorded the total number of rat images visible on the camera within each 24 h period over four consecutive days mid-month. When the full bodies of individual rats were visible within images, we determined their approximate age by comparing their total nose to tail length (juveniles < 175 mm > adults; Calhoun 1963,

p. 266) to a scale bar visible within each image. All images for each camera were scaled to pixel number and analyzed using ImageJ.NIH.gov software. For each monthly sampling period we recorded the number of juvenile and adult rats visible, and the total number of rat images. We then calculated a generalized index (GI) of rat abundance (Engeman 2005; Lambert et al. 2017), which equaled the number of images containing more than one rat within each 24 h sampling period averaged (±95%CI) across all survey days for that site. We analyzed each study location separately because they were physically and geographically distinct (6.3 km apart), and because camera malfunction prevented image sampling for one location in March 2020.

Study locations

Oglethorpe Street: was identified within a ¼ mile long alley embedded within residential properties in northern Washington, DC. Little trash was available, but human residents provided food for feral cats. Rat burrows were common. We deployed seven bait stations in November 2019. Camera data were collected from a single camera mounted over the middle bait station during four, 24 h sampling nights per week from November 2019 through October 2020.

Reservoir Road: was identified within a ½ mile long easement with nearby commercial and residential districts in eastern Washington, DC. Trash and food refuse were abundant. We deployed three bait stations in November 2019. Camera data were collected from a single camera mounted over the middle bait station during four, 24 h sampling nights per week from November 2019 through October 2020. A camera malfunction prevented sample collection during March 2020.

Tests of empirical hypotheses

Empirical Hypothesis 1: We compared the numbers of adult and juvenile rats observed in monthly camera samples in the first six months and in the last six months of the study using two analyses. First, for each location, we used a general linear mixed model (GLMM) to examine the proportion of juvenile rats detected in daily camera samples in each study location over the study duration. The null hypothesis predicted no change in proportion of juvenile rats, in each location, over the 12-month study. In each analysis we identified Month as main effect and accounted for variation in recording days by considering Camera Day as a random effect. Because the data consisted of proportions, we fitted our data to a Binomial distribution with a Logit-link function.

Secondly, we used a 2×2 G-test to test the null hypothesis of no expected deviations in the total number of rats across the sample intervals or in the proportions of adult and juvenile rats within each sample interval. For each location, we first tested the overall significance of this 2×2 comparison and then examined the interaction between life stage and sampling interval by comparing cells A + D vs B + C using a k = 2 G-test.

Empirical Hypothesis 2: For each location, we used a general linear mixed model (GLMM) to examine the total number of rat images recorded in each day of each monthly sample across the entire 12-month study. The null hypothesis predicted no change in total rat numbers over the duration of the study in each location. In each analysis, we identified Month as the main effect and accounted for variation in recording days by considering Camera Day as a random effect. Because the data consisted of counts, we fitted our data to a Poisson distribution with a Log-link function. We plotted the value of the generalized index (GI; Engeman 2005; Lambert et al. 2017) with 95%CI over the duration of the study for each location.

Results

Preliminary simulations

Control

Our control simulation of population growth in a hypothetical iteroparous mammal stabilized within six generations (Gen06), with a finite rate of increase, λ, and intrinsic rate of increase, r [= log(λ)] of 1.49, 0.4 respectively. The population size increased from the initial 100 females to 6,911 females by Gen12 (Fig. 1a).

Age-specific fertility reduction 1

Compared to the control, fertility reduction imposed early in female lifetimes sharply decreased the rate of population growth (λ = 0.92; r = −0.08). Fertility reduction imposed in the middle of female lifetimes also decreased the rate of population growth but to a smaller degree (λ = 0.94; r = −0.06). Each of these conditions led to decreases in population size (N) by Gen12 (Early: $N = 26$; Mid-life: $N = 42$; Fig. 1a). Fertility reduction imposed late in female lifetimes slowed but still allowed population growth ((λ = 1.18; r = 0.16; $N = 281$; $N_{control} = 6{,}911$; Fig. 1a).

Episodic fertility reduction

Compared to the control (λ = 1.49, r = 0.4, $N = 6{,}911$) fertility reduction imposed in Gen01 (Fig. 1b) and in Gen01 and Gen02 (Fig. 1c) reduced the rate of population growth for all fertility reduction treatments (Early, Mid-life; Late). The effects of two successive generations of reduced fertility

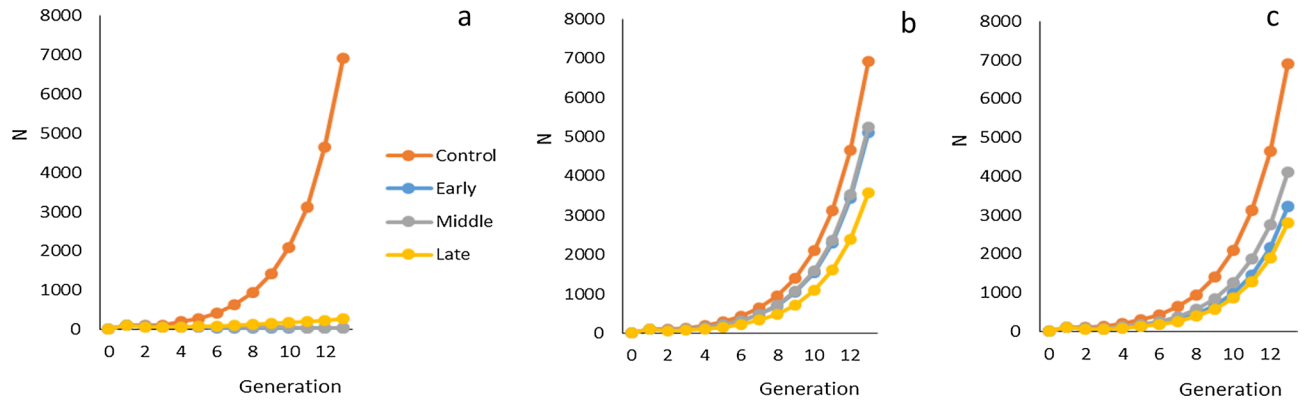

Fig. 1 The effect of age-specific fertility reduction (6–3 offspring) and the effect of episodic fertility reduction (1–2 generations) on the growth of four hypothetical iteroparous mammal populations. Sustained fertility reduction was more effective in delaying the return to exponential growth than episodic fertility reduction. **a** Sustained fertility reduction, with age-specific fertility reduction imposed in all 12 generations; **b** Fertility reduced once in Gen01 of 12 generations; **c** Fertility reduced twice in Gen01 and Gen02 in 12 generations; Control (no reduction, orange line); Early life fertility reduction (age-specific fertility = [0,1,2] blue line); Mid-life fertility reduction (age-specific fertility = [1,0,2], grey line); Late life fertility reduction (age-specific fertility = [1,2,0], gold line)

were more pronounced than with one, although in each of these simulations, fertility reduction only delayed a return to exponential growth, which matched that of the control by Gen12 ($\lambda = 1.49$, $r = 0.4$; Fig. 1b–c).

Sustained, age-dependent fertility reduction had clear and ordered effects on total population size. Early reduction had the greatest effect and late reduction had the smallest effect by Gen12 [Early ($N = 26$) > Mid-life ($N = 42$) > Late ($N = 281$), Fig. 1a]. Episodic fertility reduction changed this order. With fertility reduction in Gen01, the order of age-dependent effects on population size by Gen12 was Late ($N = 3564$) > Early ($N = 5{,}098$) > Mid-life ($N = 5237$; Fig. 1b). With fertility reduction in Gens01 and 02, the order of age-dependent effects on population size by Gen12 also was Late ($N = 2814$) > Early ($N = 3223$) > Mid-life ($N = 4113$; Fig. 1c) but the reduction in the fertility of Early to Mid-life females was proportionately greater (0.97 vs 0.78; Fig. 1b, c).

Age-specific fertility reduction 2

The combined effects of age-specific reproduction with progressive reduction in fertility showed that fertility reduction focused early in life [0,0,6], with remaining female lifetime fertility (LF) reduced from 6 to 2 offspring ($LF_{6-} > LF_2$), led to decreased population size (N) by Gen12 for all lifetime fertilities of five and fewer offspring ($LF_{control}$; $N = 6{,}911$;

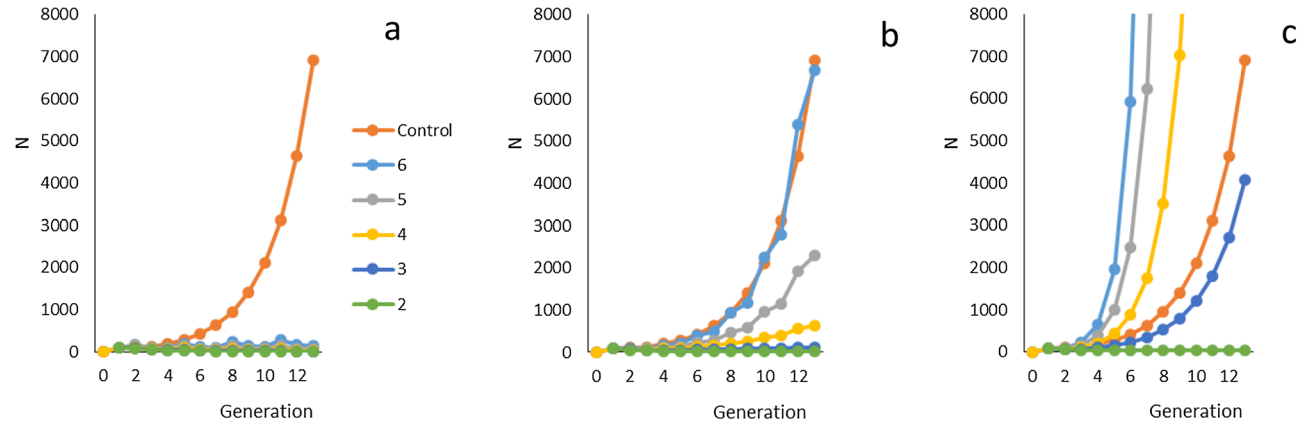

Fig. 2 The effect of age-specific fertility reduction (6 to 2 offspring) on the growth of six hypothetical iteroparous mammal populations. Fertility reduction was more effective when female fertility was reduced early in life than when female fertility was reduced in the middle or late in female lifetimes; reduction in female fertility was focused at **a** Early, **b** Middle and **c** Late ages; Control: no reduction, orange; offspring number: light blue: 6; grey, 5; gold 4; dark blue 3; green 2)

LF_6: $N=152$; LF_5: $N=74$; LF_4: $N=31$; LF_3: $N=10$; LF_2: $N=2$; Fig. 2a).

Fertility reduction focused in mid-life [3,0,3], with simultaneous reduction of remaining female fertility early and late within female lifetimes reduced from 6 to 2 offspring, decreased population size only for female lifetime fertilities of two offspring ($LF_{control}$; $N=6{,}911$; LF_6: $N=6{,}911$; LF_5: $N=2{,}304$; LF_4: $N=629$; LF_3: $N=119$; LF_2: $N=12$; Fig. 2b). All other simulated populations continued to grow but at slower rates than the control.

Fertility reduction focused in late life [6,0,0], with remaining female fertility decreased from 6 to 2 offspring also reduced population size only for female lifetime fertilities of two offspring, but also allowed expansion of population size beyond that of the control for female fertilities greater than three offspring (LF_6: $N=1.2\times10^7$; LF_5: $N=1.52\times10^6$; LF_4: $N=1.1\times10^5$; LF_3: $N=4{,}075$; LF_2: $N=42$; Fig. 2c). As we predicted, for the starting conditions for these simulations (Early: 0,0,6; Mid-life: 3,0,3; Late: 6,0,0) fertility reduction at early, middle and late ages decreased, matched and increased population growth rates relative to the control (Fig. 2a–c).

Expanding populations

When fertility reduction was focused early in life [0,0,6] on an expanding population, with lifetime fertility progressively reduced as described above, population growth was affected at all female fertilities (six to two progeny; Fig. 3a). Lifetime fertility of six progeny initially slowed but did not arrest population growth by Gen24 ($LF_{control}$: $N=1.21\times0^7$; LF_6: $N=1.2\times10^5$); LF_5 returned sustained but oscillating population sizes between 5 and 7×10^4 (LF_5: $N=5.6\times10^4$); LF_{4-2} caused progressive decreases in the rate of population growth by Gen24 (LF_4: $N=2.2\times10^4$; LF_3: $N=6{,}417$; LF_2: $N=1{,}166$; Fig. 3a).

When age-specific fertility reduction was focused in mid-life [3,0,3] on an expanding population, with female lifetime fertility (LF) progressively reduced as described above, population growth had accelerated by Gen24 with female lifetime fertility of six progeny ($LF_{control}$: $N=1.21\times0^7$; LF_6: $N=2.1\times10^7$). While population growth was slowed by fertilities of five to three progeny (LF_5: $N=6.1\times10^6$; LF_4: $N=1.5\times10^6$; LF_3: $N=2.3\times10^5$), again only a lifetime fertility of two progeny had a lasting effect on population growth, in this case arresting growth by Gen14 and causing a progressive decrease in population size to 2×10^4 by Gen24 (Fig. 3b).

When age-specific fertility reduction was focused late in life [6,0,0] on an expanding population, with female lifetime fertility progressively reduced as described above, population growth was arrested only at maximum reduction in female fertility (LF_2). In this simulation population growth ceased by Gen14, with a maximum population size of at 9×10^4, which was maintained through Gen24 (Fig. 3c). All other lifetime fertilities accelerated the rate of population growth beyond that of the control ($LF_{control}$: $N=1.21\times0^7$; LF_5: $N=8.3\times10^9$; LF_4: $N=4.9\times10^8$; LF_3: $N=1.3\times10^7$; Fig. 3c).

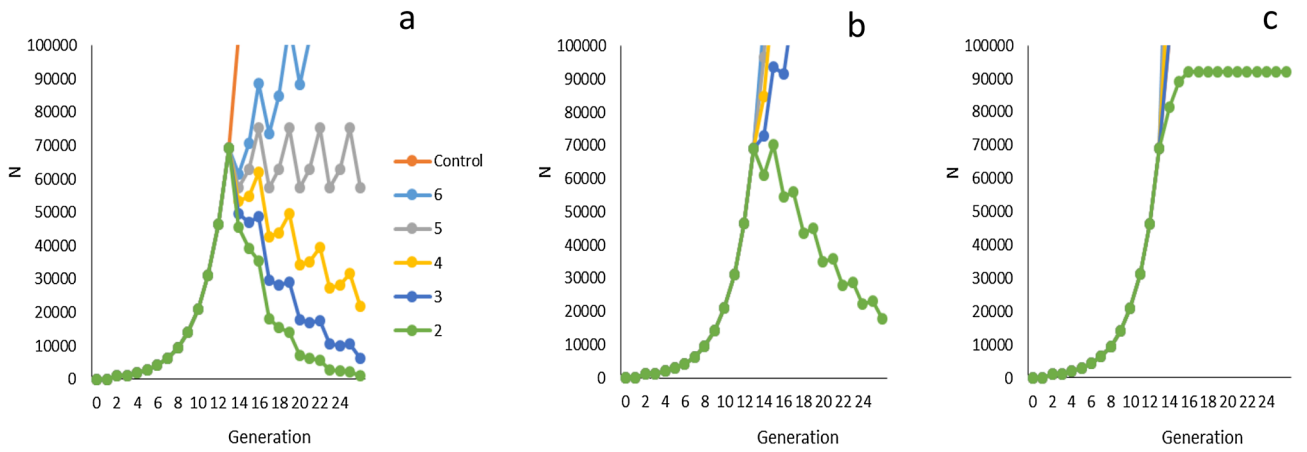

Fig. 3 The effect of age-specific fertility reduction (6 to 2 offspring) on the growth of six hypothetical iteroparous mammal populations that began with an initial size of 100 females and were allowed to expand for 12 generations. Fertility reduction early in life allowed population control; only extreme fertility reduction was effective when female fertility was reduced in middle and late female lifetimes; reduction in female fertility was focused at **a** Early, **b** Middle and **c** Late ages; Control: no reduction, orange; offspring number: light blue: 6; grey 5; gold 4; dark blue 3; green 2; the Y-axis was truncated at $N=10^4$ because lines extending above this value eventually resumed exponential growth

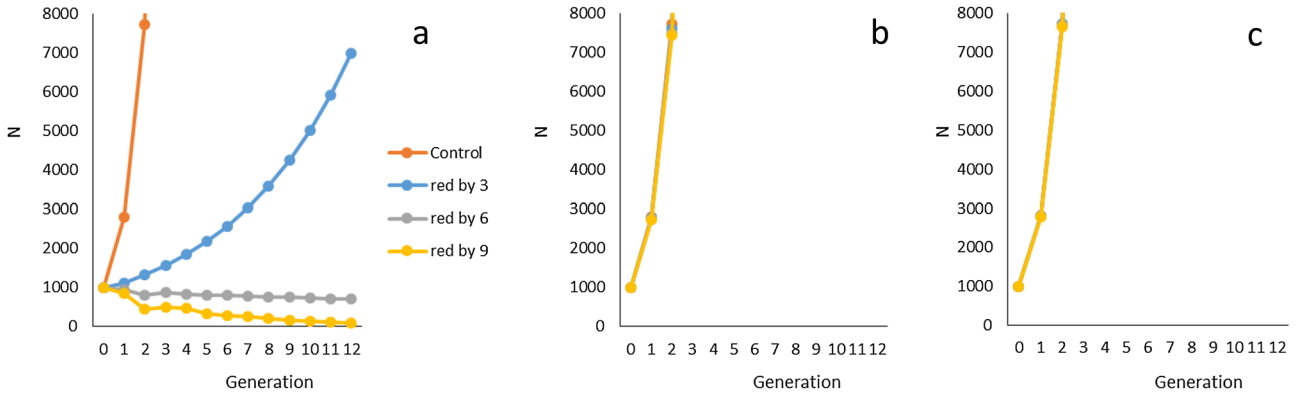

Fig. 4 The effect of age-specific fertility reduction on population size in brown rats (*Rattus norvegicus*) with an initial population size of 1,000 females;[1] **a** Fertility reduction imposed early in life delayed or reversed population growth, with observed effects corresponding to increasingly severe fertility reduction; fertility reduction imposed in **b** Middle-life and **c** Late in female lifetimes had no apparent effect on rat population growth; N progeny reduction: 3, blue; 6, grey; 9, gold; Control, orange; the Y-axis was truncated at $N = 8$ K because lines extending above this value had assumed exponential growth and became indistinguishable

Application to rats

Control

Our control simulation using *R. norvegicus* data (Table 2; SI Table 2) stabilized by Gen05 with a finite reproductive rate, $\lambda = 2.74$, and intrinsic rate of increase, r [$= \log(\lambda) = 1.01$]. By Gen12, the population size increased from the initial 1,000 to 1.8×10^8 females (Fig. 4a).

Model hypothesis 1

Fertility reduction imposed early in life (ages 1–3) either delayed exponential growth to Gen12 [$LF_{control}$; $N = 1.83 \times 10^8$; $LF_{28.2}$ (= reduction by three progeny ≈ 10%); $N = 6{,}998$ at Gen12; Fig. 4a] or reversed its trajectory entirely. Increasingly severe fertility reduction had corresponding effects on total population size [reduction by six progeny (≈20%); $N = 555$ at Gen12; reduction by nine progeny (≈30%); $N = 89$ at Gen12; Fig. 4a).

In contrast, fertility reduction imposed in mid-life (ages 4–6; Fig. 4b) and late in life (ages 7–9; Fig. 4c) had little

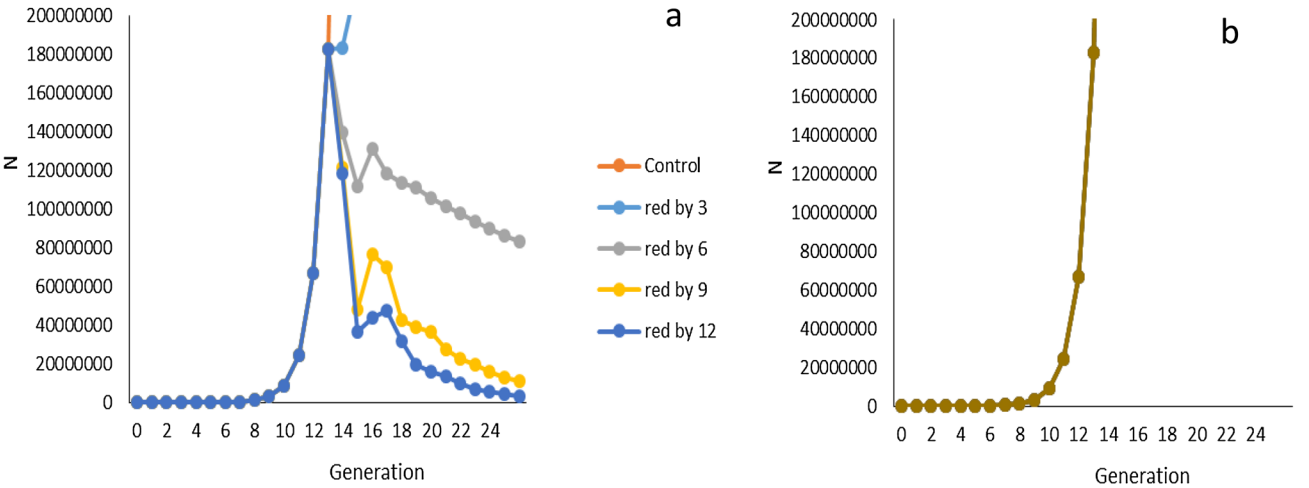

Fig. 5 The effect of age-specific fertility reduction on population size in brown rats (*Rattus norvegicus*) with an initial population size of 1,000 females that was allowed to expand for 12 generations. Fertility reduction imposed early in life **a** was most effective in controlling rat population growth; **b** fertility reduction imposed in mid-life and late in female lifetimes had no apparent effect on rat population growth; N progeny reduction 3, blue; 6, grey; 9, gold; 12, dark blue; Control, orange; the Y-axis was truncated at $N = 2 \times 10^8$ because lines extending above this value resumed exponential growth

effect on rat population growth, with growth trajectories nearly indistinguishable from those observed in the control simulation by Gen12 (Mid-life reduction: $LF_{control}$; $N = 1.83 \times 10^8$; $LF_{28.2}$; $N = 1.78 \times 10^8$; $LF_{25.2}$; $N = 1.74 \times 10^8$; $LF_{22.2}$; $N = 1.72 \times 10^8$; Late-life reduction: $LF_{28.2}$; $N = 1.83 \times 10^8$; $LF_{25.2}$; $N = 1.82 \times 10^8$; $LF_{22.2}$; $N = 1.81 \times 10^8$).

Model hypothesis 2

Age-specific fertility reduction imposed early in life (ages 1–3) with fertility reduced by three progeny (≈10%) decreased the trajectory of exponential growth in the expanding population, but did not prevent the population from resuming this rate of expansion within the next two generations (Fig. 5a). With this level of fertility reduction, the population size was reduced by 10^4 by Gen24 (64 K-fold; $LF_{28.2}$; $N = 1.38 \times 10^9$) compared to the control ($LF_{control}$; $N = 8.87 \times 10^{13}$), although the population continued to grow. However, increasingly severe fertility reduction returned corresponding reductions in population growth. Specifically, reduction of lifetime fertility by six pups (≈20%) reduced the population size by 10^6 by Gen24 (1.1 M-fold; $LF_{25.2}$; $N = 8.30 \times 10^7$). Fertility reduction by nine pups (≈30%) reduced the population size by 10^6 (8.1 M-fold; $LF_{22.2}$; $N = 1.11 \times 10^7$), and reduction by 12 pups (≈40%) reduced the population size still further (28.1 M-fold; $LF_{19.2}$; $N = 3.15 \times 10^6$; Fig. 5a).

In contrast, fertility reduction imposed in mid-life (ages 4–6), and late in life (ages 7–9) on an expanding brown rat population, had little apparent effect on population growth, again with growth trajectories nearly indistinguishable from those observed in the control simulation (Mid-life reduction: $LF_{control}$; $N = 8.87 \times 10^{13}$; $LF_{28.2}$; $N = 8.61 \times 10^{13}$; $LF_{25.2}$; $N = 8.64 \times 10^{13}$; $LF_{22.2}$; $N = 8.62 \times 10^{13}$; $LF_{19.2}$; $N = 8.61 \times 10^{13}$; Late-life reduction: $LF_{28.2}$; $N = 8.87 \times 10^{13}$; $LF_{25.2}$; $N = 8.87 \times 10^{13}$; $LF_{22.2}$; $N = 8.85 \times 10^{13}$; $LF_{19.2}$; $N = 8.81 \times 10^{13}$; Fig. 5b).

Application to voles

Control

Our control simulation using *M. agrestis* data (Leslie and Ranson 1940; Table 3; SI Table 3) produced an expanding population that stabilized by Gen02 with a finite reproductive rate, λ = 1.19, and intrinsic rate of increase, r[= log(λ) = 0.17], with population size increasing from the initial 1,000 females to 7,894 by Gen12 (Fig. 6a).

Model hypothesis 1

Fertility reduction imposed early in life (ages 1–3) at all levels of reduction caused the vole populations to decline. A reduction of 10% (1.27 progeny) reduced the initial population size of 1,000 to 624 by Gen12; reductions of 20% (2.53 progeny) and 30% (3.80 progeny) reduced population sizes to 117 and 31 females respectively (Fig. 6a). Fertility reduction imposed in mid-life (ages 4–5; Fig. 6b) slowed population growth, with greater reductions in fertility having larger effects. However, all simulated populations had resumed positive trajectories by Gen12. ($LF_{control=12.67}$; $N = 7{,}894$; $LF_{11.40}$; $N = 6{,}804$; $LF_{10.14}$; $N = 5{,}672$; $LF_{8,87}$; $N = 5{,}369$; Fig. 6b). Fertility reduction imposed in late life (ages 5–9; Fig. 6c) had little effect on vole population growth, with growth trajectories nearly indistinguishable from the control simulation by Gen12 (Late-life reduction: $LF_{control}$; $N = 7{,}894$; $LF_{11.40}$; $N = 7{,}886$; $LF_{10.14}$; $N = 7{,}773$; $LF_{8.87}$; $N = 7{,}415$).

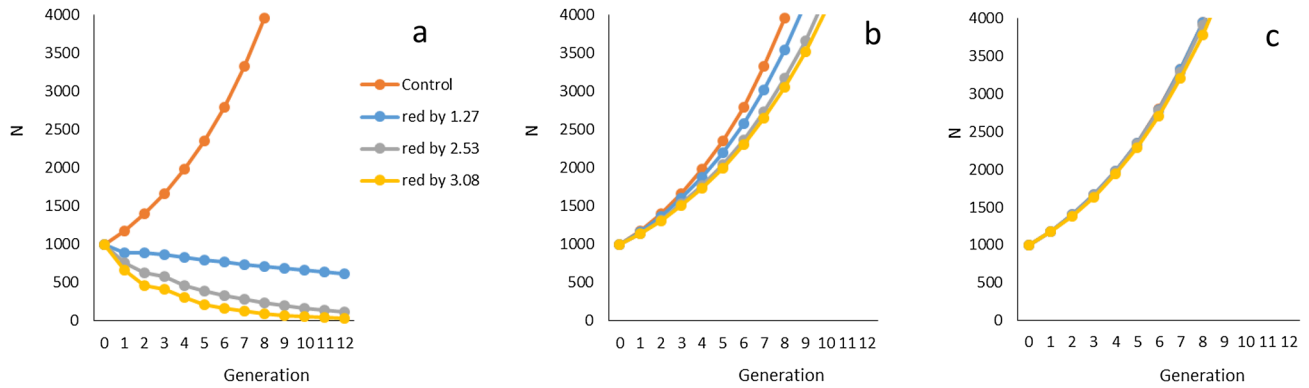

Fig. 6 The effect of age-specific fertility reduction on population size in field voles (*Microtus agrestis*) with an initial population size of 1,000 females; **a** Fertility reduction imposed early in life caused all vole populations to decline, with observed effects corresponding to increasingly severe fertility reduction; fertility reduction imposed in **b** Middle-life slowed population growth; **c** Late in female lifetimes had no apparent effect on vole population growth; N progeny reduction: 3, blue; 6, grey; 9, gold; Control, orange; the Y-axis was truncated at $N = 4$ K because lines extending above this value eventually assumed exponential growth

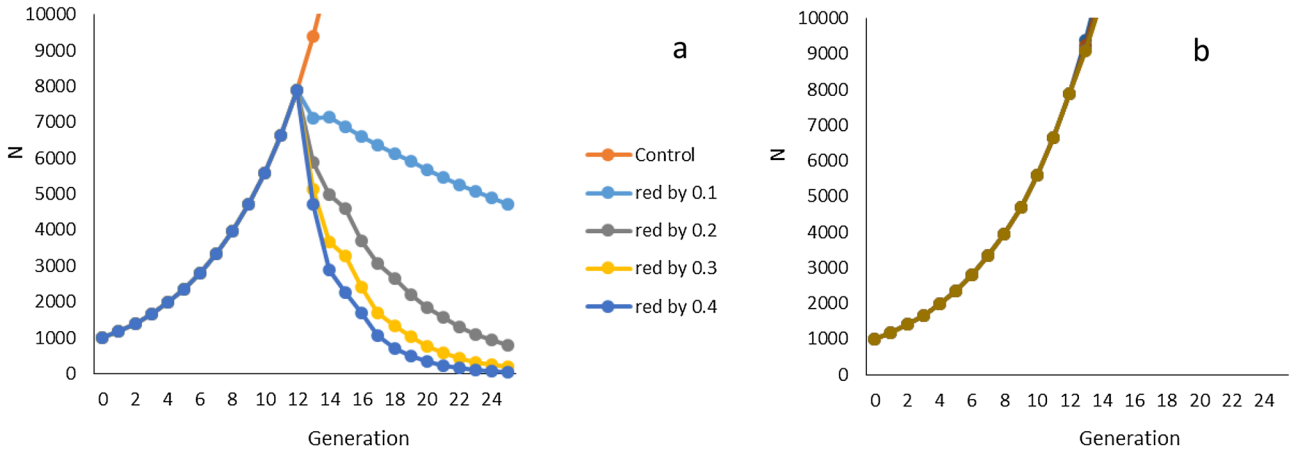

Fig. 7 The effect of age-specific fertility reduction on population size in field voles (*Microtus agrestis*) with an initial population size of 1,000 that was allowed to expand for 12 generations; **a** Fertility reduction imposed early in life reversed the trajectories of all expanding vole populations; fertility reduction imposed in **b** mid-life and late in life had little apparent effect on vole population growth; N progeny reduction 3, blue; 6, grey; 9, gold; 12, dark blue; Control, orange; the Y-axis was truncated at $N = 2 \times 10^8$ because lines extending above this value resumed exponential growth; the Y-axis was truncated at $N = 10^4$ because lines extending above this value assumed exponential growth and in b were indistinguishable

Model hypothesis 2

Fertility reduction imposed early in the lifetimes of female voles (ages 1–3), decreased the trajectories of all expanding populations (Fig. 7a). By Gen24, with litter size reduced by 10% (1.27 pups), the population had decreased in size by 15.9 fold ($LF_{11.4}$; $N = 4{,}702$) compared to the control ($LF_{control=12.67}$; $N = 74{,}640$), and continued to shrink. Increasingly severe fertility reduction returned corresponding reductions in population growth. Reduction by 20% (2.53 pups) reduced the population size by 96-fold; $LF_{10.14}$; $N = 779$). Reduction by nine pups (30%) reduced the population size by 405-fold; $LF_{8.87}$; $N = 184$). Reduction by 12 pups (40%) reduced the population size by 1,452-fold; $LF_{7.60}$; $N = 51$; Fig. 7a).

In contrast, fertility reduction imposed in mid-life (ages 4–6) and late in life (ages 7–9) on an expanding field vole population had little effect, with growth trajectories only slightly diminished with mid-life reduction ($LF_{control=12.67}$; $N = 74{,}640$; $LF_{11.40}$; $N = 62{,}699$; $LF_{10.14}$; $N = 52{,}377$; $LF_{8.87}$; $N = 49{,}434$; Fig. 7b), and nearly indistinguishable from those observed in the control simulation with late-life reduction ($LF_{control=12.67}$; $N = 74{,}640$; $LF_{11.40}$; $N = 74{,}563$; $LF_{10.14}$; $N = 73{,}493$; $LF_{8.87}$; $N = 69{,}937$; Fig. 7b).

Field tests of model predictions

Empirical hypothesis 1

Our GLMM test to identify significant changes in the proportion of juvenile rats in camera samples for Reservoir Road was significant overall with a significant effect of

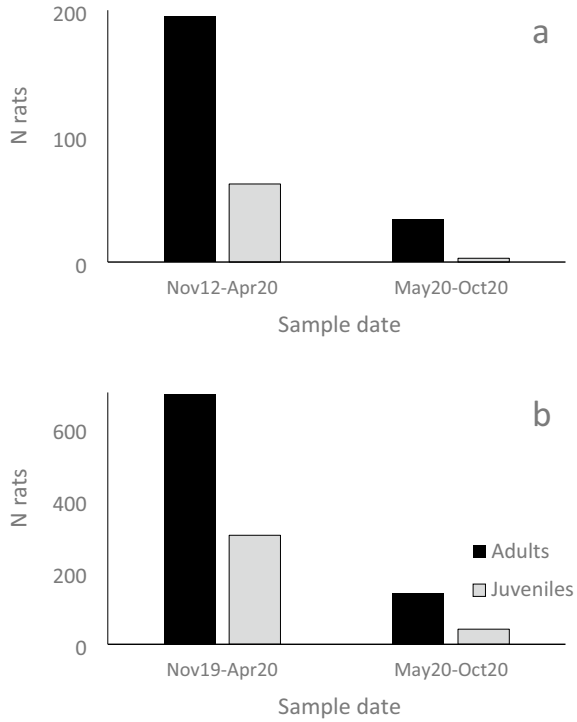

Fig. 8 Test of Empirical Hypothesis 1: The fraction of juveniles comprising the urban rat population will decrease over time when fertility control is deployed; **a** Oglethorpe Street, overall G = 14.3, df = 1, $P < 0.001$; life stage x study interval interaction, G = 19.4, df = 1, P<0.001, $N = 303$; **b** Reservoir Road, overall G = 4.6 df = 1, $P < 0.05$, life stage x study interval interaction, G = 72.3, df = 1, $P < 0.0001$, $N = 1{,}183$; black bars = Adults; grey bars = Juveniles

Month ($F_{9,4.00} = 37.5$, $P < 0.0001$, LogWorth Month 13.18, $P < 0.00001$; SI Table 4), indicating that the proportion of juveniles changed significantly over the study duration, although Camera Day expressed as a random effect within the model explained nearly all of the variation in the proportion of juveniles in camera samples, indicating that the proportion of juveniles was highly variable within as well as among sample months. A similar GLMM analysis for Oglethorpe Street showed no significant effect of Month (F11,3.57 = 0.78, $P = 0.66$; SI Table 5). In this analysis, Camera Day explained none of the variation. However, in both locations, consistent with Empirical Hypothesis 1, many of the camera samples in later months of the survey recorded no juveniles at all, and in most of these samples, no adults were recorded either (Fig. 9a 8).

Consistent with Empirical Hypothesis 1, 2 × 2 G-tests, in both locations, showed that the numbers of juvenile and adult rats deviated significantly from that expected by chance (Oglethorpe Street: G = 14.3, df = 1, $P < 0.001$, $N = 303$; Reservoir Road: G = 4.6, df = 1, $P < 0.05$, $N = 1{,}183$). In both locations, the numbers of adults and juveniles decreased over the 12-month duration of the study, but also in both locations, the proportional decrease in juvenile numbers was greater than that observed in adults (life stage x study interval interaction, Oglethorpe Street, G = 19.4, df = 1, $P < 0.001$, $N = 303$; Reservoir Road, G = 72.3, df = 1, $P < 0.0001$, $N = 1{,}183$, Fig. 8a, b).

Empirical hypothesis 2

Our GLMM tests to identify significant changes in the total number of rats identified in camera samples were significant overall with a significant effect of Month (Oglethorpe Street: $F_{11,\ 770} = 19.5$, $P < 0.001$, LogWorth Month = 8.97, $P < 0.00001$; Reservoir Road: $F_{10,3352.9} = 38.5$, $P < 0.001$; LogWorth Month = 10.8, $P < 0.00001$; SI Tables 6–7) indicating that rat abundance in both locations decreased significantly over the study duration. For Oglethorpe Street, Camera Day expressed as a random effect within the model explained only 9.7% of the total variation in the data. However, for Reservoir Road, Camera Day explained nearly 100% of the variation, indicating that rat numbers were highly variable within as well among sample months. This result is consistent with our plot of the generalized index of rat abundance (GI, Engeman 2005; Lambert et al. 2017) which, while showing consistent decrease in rat number in both locations over the study duration, showed Reservoir Road samples to considerably more variable than those from Oglethorpe Street (Fig. 9a). Due to the incomplete record of bait consumption (November 2019–April 2020), we did not attempt to correlate decreases in rat population size with consumption of contraceptive bait. Bait consumption is not a reliable indicator of rat population size because rats whose fertility is impacted by contraceptive treatment continue to consume bait. Rats vary in their responsiveness to novel foods and devices within and among populations and can remain bait-shy for up to a month before establishing regular consumption patterns (Witmer and Raymond-Whish 2021). Consistent with this observation, bait consumption increased differentially between locations within the first six months of the study (Fig. 9b).

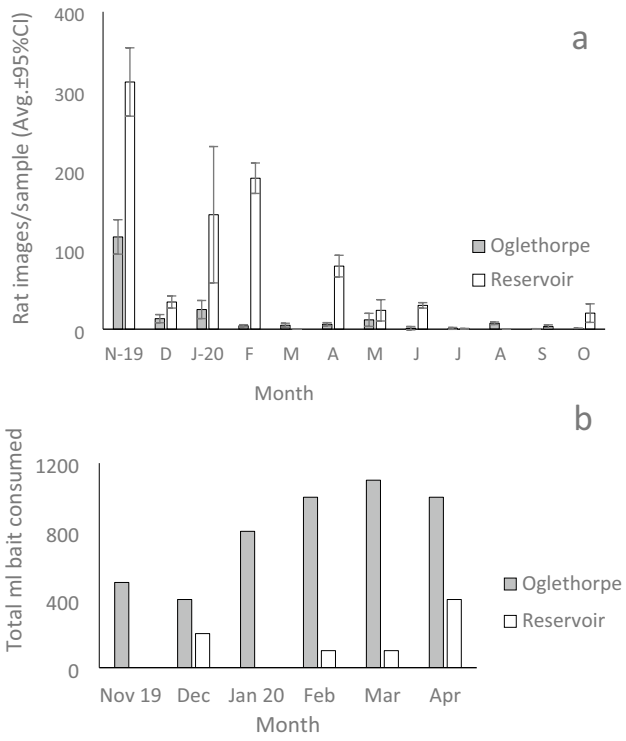

Fig. 9 Test of Empirical Hypothesis 2: Urban rat populations that appear nonresponsive to rodenticides will decrease in size over time when fertility control is deployed; **a** total rat images recorded in both locations in camera samples decreased significantly over the 12-month study; Oglethorpe Street: $F_{11,\ 770} = 19.5$, $P < 0.001$, LogWorth Month = 8.97, $P < 0.0000$; Reservoir Road: $F_{10,\ 3352.9} = 38.5$, $P < 0.001$; LogWorth Month = 10.8, $P < 0.0000$; **b** consumption of contraceptive bait appeared to increase in both location over the first six months of the study; grey bars = Oglethorpe; white bars = Reservoir, error bars = 95%CI

Discussion

Preliminary simulations

Our preliminary results were consistent with other demographic research suggesting that population growth can be influenced either by changing the age of first reproduction or by reducing fertility overall (Caswell 2018; Caswell et al.

2018). We found that when lifetime fertility was collapsed into one age class (or two age classes for mid-life fertility reduction), compared to our control, fertility reduction imposed early, in mid-life, and later in female lifetimes decreased, matched and accelerated, respectively, the rate of approach by the population to exponential growth. Thus, fertility control applied early in life could be most effective in controlling population growth in iteroparous mammalian species and substantiated exploration of our specific hypotheses with actual rodent data.

Fertility reduction was only effective in reducing population size when sustained over multiple generations (12 in our simulations). Episodic reduction was not effective when imposed within the first two episodes of reproduction. These results suggest that the strongest effects of contraceptives on rodent population growth are likely to be observed when treatment is applied continuously (see below). Our preliminary simulations indicated further that delaying the age of first reproduction led to a more rapid and sustained reduction in population growth than overall fertility reduction. When these two conditions were applied in combination, even expanding populations slowed or reversed their growth.

Application to rats and voles

Our results using population parameters for natural populations of brown rats and field voles substantiated our preliminary results, confirming that fertility reduction applied early in female lifetimes was effective in controlling population growth. Moreover, early fertility reduction was also effective in controlling rodent populations that were expanding. This result stands in contrast to other studies, which considered this outcome unlikely (Hone 1992; 2004; Stenseth et al. 2001; Jacob et al. 2004, 2006a; Massawe et al. 2018), although these latter analyses did not target their treatment to specific female age classes, or sterilized females rather than reducing their fertility. Our analysis suggests that attention to the age of individuals whose fertility is reduced, as well as sustained treatment over sufficient time to affect the fertility of young females, could influence the success of fertility reduction programs. We considered it beyond the scope of this study to recommend specific schedules of fertility control for natural populations but plan to address these questions elsewhere. We note that our rat and vole simulations produced similar results, indicating that the initial time step of 90 days in our rat life table did not affect our simulation results.

We did not specifically examine the effects of stage-specific variation in fertility within age classes in this study (Caswell 2018). Neither did we consider the specific effects of seasonal reproduction on our results, although we note that the successes of previous studies were variable depending on available food resources (Leslie et al. 1952; Shi et al. 2002). We also did not specifically explore the effects of density-dependent processes that could influence the rate of population growth. Although density-dependent influences on rodent population growth are presumed to be ubiquitous, Wolff (2003) argued instead that social and behavioral influences on rodent population density regulation will be small or negligible relative to food availability. Consistent with this hypothesis, Davis et al. (2003) showed that in house mice, the observed rate of population increase during the usual period of the seasonal increase was independent of density and reported no evidence of compensation to fertility control when it was applied during the seasonal increase phase. Jacob et al. (2006b) also found no evidence of reproductive compensation in rice field rats when over 75% of the female population was sterilized, although the scale of these experiments was small. Clearly, more study is needed to explore the effects of density on fertility reduction in rodent pest species. For the conditions we explored, we expect the negative influences of density on rodent population size to mainly *reduce* the rates at which rat and vole populations might increase.

Field tests of model predictions

Fertility reduction on two urban populations of brown rats in Washington, DC, USA using contraceptive bait confirmed our model and our empirical predictions. In both locations, (a) the proportional decrease in juvenile rats was greater than that for adult rats over the study duration, and (b) overall, rat populations decreased to negligible levels within one year of treatment (approximately six generations). Although these urban rat populations had a considerable history of conventional second-generation anticoagulant rodenticide experience, the success of SGAR treatment appears to have been limited, even before contraceptive treatment began. This result is consistent with our model hypotheses that fertility reduction imposed early in female lifetimes is effective on rodenticide-resistant rat populations. The more rapid and less variable response of the Oglethorpe Street population to contraceptive treatment compared to that of Reservoir Road is likely due to the larger number of bait stations (7 vs 3) deployed per unit area (1/4 vs 1/2 mile) in each location.

Implications for known contraceptives

Our results have implications for the use of known contraceptives for rodent population control. Previous research has shown that fertility reduction using contraceptive chemicals such as 4-vinylcyclohexene diepoxide (VCD) and triptolide reduce rodent fertility by delaying the age of first reproduction (Dyer and Mayer 2013; Dyer et al. 2014; Siers et al. 2017). Dose-dependent reduction of litter number and size using this treatment allow remarkably precise manipulation

of total fertility (Mayer et al. 2002, 2004; Dyer et al. 2013). These characteristics differ from contraceptive treatments that lack age-specific effects (Norbury 2000; Jacob et al. 2004, 2006a; Kirkpatrick 2007). Control of age-specific fertility may also allow greater precision in pest population management (Shi et al. 2002).

Implications for evolved resistance to treatment

In addition to their potential for controlling population growth, contraceptives have been shown to reduce the opportunity for selection favoring the evolution of resistance to treatment (Shuster et al. 2018). As is widely known, rodenticides can severely reduce pest population size, but seldom extirpate all individuals. Most survivors bear traits conferring resistance to further treatment. When such populations rebound, genes underlying resistance become established at high population frequency, i.e., resistance to treatment evolves. The evolution of resistance to sterilants is identical to that of rodenticides because only non-responsive individuals contribute to future generations.

4.6. Contraceptives also reduce pest population size, but unlike rodenticides and sterilants, they do not eliminate individual fertility. Because variation in fitness among females remains small, selection favoring resistance to treatment remains weak (Shuster et al. 2018). After treatment, genetic factors conferring resistance to contraceptives remain embedded within a smaller but still genetically variable pest population (Bila et al. 1999). Thus, because the population frequency of alleles responsible for non-responsiveness is low even after contraceptive treatment, the fixation probability of these "favored" alleles also remains small (Haldane 1927; Wright 1942; Kimura 1955, 1962; Wade and Shuster 2010). Moreover, the probability that alleles conferring resistance to contraceptive treatment will be lost from the population by genetic drift equals 1–(1/2N), where N equals the pest population size (Wright 1942). Thus, even when fertility-controlled populations become small (e.g., $N = 10$), the likelihood that genetic drift will remove alleles conferring resistance to contraceptives from the population remains surprisingly high (0.95).

Conclusion

We have shown that in theory, in simulations, and in urban settings, fertility control using contraceptive bait can reduce rodent population size. Contraceptives acting early in female lifetimes appear to be most effective at controlling population growth, and when combined with moderate reductions in fertility (< 50%) can rapidly reduce expanding populations to negligible size. Unlike rodenticides and sterilants, contraceptives preserve individual fertility as well as genetic diversity within pest populations. By this process, contraceptives simultaneously reduce the probability that resistance to their use will evolve and enhance the probability that alleles underlying resistance will be lost by drift (Shuster et al. 2018). These advantages could inform the development of sustainable solutions to pest population control.

Authors consent

All authors have consented to participate in the writing and publication of this manuscript.

Author contributions

SMS conceived and designed modelling research and analyzed data; LPM designed field experiments; BP and CR supervised and executed field experiments and collected data; SMS wrote the manuscript. All authors read and approved the manuscript.

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Data availability All life table and projection matrix methods are available in Supplementary Information; additional information from simulations are available from the corresponding author upon request; these will be archived on Dryad upon acceptance.

Declarations

Conflict of interest CR is a paid employee of SenesTech, Inc., a developer of proprietary technologies for managing pest populations through fertility control; SMS is a paid consultant of SenesTech, Inc.

Ethical approval There was no ethics approval required for the modelling portion of this project; the field portion of this project was not overseen by an ethics committee as this was deployed by a Pest Control Provider in Washington DC that purchased the product for use as a rodent control tool. ContraPest is a US Environmental Protection Agency (EPA) registered product, #91601–1.

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